SMALLPOX

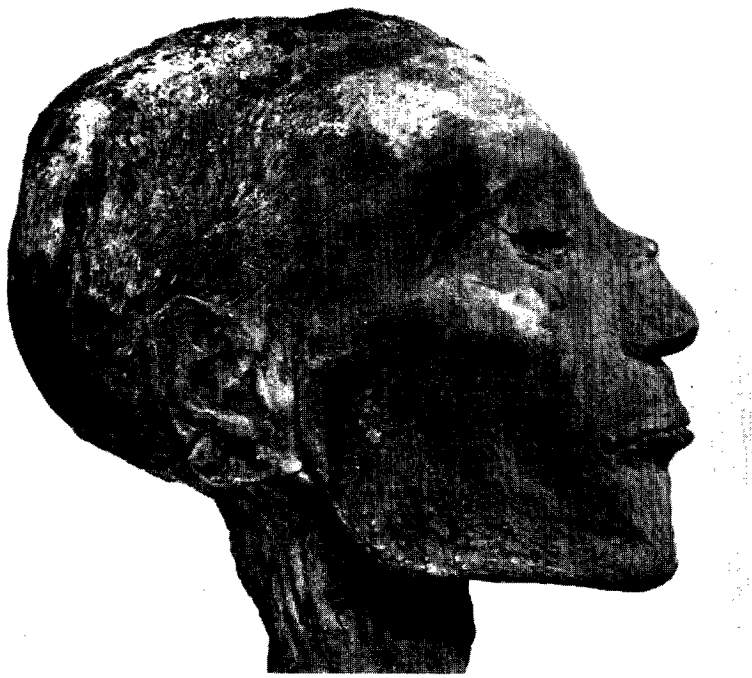

FIG. 1. Rameses V (*c.* 1100 B.C.)
Allowing for changes due to the process of mummification the lesions bear a considerable resemblance to smallpox. Rameses died from an acute illness at the age of forty.

SMALLPOX

by

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PREFACE

In this book I have endeavoured to present both the clinical and public health aspects of smallpox. To many this disease is a rarity and I have therefore included a large number of coloured and black-and-white illustrations so that the clinician may learn, or refresh his memory, when confronted with a doubtful case. All showing detail of rashes or of vaccination lesions are natural size.

In many countries with highly developed hospital services the first case is likely to be diagnosed in hospital, so some attention has been given to the problems of smallpox occurring in a general hospital as well as the organization of special accommodation for the isolation and treatment of the disease.

The medical officer of health needs an overall knowledge of the subject, but he is particularly concerned with control methods and vaccination policy and practice and I have devoted considerable space to the discussion of the basic principles in the epidemiology of smallpox and the lessons to be learnt from classic outbreaks of the disease. I have been frank in my comments on the situations presented as much can be learnt from the mistakes of others. My criticisms are not made in the spirit that I know all the answers—far from it. There is a little duplication of material in some chapters as I have kept in mind the separate needs of the clinician, the pathologist, the hospital administrator and the public health medical officer so that when smallpox occurs each will find information of most immediate value to him, without having to search from one section of the book to another, although I hope, when there is time, all will look at smallpox from a much wider view.

The history of smallpox, variolation and vaccination is not only interesting in itself and necessary to the proper understanding of practical smallpox control but it teaches much which is fundamental to our appreciation of the development of the public attitude towards inoculation procedures in general. Even when smallpox is finally eradicated I feel the story will provide a fund of knowledge useful in controlling other diseases.

I have possibly been unwise to put forward new views on some aspects of this subject and to suggest explanations based on clinical or epidemiological observations and not on laboratory investigations. These ideas, lacking scientific exactitude, are advanced in the hope of stimulating others to think, to investigate, and confirm or refute so that we may progress to a fuller understanding of this and, perhaps, similar diseases.

Part of this book was written while I was Reader in Epidemiology in the University of Leeds and I am grateful to Professor I. G. Davis for supporting me in my interest in this subject, and to the University Council who granted me leave of absence to accept an appointment with the World Health Organization as a consultant in smallpox.

In the list of references I have tried to acknowledge all my sources but if I have failed perhaps authors will bear with me and accept my apologies. "For in all these things I have been hindered neither by avarice nor by sloth, nor by fear, but only and always by time." (Leonardo da Vinci).

C. W. DIXON

ACKNOWLEDGEMENTS

I owe a special debt of gratitude to Dr. J. Pickford Marsden of Joyce Green, Dartford. We have met and discussed smallpox at intervals over the last fourteen years. He read the script of the clinical chapters and made many useful comments but this does not necessarily imply that he agrees with all my views.

Photography is very important in a book of this kind and many of the photographs are the work of Mr. W. Blackledge, A.I.B.P., A.R.P.S., F.R.S.A., Photographer to the University of Leeds. I would particularly like to acknowledge my deep appreciation of his assistance and in particular his willingness to come out to the smallpox hospital with me in the evenings, at week-ends and at other inconvenient times to take particularly valuable photographs. His uncanny steadiness of hand enabled us to take so many full-sized details of skin rashes, in desperately ill patients, where the depth focus was little more than an eighth of an inch. Apart from fifteen photographs which I took myself at Berkeley and Joyce Green, and those acknowledged below, the remainder are all Mr. Blackledge's work.

The photographs used for Figs. 30 and 31 were taken by Mr. R. M. Clemson of the Photographic Department of the University of Leeds, who visited Glasgow with me. Figs. 165, 169 to 174, 179, 180 are made from photographs taken for me by Mr. F. H. Knight, Senior Photographer of the Medical School, University of Otago.

Dr. M. L. Millard, son of Dr. C. Killick Millard, kindly gave me a large collection of smallpox photographs taken by his father. Many of these illustrate rare cases. The following illustrations are from this source: Figs. 16, 17, 39, 46, 63, 79, 80, 88, 89, 91, 92, 146 to 148, 153, 181, 182, 261.

I am also indebted to many friends who have allowed me to use their photographs and these are included in the following list of sources:

Dr. Abriol, Fig. 230; Dr. E. C. Allibone, Fig. 185; Dr. D. M. Blair, Figs. 83, 84; The Marquess of Bute, Fig. 202; Dr. A. F. Cameron, Figs. 8 to 10; Mr. Warren R. Dawson, Fig. 1; Dr. A. Douglas, Fig. 197; Professor A. W. Downie, Figs. 144, 145; Dr. T. H. Flewett, Fig. 164; Drs. R. A. Good and I. M. McLachlan, Fig. 140; Dr. C. J. Hackett, Figs. 38, 78, 154; Dr. P. Hansell, Figs. 151, 152, 184; Mr. E. H. Jesty, Fig. 209; Dr. S. E. Keidan, Figs. 188 to 190; Dr. B. Laurence, Figs. 191, 192, 194, 195; Dr. P. MacArthur, Figs. 162, 221 to 224; Professor A. S. McFarlane, Fig. 163; Dr. J. Pickford Marsden, Figs. 135, 139, 186, 187, 262 to 268; Dr. G. R. Painton, Figs. 123 to 131, 241, 270; Dr. C. D. Rosenwald, Figs. 155, 159 to 161; Mr. Thackrah, Figs. 114, 115; Professor C. E. Van Rooyen, Figs. 142, 143.

Miss D. McHugh, of the Medical School, University of Otago, copied the old illustrations for Figs. 221 to 224.

The attractive and clear diagrams are the work of H. Grayshon Lumby, Esq., M.S.I.A., N.D.D., Medical Illustrator to the Department of Preventive Medicine and Public Health, University of Leeds. I am indebted to him for a great deal of assistance. For many years we worked together experimenting with methods of graphic presentation and he designed about

half the diagrams whilst I was in England, but the remainder have been done since I came to New Zealand and have required much correspondence on my part and much skill in interpretation on Mr. Lumby's part. He also painted the originals for Figs. 5 and 27a and has given much advice on layout and typography. Mr. Lumby has also supervised the coloured illustrations with the colour lithographers, Vauvelle and Sons of Leeds. I would like to express my very sincere thanks to them for the original lithographs which they made and presented to me for use in my booklet on the "Diagnosis of Smallpox", and which were printed free through the generosity of Mr. N. Watson of John Waddington Ltd. Some of these are included in this book, as well as the lithographs of variola minor which Messrs. Vauvelle originally gave to me in 1953 and which have not previously been reproduced. I would also like to express my appreciation of the great pains they have taken to secure a lifelike appearance in the coloured illustrations, and to John Waddington Ltd. for such excellent colour printing.

I wish to thank Mr. H. D. Erlam, Librarian, University of Otago Medical School Library, for much useful advice on the compilation of the indexes and in other ways.

Over the years many secretaries have helped to shape the script: in particular Miss Eve Pigott, Miss Barbara Gill, Miss Christine Panes of the Department of Preventive Medicine and Public Health of the University of Leeds; Miss Veronica Hessian, Miss Margaret Laurie, and Miss Eileen Thomson of the Department of Preventive and Social Medicine, University of Otago. I am indeed grateful to them for their patience and industry.

Finally I wish to thank Mr. J. A. Rivers and others of the staff of Messrs. J. and A. Churchill Ltd. for their patience with the manuscript and their great help in solving many problems accentuated by my being across the other side of the world. I much appreciate Mr. Rivers' understanding of my desire for quality in the diagrams and illustrations, and in particular for allowing the colour illustrations to be produced by eight-colour lithography.

CONTENTS

CHAPTER 1 | *Introduction*

In a monograph it is usual to commence with the history of the disease, follow with the aetiology and pathology, and subsequently deal with the clinical and preventive aspects.

It hardly seems possible to understand the history and epidemiology of smallpox unless one fully appreciates the varied clinical manifestations. For this reason the clinical aspects of the disease are dealt with first, followed by pathology and immunology, so that the history, epidemiology, and methods of control can be examined more critically.

Smallpox is an acute virus infection, and, in spite of views sometimes expressed to the contrary, the virus appears to exist in only two distinct variants—that giving rise to variola major and that giving rise to variola minor. The laboratory differentiation and the possibility of different strains within these two forms is discussed later. Given a single case of smallpox it may be impossible to be certain which infection is present. When a number of cases occur and the epidemiological pattern is clear, variola major and variola minor appear to be two distinct variants which have never been known to change from one into the other. The title smallpox, therefore, includes both variola major and variola minor, and when this term is used it includes both variants. In the clinical diagnosis, in the epidemiology and control, it is necessary to distinguish one from the other, and the terms variola major and variola minor are then used. This gives a mixture of terms, but, apart from other reasons, smallpox is a very old English word and worth retaining. The term alastrim and local names such as amaas, Cuban itch, etc., as alternatives for variola minor, all tend to confuse the issue and imply that the disease is not a form of smallpox, and this may be dangerous.

The term "varioloid" (Thomson, 1818) is still sometimes used to describe variola major in vaccinated persons as a "smallpox-like" disease. This use tends to suggest that it is a distinct disease, which is untrue, and may mask the fact that such a clinical condition occurring in a partly immune person is infectious and gives rise to any of the normal varieties of variola major in contacts. To add to the confusion, varioloid is also sometimes used to describe variola minor. It is a most undesirable term and should be abandoned.

Other terms have been handed down over the years, and although the meaning of many was probably clear fifty or seventy-five years ago when smallpox was common, they may lead to confusion in the minds of those whose experience of smallpox is limited. From the middle of the nineteenth century much smallpox in Europe and North America occurred in persons vaccinated some years previous to attack. In some outbreaks, over 90 per cent (Edwardes, 1902) of the cases were in vaccinated persons. A distinction was made between natural smallpox where variation in severity was determined by "nature" and modified smallpox where its severity was affected by art (vaccination). It became the fashion to talk of *natural* smallpox, which was often severe, and *modified* smallpox, which was frequently mild, and by implication to assume that mild smallpox could not be the natural disease. The term "natural" is only confusing and should not be used in this context.

Perhaps due to blind faith in vaccination the idea also grew up that because some mild cases showed "modification" or some departure from "normal" smallpox, all mild cases of variola major must be modified and that this modification must only be due to vaccination, variolation, or a previous attack. Relying largely on hospital experience, Killick Millard (1896) asserted that mild cases in the unvaccinated were so excessively rare that he hardly believed they existed and that frequently they were due to previous successful vaccination of which the patient was unaware. Cameron (1903) had much experience of smallpox, but wrote rather unconvincingly of this condition. Exceedingly mild smallpox in the unvaccinated had been observed by many of the older writers. De Haen (1775) described *variola sine variolis* and thought that this condition was not uncommon, but, of course, such cases rarely find their way into hospitals. Ricketts (1908) made his use of the words quite clear by saying, "by the use of the terms 'modified smallpox' and 'abortive lesions', no assumption is made as to the state of the patient with regard to vaccination. All that is implied is that he exhibits lesions which in certain particulars differ from the type most common among unvaccinated patients." In this book the unqualified term "modified" refers to clinical characteristics of the eruption and in no way implies post-vaccinial immunity.

Mild attacks occur both in individuals who have never been vaccinated and in individuals who have been successfully vaccinated, either many years before or during the incubation period in which it is impossible to decide whether the mildness is due to "man-made" immunity or to natural causes. It is always tempting to assume that a mild attack is the result of our own efforts when we have no proof that it is.

The term "haemorrhagic" has been used extensively in both the medical and lay press, usually to imply smallpox of considerable severity. Ricketts used the terms "haemorrhagic" and "toxic smallpox" indiscriminately, but he also pointed out that "haemorrhage from smallpox is not synonymous with haemorrhagic smallpox". It is to be noted that while haemorrhages are a feature of many types, particularly of the fatal cases, they may also be present in quite mild cases and have no unqualified prognostic significance. The writer is in complete agreement with Ricketts in being particularly averse to Curshmann's (1875) classification and his use of the two terms *variola haemorrhagica pustulosa* and *purpura variolosa*. Attempts to use these terms confused Bancroft (1906) in his clinical descriptions, and also Bras (1952*b*) in his attempt to classify cases and fit them to the pathological findings. In this book the term *purpura variolosa* is still used because it does describe a very clear-cut clinical entity, but it is only regarded as a word-picture of one form of "fulminating, type 1".

A term that has been used in a number of systems of classification is *variola vera*. It is this idea of true or typical smallpox so often forming the subject of illustrations in text-books of medicine that has fixed in the minds of practitioners a single picture of what smallpox should look like. The literature on smallpox abounds with statements that a case, particularly the first in an outbreak, was "atypical" as it did not fit the clinician's preconceived ideas on the subject. It must be emphasized that there is no such thing as atypical smallpox. The wide range of severity and variation in signs and symptoms is characteristic of the disease, and depends on the reaction of the host to the virus attack. It is therefore misleading to describe cases as typical or "classical" smallpox, sometimes calling it *variola vera*, and regard all other forms as unusual variations.

For the descriptions in this book smallpox is regarded as a disease with two main phases, the "initial", sometimes called the pre-eruptive stage, of sudden onset, followed by the "eruptive"

stage with the development of a focal (Ricketts, 1908) rash with many diagnostic and prognostic characteristics. In certain cases, both very severe and very mild, the main "pock" or "focal" eruption may be absent. The term "pre-eruptive stage" is convenient and often accurate, but other non-focal rashes may appear at this time so that it is more convenient to use the term "initial".

The focal lesion, which is later described in detail, commences as a macule, becomes a papule, then a vesicle which is filled with colourless fluid. Usually, the contents change so that the fluid has a milky or purulent appearance and is described as a pustule. Until quite recently this term was used in the sense that the lesion was an intracuticular collection of pus. Even Ricketts (1908) describes it as a "miniature boil". In some instances, especially in the tropics and where hygiene is deficient, lesions contain ordinary pus with white cells, cellular debris and secondary pyogenic bacteria. However, many lesions only contain cellular debris from the epidermis, a few leucocytes and no bacteria, although they look as if they contained pus. The term pustule is therefore used, as it has been for hundreds of years, to describe a stage in the development of the rash without implying that it has a pathological basis similar to a purulent lesion of the skin due to ordinary pathogenic bacteria.

Marson (1866), Ricketts (1908) and others have stated that the prognosis is greatly influenced by the extent of the eruption. These views have often been misinterpreted by those with little experience of smallpox to mean that extent of eruption and severity of attack are directly correlated. It has always been recognized that some moderate eruptions have a poor prognosis.

Like the word "haemorrhagic", "confluent" tends to be used loosely by the lay and medical press to describe any severe case. The term confluent is used when the individual lesions touch one another and coalesce, forming a network of lesions with small islands of unaffected skin. It is normally applied to the late vesicular or early pustular stage, although in very severe cases papular lesions may merit this description. When a few lesions touch one another, the term coherent has also been used. In many cases local increase in number of lesions with coalescence occurs over pressure points, but it seems unnecessary to use any special descriptive term. With a little experience, recognition of this local effect is easy. Descriptions and photographs of cases in the literature show that there is a tendency to use the term confluent far too freely, with the result that the reader obtains an exaggerated picture of the severity of cases and the possible effect of treatment. The term confluent should not be used without qualification, as the mere presence of confluence is not the most important prognostic sign. In this book the terms malignant confluent and benign confluent are used, the significance of which is described later. Confluence practically never occurs on the whole body, and this term is, in my opinion, best restricted to those cases which show general confluence of mature lesions on the face and forearms, the term semi-confluent being used where confluence occurs only on the face. This is the definition adopted by Ker (1939), whereas in Rickett's (1893) classification the term confluent includes all those cases where there is confluence on the face. In spite of increasing the number of terms, I feel the category semi-confluent is valuable, particularly in the malignant type where the moderate eruption on the trunk may lead the inexperienced physician to give an unwarranted good prognosis. The terms discrete, mild and abortive are used in relation to the number of lesions as set out in the table on pages 6 and 7.

Clinical methods used in the diagnosis of smallpox are similar to those used in other diseases, but it is as well to review the particular examinations needed.

One is taught to take a history before examining the patient, but there is considerable force

in Wanklyn's (1913*a*) argument that the history of the initial stage and of the vaccination state may produce sufficient bias to trap the inexperienced. If a definite eruption is present, that in itself should decide the diagnosis. On the other hand, when the rash is at a very early or very late stage inspection may be inconclusive and evidence from the history should be considered carefully. An accurate history should include details of the patient's movements within at least sixteen days before the onset of symptoms. It should be known whether the patient has been in any country or place where smallpox is present. Contact with cases of infectious disease should be noted, particularly if called chickenpox or measles, as this may be of significance whether the diagnosis is correct or not. The vaccination history should be obtained with date of primary vaccination and of any revaccinations, and as far as possible, a description of the kind of reaction obtained. This will have to be confirmed in the case of primary vaccination by examination for the presence of a scar. Revaccination may leave no identifiable scar but too much importance should not be attached to the patient's story or records. If first seen when the focal rash is present, the history of symptoms such as backache, headache, vomiting in the initial stages is very important. The type of onset should be determined, whether sudden or gradual, as this is of some diagnostic significance. With the appearance of the rash the continuance or intermission of symptoms should also be noted.

The usual methods are used for the examination of a rash. The entire skin should be examined, preferably with the patient completely stripped, in a good light, daylight if possible. Close inspection of the individual lesions is valuable, but the most important thing is to examine the body as a whole so as to observe the distribution. The stage of development of the various lesions should also be assessed, bearing in mind that many patients do not notice the earliest macules, particularly when they are scanty. The mouth and throat should also be examined. Examination of other systems gives no positive help in the diagnosis of smallpox. The prudent physician should note the presence of signs of other infections, for example pneumonia, but should bear in mind that this should not lead him to discount any evidence of smallpox, as the necessity for a double diagnosis occasionally arises.

Material may be taken from the patient for laboratory tests. A specimen of blood from a vein can be used for the culture of virus, the detection of soluble antigen or the complement fixation reaction. Scrapings may be taken from cutaneous lesions with a needle or scalpel and smeared on to glass slides and vesicle fluid or scabs collected. These may be used to detect virus by microscopy, by culture or for serological tests. Methods of collection and the significance of the results are discussed in Chapter 4.

CHAPTER 2 | *Classification of Cases*

A clinical classification is necessary to determine prognosis and is essential for the proper assessment of treatment, but it is also of much assistance in diagnosis which rests on the appreciation of the varied general and skin manifestations occurring in a definite time relationship to one another. It cannot be too strongly emphasized that in the "difficult" case of smallpox the skin lesions may closely resemble those occurring in other diseases, but the timing of their appearance in relation to the general symptoms determines whether the disease can or can not be smallpox.

The accompanying chart (Fig. 2) sets out the principal clinical characteristics of nine types of smallpox based on cases seen in Tripolitania (Dixon, 1948). Although originally worked out on the disease occurring in a predominantly Arab population, subsequent observations in Glasgow in 1950, Rochdale in 1952 and the West Riding in 1953, and by Murphy (1954), have confirmed that it applies equally well to the disease in a European population. Banks (1952) has advocated its use. Some writers assert that the variation in type from severe to mild is a gradual indefinite change; with this I cannot agree. There is an entirely different "pace" in the fulminating and malignant types, which sharply differentiates them from the benign. Many of the older writers recognized this, particularly Moore (1815). He even used the descriptions malignant and benign, although I adopted these in Tripolitania when unaware of this. The classification applies to both variola major and variola minor and in the vaccinated and in the unvaccinated. The case which has not fitted well into many of the previous classifications is the "discrete". As pointed out by Ricketts (1908) and others, although normally free from toxic symptoms in the eruptive stage, this type of case may occasionally show this feature and include small haemorrhages in the skin. The diagram in Fig. 5 shows the relationship of the types to one another and that the discrete may sometimes show some of the characteristics of both the malignant and the benign types.

It will be seen in Fig. 2 that a number of general and local features make up the character of each type. The term confluent is used with qualification, and the division between types 6, 7 and 8 is based on a numerical difference in the eruption. It should be noted that where vaccino-modification occurs, the differences in the type of lesion should be disregarded in making the classification, but such effects can be noted by using the term vaccino-modified as a supplementary description. The value of this procedure is not apparent until it is realized that vaccination, particularly when performed during the incubation period, may have no effect on the number of lesions but only on their maturation.

TYPE 1—FULMINATING—(PURPURA VARIOLOSA)

In a small proportion of individuals smallpox infection runs a hyper-acute course. After an incubation period of about eleven to twelve days the patient is suddenly taken ill, with a feeling

FIG. 2. Principal clinical characteristics

Type	Name	Initial fever	Secondary fever	Laryngeal lesions	Mental symptoms
1	Fulminating (Purpura variolosa)	+ −	−	+ −	Anxiety +++
2	Malignant confluent	++	+++	++	++
3	Malignant semi-confluent	++	++	++	++
4	Benign confluent	+++	+	+ −	−
5	Benign semi-confluent	+++	+	−	−
6	Discrete	+++	+ −	−	+ −
7	Mild	+++	−	−	−
8	Abortive	+++	−	−	−
9	Variola sine eruptione	+++	−	−	−

of the nine types of smallpox

Haemorrhages	Rash	Pustulation (untreated)	Extent of focal eruption	Approx. mortality (%)
Early, esp. mucous membranes +++	Soft, velvety; often absent	Nil	—	100
Late in the skin and mucosa ++	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face and arms	70
Late in the skin and mucosa ++	Soft, velvety, hot and tender. Slow evolution, pseudo cropping	Nil	Confluent on face only	25
—	Hard, pearly. Normal evolution, uniform on each anatomical part	Severe	Confluent on face and arms	20
—	The same as in type 4	Severe	Confluent on face only	10
Very occasionally in individual vesicles	Usually hard, pearly	Slight	No area confluent over 100 lesions	2
—	Hard, pearly. Some lesions abort	Slight	20–100 lesions	0
—	Pearly. Many macules and papules abort	Nil	Less than 20 lesions	0
—	No focal rash	Nil	Nil	0

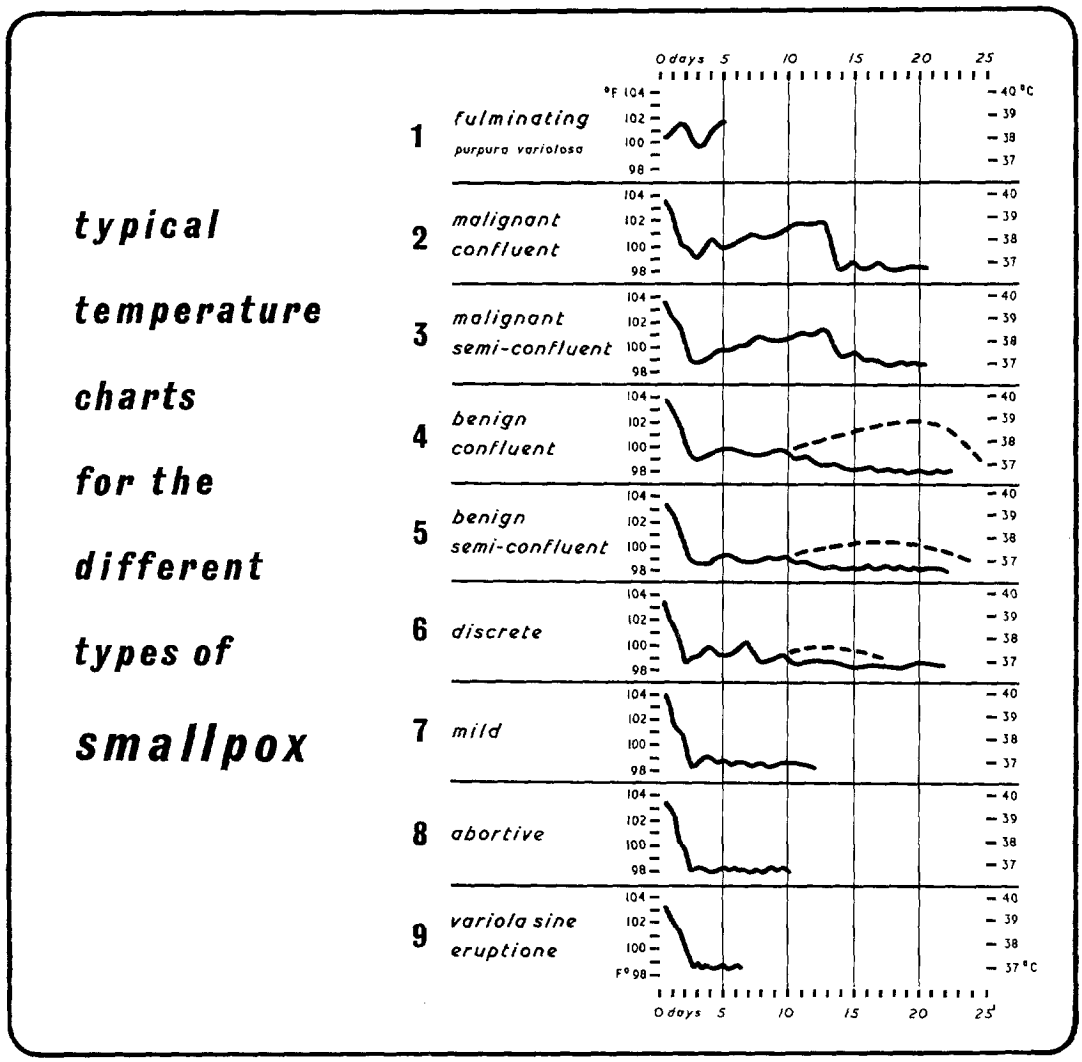


FIG. 3. Typical temperature charts for the different types for smallpox. Primary fever occurs during the first three to four days, secondary fever from the fourth to twelfth day in malignant types, from the fourth to tenth in the more severe benign types, in the latter merging with the tertiary fever to about the twentieth day or more if secondary sepsis intervenes. Types 7, 8 and 9 have no secondary fever.

of intense prostration accompanied by severe headache, and often backache. In spite of these symptoms the patient is very "wide awake" and peculiarly apprehensive. In some patients the infection is so overwhelming that death may occur within twenty-four to thirty-six hours with no outward manifestations at all. Consciousness is retained to the point of death, and the patient quietly expires. At post-mortem there may be a few haemorrhages in the submucosa, in the respiratory (Fig. 4) and alimentary tracts and in the heart muscle, the latter

FIG. 4. Fulminating, haemorrhage at the tip of the epiglottis, and in the left pyriform fossa.

To face p. 8

possibly contributing to death in some cases. The appearances are very indefinite, with no findings on which to base a certain diagnosis. The most likely one is some unknown acute infection or possibly an acute lymphatic leukaemia. The blood film shows a leukaemic picture with the white cells almost all lymphocytes and there may be many myeloblasts. This is "sledge-hammer" smallpox, and the diagnosis both clinical and at autopsy is impossible unless smallpox

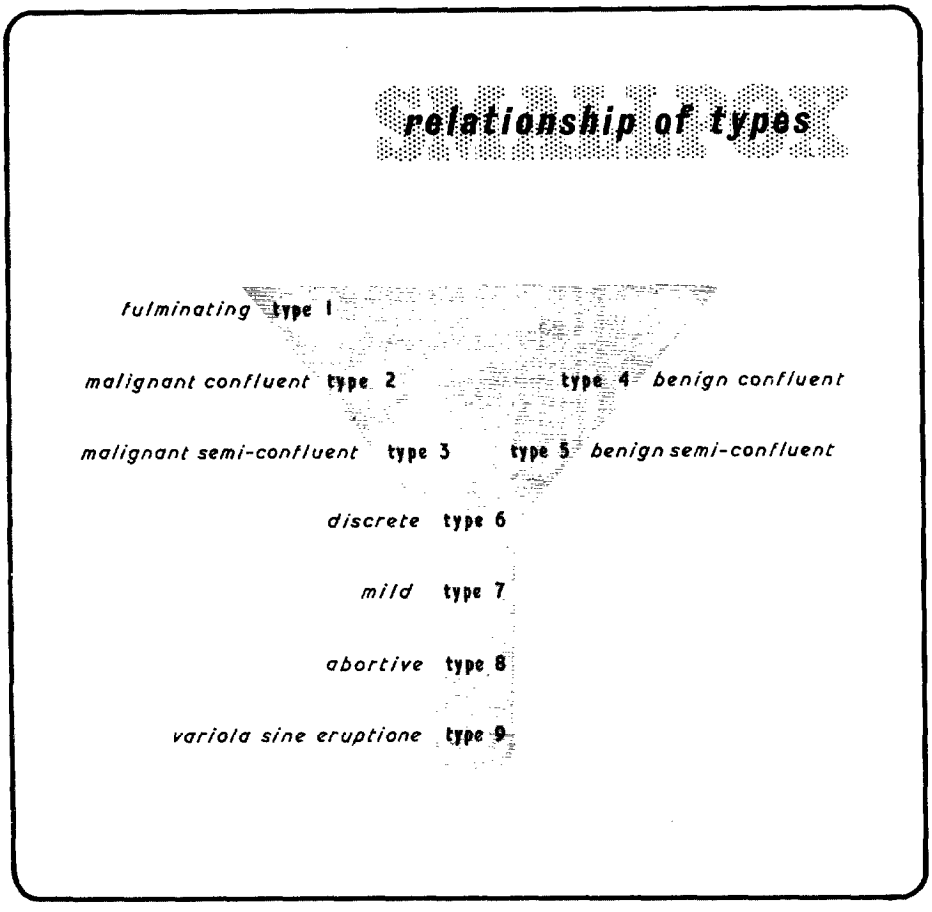


FIG. 5.

is thought of and unless laboratory facilities are available and used to grow the virus or detect soluble antigen in the blood during life, or after death. If the patient survives more than forty-eight hours there is often a slight but temporary improvement in the general condition, followed by the appearance of an erythema on the face and back of the hands, and a blotchy erythema on the arms and trunk, particularly the anterior abdominal wall and the upper part of the thighs (Figs. 6, 7, 9 and 10). The patient's general condition deteriorates, there is increasing prostration, but the temperature remains at about 101–102° F. (38·3–38·9° C.).

Wanklyn's description (1903) is particularly apt. After three to four days the patient "has the general aspect of one who has passed through a long and exhausting struggle. His face has

lost its expression. The lines have partly disappeared. As it has been expressed, his face is mask-like and there is a want of tone in all the muscles. When he speaks, this condition becomes more apparent. He speaks with evident effort and his voice is low and monotonous. He is list-

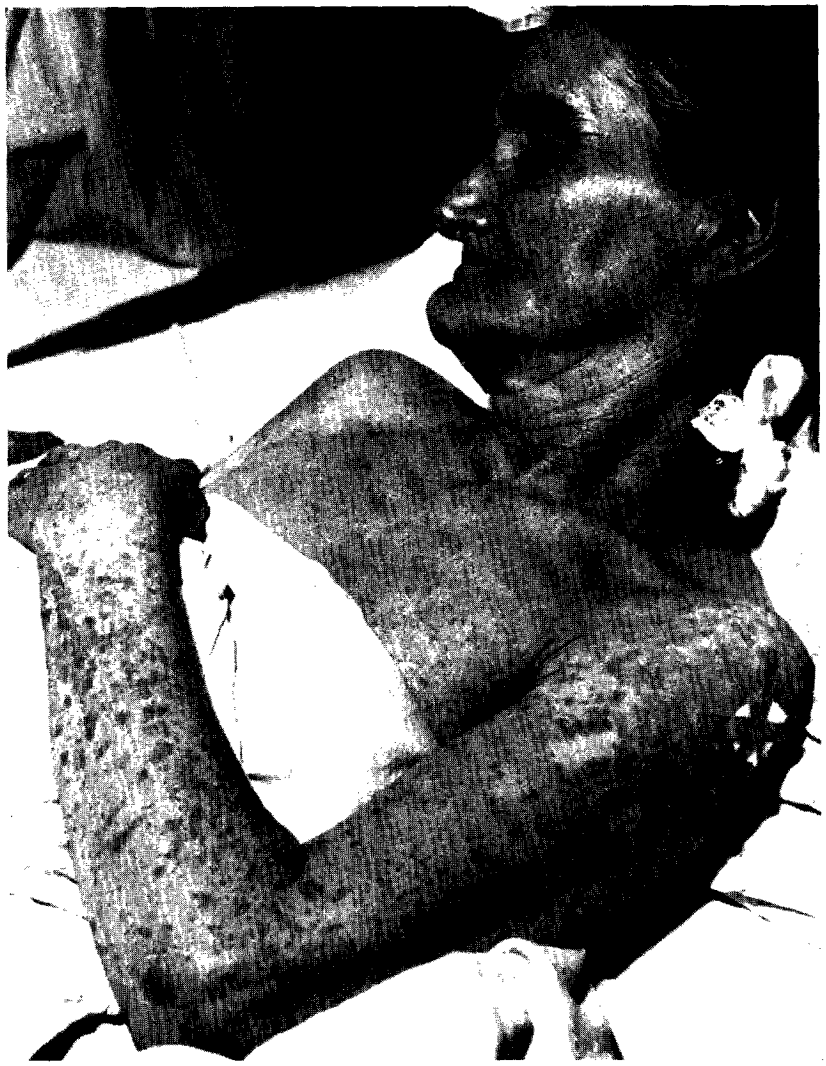


FIG. 6. Variola major, fulminating, third day. Dusky erythema of face and hands, patchy morbilliform eruption on arms. Note old vaccination scars on the arm, formed sixty years before.

less and indifferent to his surroundings, though his eyes may be clear and bright. The question as to the disease from which he suffers has little interest for him. The greater the physical development the more marked is this condition. The mental attitude is similar. There is loss of tension, showing itself in a lengthening of the reaction time and a defective control. When

a question is put the answer is appreciably delayed. A request to show his tongue or to put out his hand often requires to be repeated. Such movements are often retarded and tremulous or even jerky in their performance. It is evident that their completion gives relief. The patient staggers in his walk and tends to fall if not supported. Frequently he volunteers the statement that he feels much better and will soon be all right. Such is the typical condition. The more severe the attack the more striking is the picture. In the most fulminant case the aspect of the patient resembles that of one suffering from severe shock and loss of blood. His face is drawn and pallid. His respiration is sighing or even gasping. He tosses himself about continually and cries out at frequent intervals. His attention is fixed with difficulty and he complains only of agonizing pain, now in his chest, then in his back, his head or abdomen" (Fig. 8).

Examination of the mouth may reveal haemorrhages occurring under the mucous membrane and large blood-filled bullae which at first sight may be mistaken for true focal lesions. The

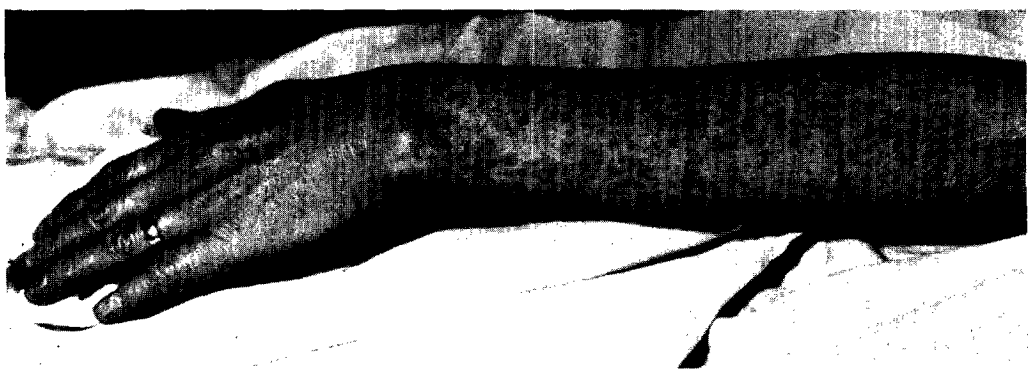


FIG. 7. Variola major, fulminating, dull erythema of hand and wrist, patchy erythema of forearm.

erythematous areas of the skin will reveal petechiae which during the next twenty-four hours rapidly enlarge forming ecchymoses of a peculiar bluish-purple colour (Fig. 19), particularly present on the abdomen and upper parts of the thighs; but just before death, which occurs within forty-eight hours of the onset of these haemorrhages, the whole body may be affected. When the haemorrhages occur only in the "bathing drawers" area (Fig. 10), a confident diagnosis of smallpox can be made; but when haemorrhages are more general, as is common, the picture has no completely characteristic features to distinguish it from other hyper-acute infections, although in smallpox there is a greater tendency towards symmetry. In infants the rash appears more frequently on the anterior abdominal wall and may be absent in the groins. With the appearance of haemorrhages in the mucous membrane or skin the patient's life may be terminated by massive haematemesis, intestinal or uterine haemorrhage. Death otherwise occurs very peacefully due to increasing toxaemia. The whole course of the disease lasts four or at the most five days, but is frequently less. Examination of the patient even on the fifth day may show no true focal lesions. In a number of these cases a diligent search of the body will reveal a very flattened type of vesicle (Figs. 11, 12 and 14), difficult to differentiate from the stripping of the epithelium which occurs over a haemorrhage. From the diagnostic point of view it cannot be overemphasized that the absence of any vesicular

eruption is the main feature of this condition and increases the difficulty in differentiating it from other acute haemorrhagic catastrophes.

The high white count in bacterial and the low count in early viral infections may help to distinguish between acute viral and acute bacterial, such as meningococcal, septicaemias, but

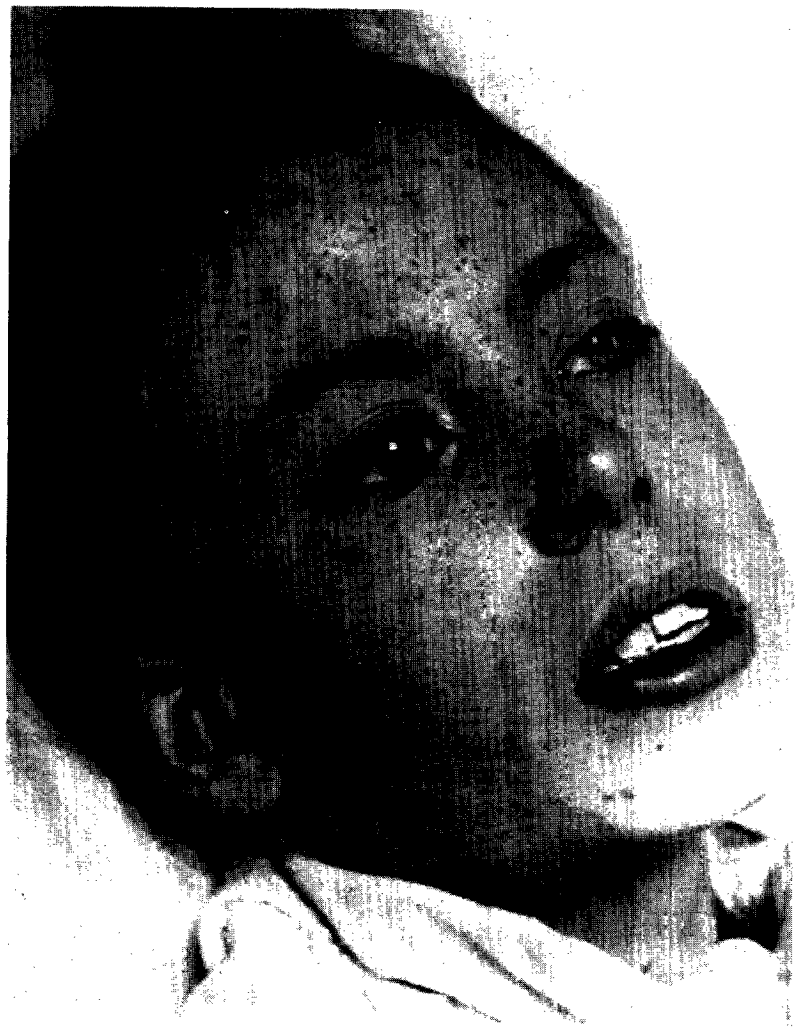


FIG. 8. Variola major, fulminating. The characteristic facial expression, loss of muscle tone, bright eyes.

too much reliance must not be placed on this, and if there is the slightest suspicion a blood culture during life or a specimen of heart blood taken after death should be sent to a laboratory for viral and bacterial examinations.

If laboratory facilities are not available do not hesitate to diagnose clinically and act accordingly.

FIG. 9. Variola major, fulminating. Erythematous and petechial eruption.

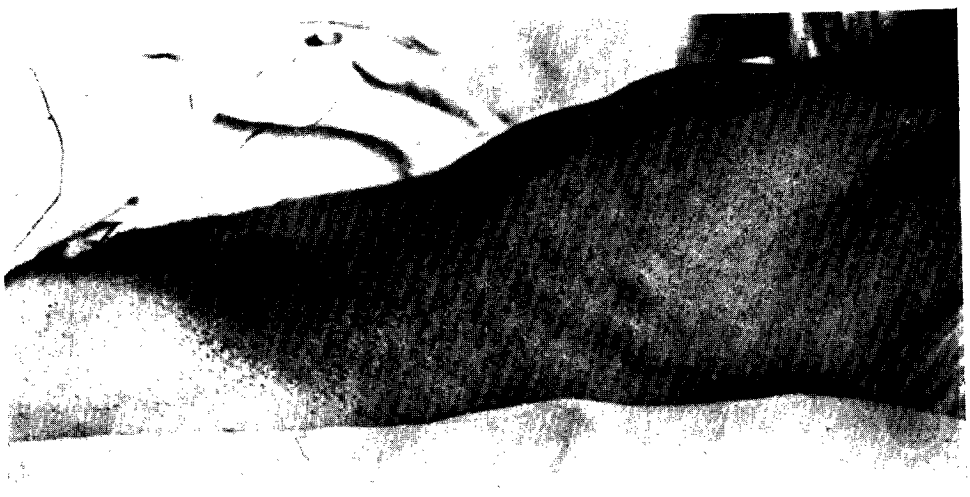


FIG. 10. Variola major, fulminating. Petechial eruption in the groin and some in the axilla.

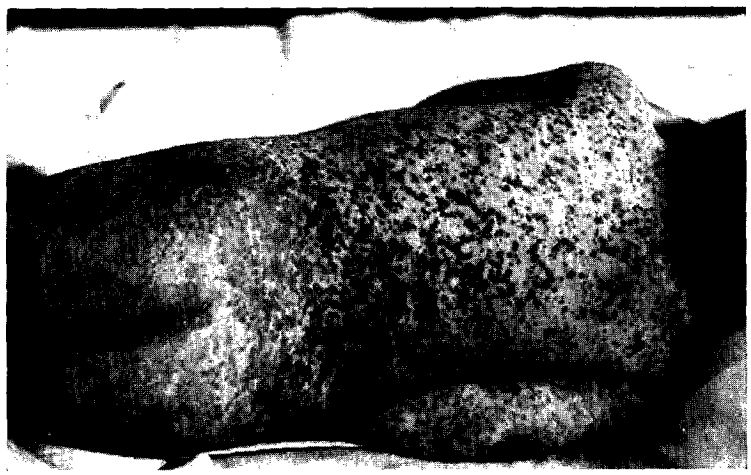


FIG. 11. Fulminating, fourth day. Although there are many haemorrhages, some very superficial vesicles are present.

FIG. 12. Fulminating smallpox, fourth day, death.

TYPE 2—MALIGNANT CONFLUENT

The onset is sudden, with a moderate temperature of 101—102° F. (38·3–38·9° C.). It should be noted that higher temperatures are common in the less severe types. Malaise, intense headache, and general aching of the muscles occur. Backache may be very severe, but is not such a constant symptom as one has been led to believe. In my experience it is less severe in Arab patients than in Europeans. Wilkinson (1942) and others noticed that this symptom was particularly severe in negroes. It seems probable that it is partly due to severity of attack

and partly due to occupation and the use of these muscles during the initial phase. Social customs may account for apparent variation with race.

When present, this peculiarly severe backache is a valuable pointer, but its absence is of no diagnostic importance.

Pain in the chest is sometimes complained of, but there are no respiratory symptoms, nor is the respiration rate raised appreciably at this stage. Vomiting is common and abdominal pain may be complained of which, by the second or third day, may be severe enough to make one suspect an acute abdominal condition. This is possibly due to mucosal or sub-mucosal haemorrhages as bleeding tends to occur in the mucous membranes before appearing in the skin. Laparotomies have been done, in error, on a number of smallpox cases of this type. Melaena may also be present, but is more profuse a little later in the disease. The patient is most anxious and has a peculiar mental alertness.

The general condition remains much the same for one or two days, but by the second or third day there may be some improvement and the temperature may fall a little, sometimes to normal. Some patients feel sufficiently well to get up and go out and may visit a doctor or hospital. The temperature rises again, but rarely above 102° F. (38·9° C.), although the patient is obviously far from well and the pulse rate has increased considerably. A dusky erythema appears on the face and a mixed petechial and macular eruption of rather irregular distribution appears on the upper chest, neck, back and upper arms (Figs. 21 and 22). Although present on the face, it is difficult to see clearly because of the general erythema. A few scattered macular lesions may be present on the lower arms and hands, but frequently there is no rash on the legs or feet. The rash is very pleomorphic in appearance and is not unlike rubella. At this stage the eruption principally affects the upper half of the body. On palpation it seems to have some substance, but the papules do not feel hard or "shotty", as is often described in the text-books. Examination of the mouth may show small areas of hyperaemia and small very early vesicles on the soft or hard palate or on the buccal mucous membrane, but their appearance is not constant and does not help very much in diagnosis.

The erythema on the face changes imperceptibly into a diffuse vesiculation. On the cheek and forehead it looks almost exactly like a very severe sunburn (Fig. 13). The appearance is not unlike a very fine-grained crêpe rubber set on a red base and seems to be due to a combination of very small nearly confluent lesions and a marked intracuticular oedema which leads to the scalded appearance of the skin at a later stage (Figs. 13 and 25). Epistaxis may occur; the lips are swollen and there may be slight bleeding from the corners of the mouth. By the fifth day the rash has not progressed very much, the papules remain soft, there may be some erythema of the backs of the hands, but many of the lesions on the chest, arm and back will have changed very little and may still consist of mixed maculo-papular and petechial elements. The appearance is so different from the usual description of "classical" smallpox where all the lesions on each anatomical part are at the same stage of development. On close inspection it may be possible to find one or two very flat thin-roofed vesicles, quite small, only about 4 or 5 mm. in diameter. The vesicles are so flattened as to be little more than a thin flake of epithelium over a flat papule separated by a very small amount of fluid. This lesion is more likely to be seen over a small haemorrhage, and, because of the appearance and apparent cropping, cases of this kind are often thought to be haemorrhagic chickenpox. This diagnosis is made as the patient's general condition remains fairly good although the apprehensive mental state remains. The prognosis is, however, very bad. During the next three days the

rash slowly continues to develop on the forearms and hands, on the upper legs, lower legs and feet, in that order. Although the general distribution follows a centrifugal pattern it is very much less pronounced than in the benign types of smallpox described later. The gradation of density of lesions on the limbs, increasing as one passes towards the periphery, is particularly slow to show, and at this stage the rash may appear as dense and sometimes more dense on the proximal parts.

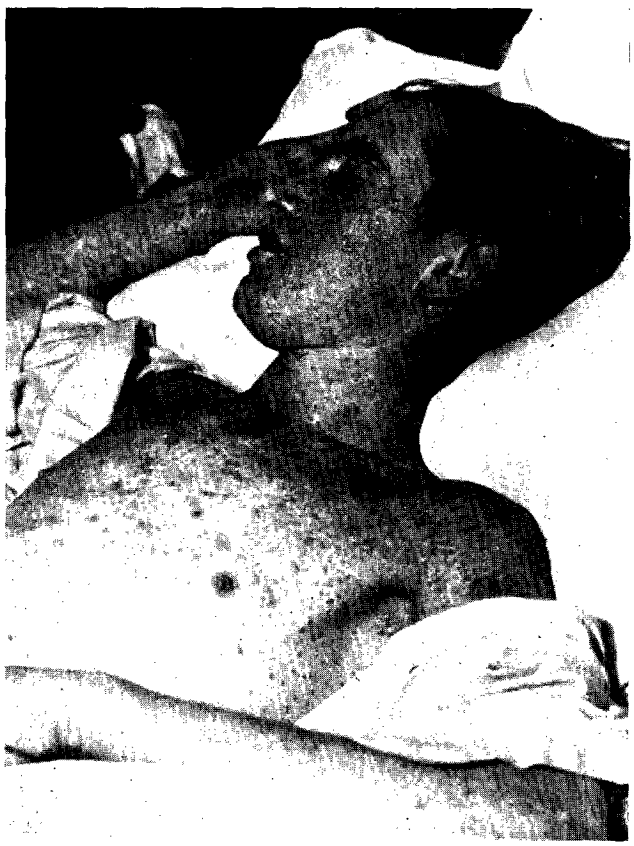


FIG. 13. Variola major, malignant confluent, seventh day, slow evolution, acute sunburn appearance of face, with tiny close-set vesicles, mixed lesions on the chest.

From about the seventh or eighth day of the disease there are complaints of increasing difficulty in swallowing, and pain on talking, due to extensive lesions in the mucous membranes (Fig. 26). The patient deteriorates slowly, being drowsy much of the day, but when roused will talk quite intelligently and unfortunately, only too frequently, realizes his ultimate fate. At night, however, he may be extremely restless, continually trying to get out of bed and requiring individual nursing attention. A condition closely resembling delirium tremens may occur and in the confused state much cunning may be shown in attempts to escape from the smallpox ward.

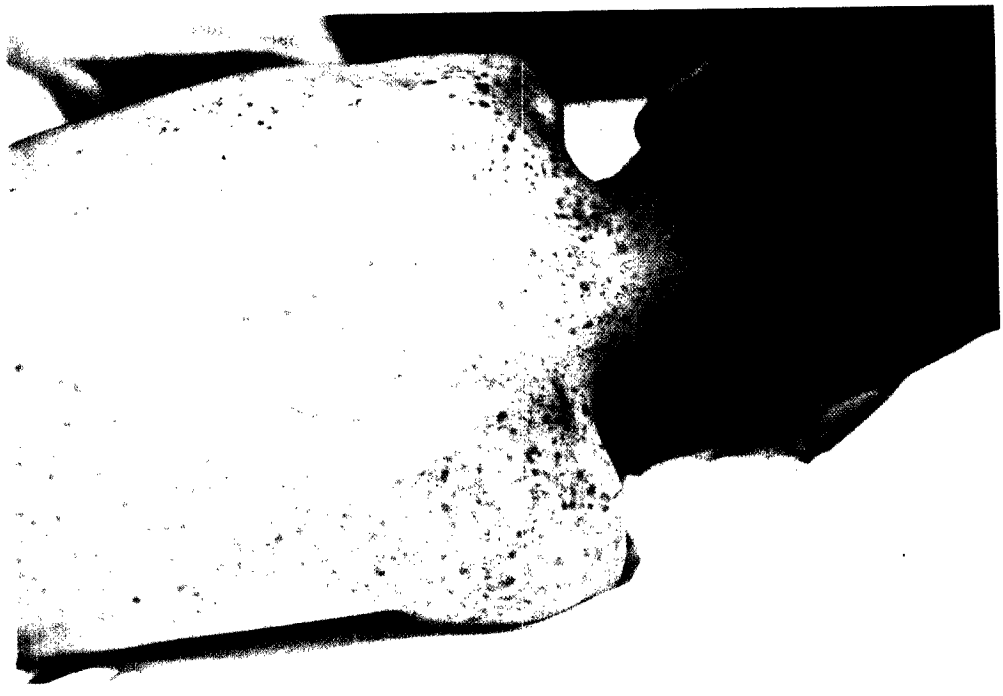


FIG. 14. Fulminating, mixed eruption on the back. On the neck are two *very* superficial flat vesicles

FIG. 15. Variola major, fulminating, fourth day, erythema of face, back of hands and wrists. Mixed morbilliform eruption elsewhere, with petechiae and ecchymoses. Haemorrhages from the angles of the mouth, anxious expression.

To face p. 16

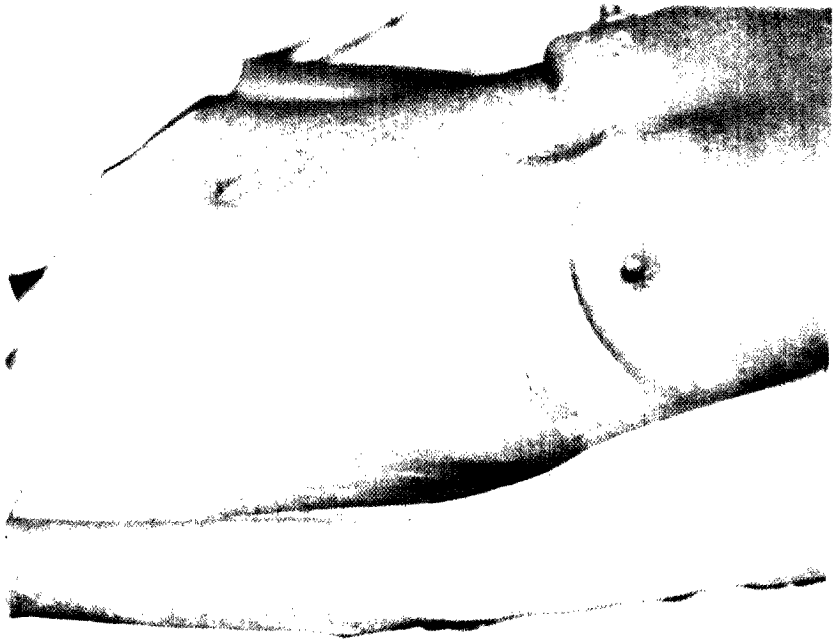
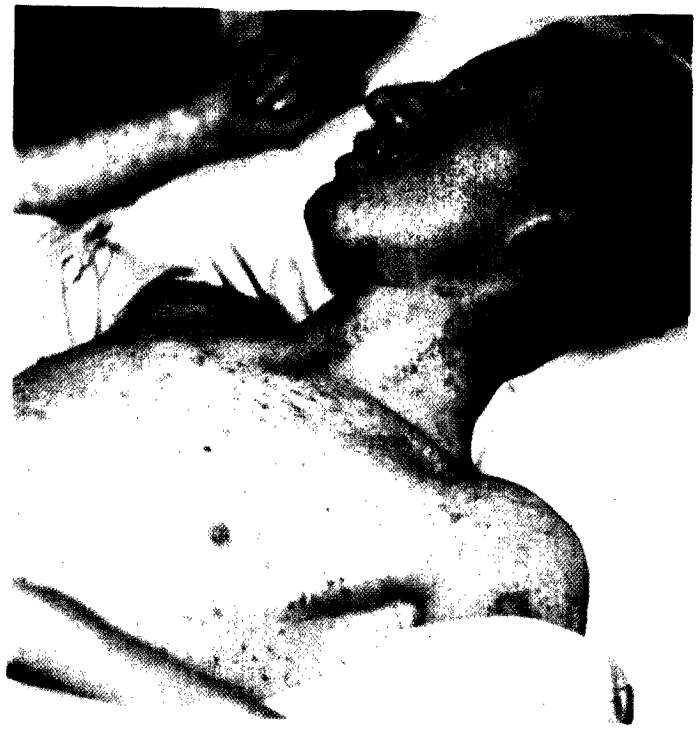


FIG. 16. Fulminating, Type 1, early diffuse erythema.

FIG. 17. Malignant confluent, Type 2, well marked "sunburnt" appearance of face and scanty, poorly developed rash on the chest.



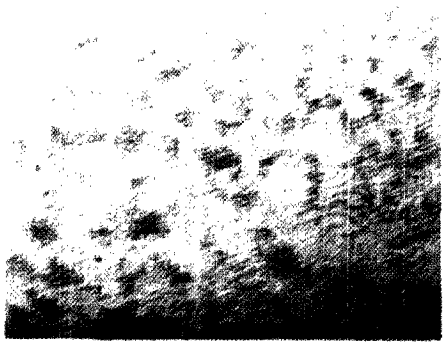


FIG. 18. Type 1, fulminating, early morbilliform eruption.

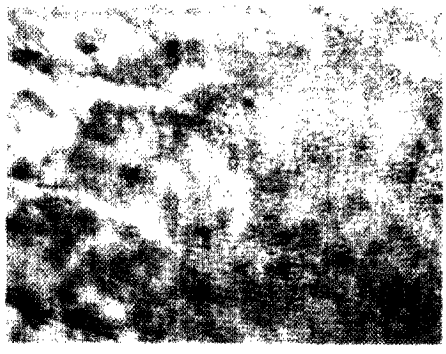


FIG. 19. Type 1, fulminating, early erythema.

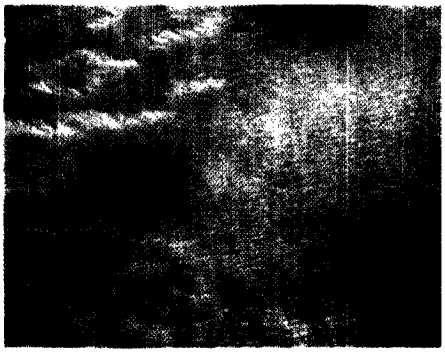


FIG. 20. Type 1, fulminating, deep haemorrhages, ink spot type.

FIG. 21. Type 2, early morbilliform eruption, fourth day.

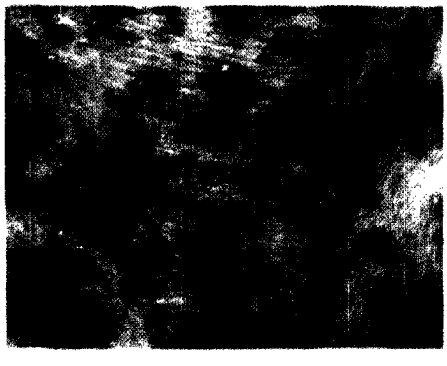


FIG. 22. Type 2, mixed elements, very slow evolution, poor superficial vesicles, eighth day.

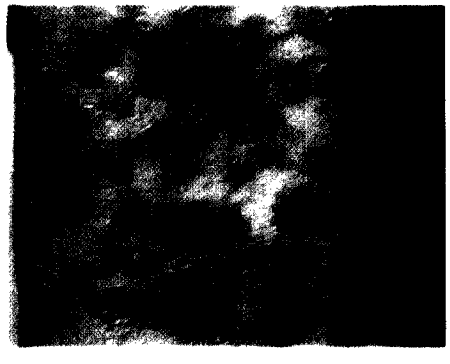


FIG. 23. Type 2, slow, poor vesiculation, tenth day.

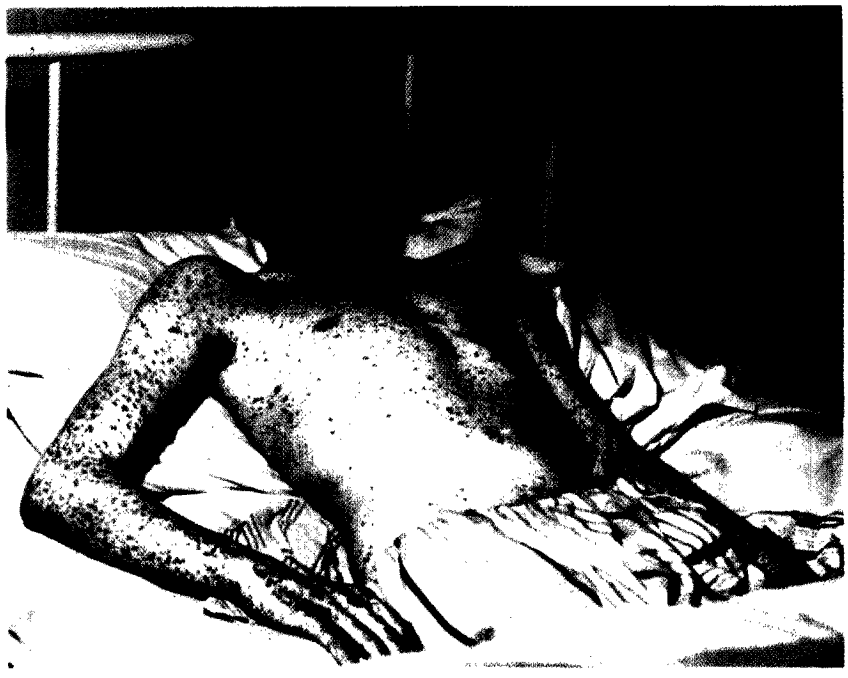


FIG. 24. Malignant confluent Type 2, early rash, mixed elements, slow evolution, sixth day.

FIG. 25. Malignant confluent Type 2, scalded appearance of face, rash limited to upper trunk, eleventh day.

FIG. 26. Variola major, extensive almost confluent vesiculation of mucous membrane of hard palate, sixth day.

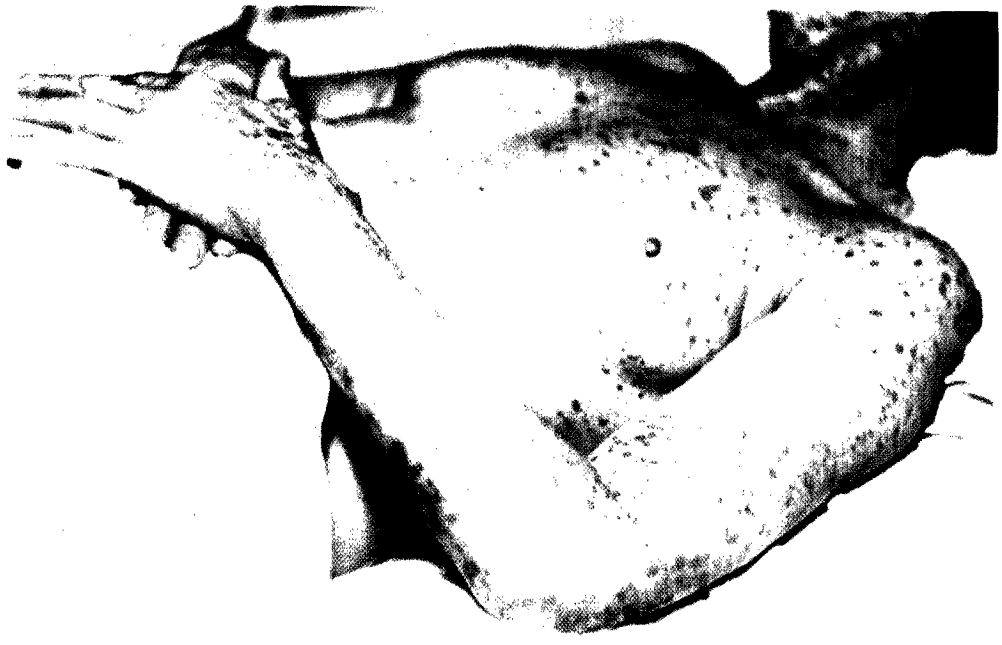


FIG. 27. Malignant semi-confluent.

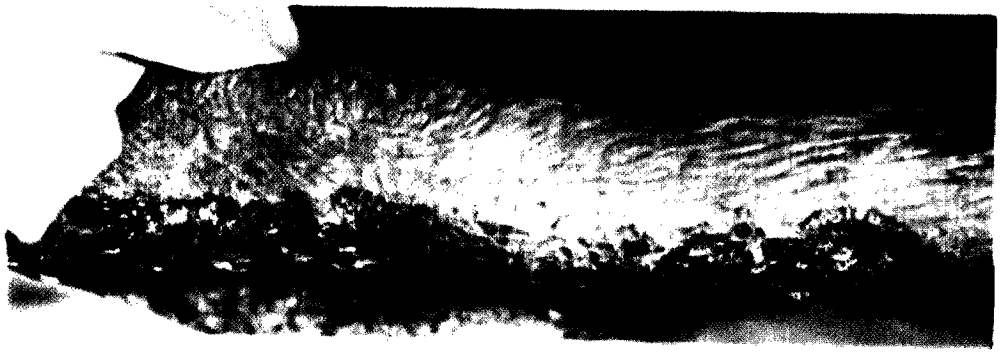


FIG. 28. Malignant confluent, exfoliation.

FIG. 29. Malignant confluent, exfoliation.

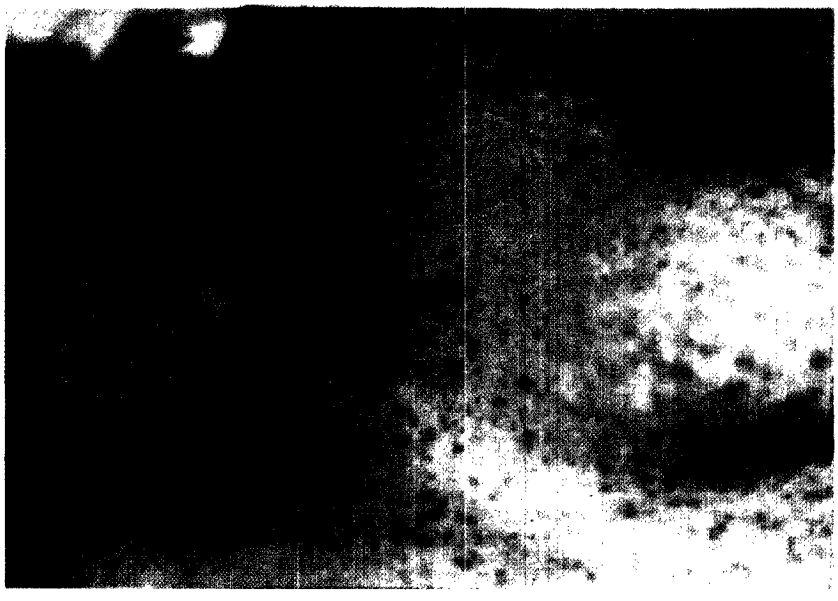


FIG. 30. Malignant confluent, tenth day, morbilliform and haemorrhagic elements. Great delay in evolution of vesicular elements.

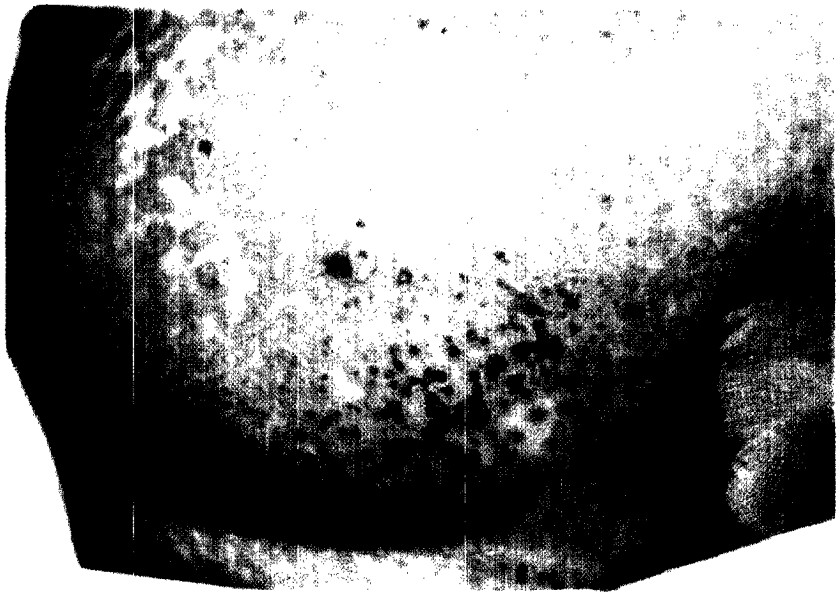


FIG. 31. Malignant eruption, fourteenth day, vesicles drying without pustulation, leaving copper-coloured superficial scars.

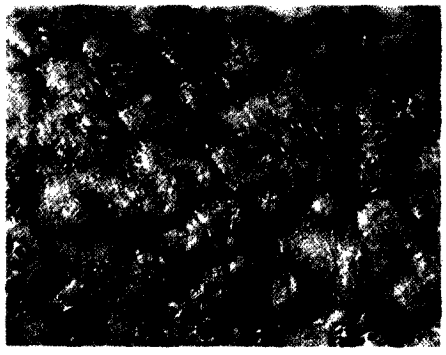


FIG. 32. Malignant. Flat soft vesicles, some with adherent roofs, simulating haemorrhage, ninth to tenth day.

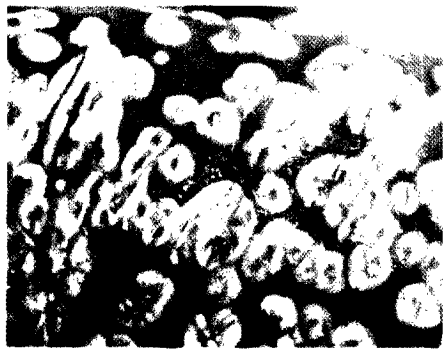


FIG. 33. Malignant, fluid absorption, "lobster" intervening skin, tenth to twelfth day.

FIG. 34. Malignant confluent, vesicles, bullae, tenth to twelfth day.

FIG. 35. Malignant, massive exfoliation, twelfth to thirteenth day.

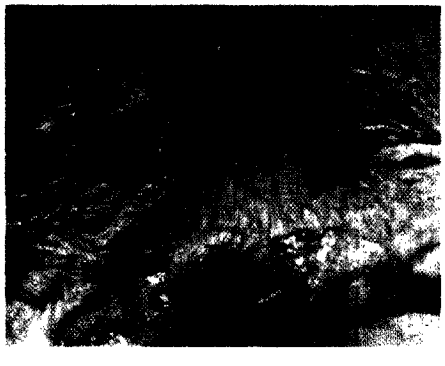


FIG. 36. Malignant, massive exfoliation, vesicle structure absent, twelfth to thirteenth day.

FIG. 37. Benign (in contrast). The birth of a macule on a typical site of solitary lesions.

Only by about the tenth day of the disease will many of the lesions on the trunk and arms have become vesicular, but they will be soft, flattened and velvety, hot and tender to the touch (Figs. 32 and 33). On confluent areas there may be large bullae containing clear fluid, but it is absorbed fairly rapidly leaving bluish-white dead sodden epithelium like a scald (Figs. 29 and 35). Haemorrhages may occur into the vesicles but more frequently in the normal skin between the lesions. Due to the general dehydration of the patient, fluid is absorbed from the lesions,

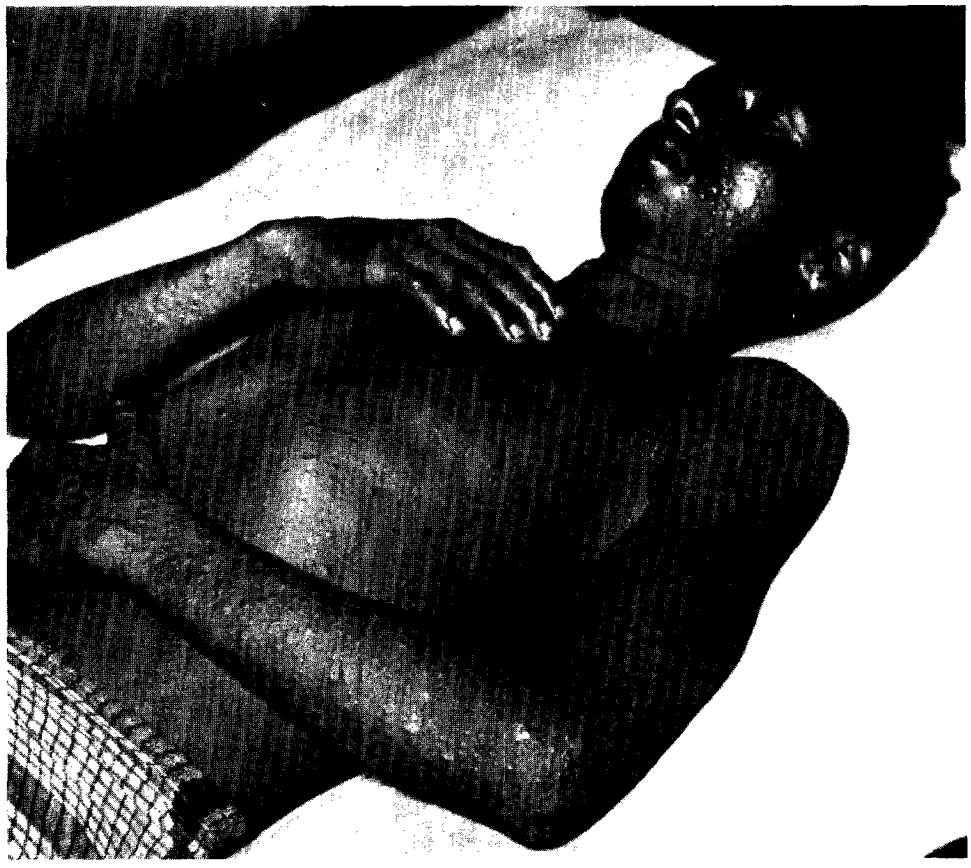


FIG. 38. Variola major, early malignant rash about the eighth day of disease.

particularly on the trunk and arms, and the flaccid roof of the vesicle adheres to the exposed dermis of the base producing a brown-coloured centre (Fig. 32) not unlike that produced by haemorrhage into a vesicle. Skin punctures made for therapy or for diagnosis continue to bleed for many hours. Uterine haemorrhages are common and may be severe; in pregnant women abortion or premature labour is almost certain to occur. Severe haemoptysis or haematemesis is common and the patient may die at this stage. The blood picture explains this part of the clinical condition. There is a complete absence of platelets, a lymphocytosis and a neutropenia. Although lesions along the palpebral margins are quite common, the rest of the

orbital skin remains surprisingly free from the rash (Fig. 40). Lesions may occur on the palpebral conjunctiva and give rise to a serous or sero-purulent conjunctivitis. Keratitis, referred to in Chapter 5, is common from about the eleventh day onwards and corneal ulceration with subsequent blindness may occur in the few cases of this type of smallpox who recover.

A peculiar sickly smell gradually develops—the foetor of smallpox. This cannot be adequately described although it is quite characteristic. It renders the discharge-sodden bed linen most offensive.

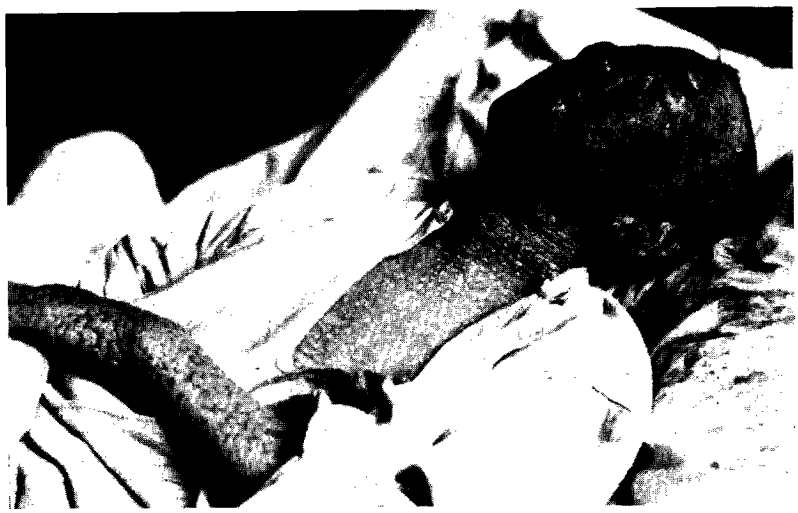


FIG. 39. Malignant confluent, so-called "black" smallpox. Death at about the twelfth day of the disease.

The relentless deterioration in the general condition continues. It is increasingly difficult to get the patient to drink, and even milky fluids seem to cause pain, due to the burning sensation in the throat on attempting to swallow. Great loss of weight, as much as 30–40 lb. (13–18 kg.) occurs during the twelve or thirteen days of illness. There is complete loss of muscle tone, and a cadaveric typhus-like appearance so transforms the patient that he would hardly be recognized by his relatives. By the thirteenth day of the disease a soft vesicular rash covers much of the body. The rash by now has a fairly definite centrifugal distribution, although it may cover such a large part of the body that recognition of this feature is difficult. It does, however, still tend to be less dense on parts of the body protected from pressure, such as the groin, the axilla and the orbit. By now many lesions have become confluent with large areas of epidermis peeling off like a scald (Figs. 28, 29, 35 and 36). Almost any part can be affected, but the back of the trunk and other areas where pressure occurs, such as the elbows, are likely to suffer most. Slight rubbing of the bedclothes or movement of the arm by the nurse or doctor may cause a large piece of dead epidermis to become detached. Although the patient may die from about the eighth day onwards, many live until the fourteenth or fifteenth day of the disease and die just as this stripping of the epithelium has become widespread. These areas are quite painful and contribute considerably to the frightful appearance and misery of the patient. The patient quietly expires, due to general toxaemia, or there may be some haemorrhagic catastrophe to

complete the picture. Although a fatty liver has frequently been recognized by pathologists at post-mortem and an enlarged liver may sometimes be palpable during life, this sign is not of any prognostic value compared with the appearance of the skin.

Even without any antibiotic treatment this type of rash never develops a "pustular" stage, although on some sites such as the pinna, palms of the hands, or soles of the feet the fluid looks cloudy, no real pus forms, even on the large desquamated areas. With so much of the dermis exposed, secondary infection can undoubtedly occur but there is little evidence of it. In the past when haemalytic streptococci were of considerable virulence and when smallpox patients

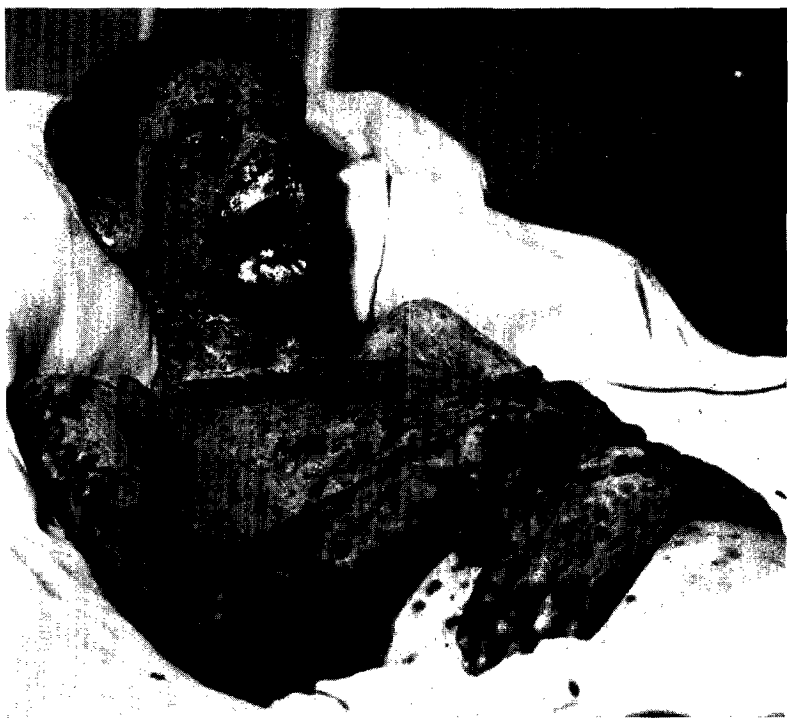


FIG. 40. Variola major, malignant confluent, eighteenth day, mortification. Patient has survived the stage of profound toxaemia between the tenth and fourteenth day, but tissue destruction is so severe that the body is unable to recover. Patient died two days later.

were nursed in large wards, terminal septicaemia must have been common and accounted for the isolation of streptococci from most cases *post mortem*. This gave rise to the frequently expressed view that haemolytic streptococcal infection plays a considerable part in causing death from smallpox. In experiments (1948) with penicillin in the treatment of this type of case, I demonstrated that the course and outcome is not due to superadded streptococcal infection, but to the essentially tissue destructive form of the disease. The few patients who recover from this form of attack are, however, in a most vulnerable state and susceptible to secondary infection with streptococci or staphylococci. The mortality would appear to be about 70–80

per cent, but the course of events today does not appear to be very different from the description of the illness and death of Queen Mary in 1694 (Chapter 10).

Occasionally, malignant confluent smallpox will proceed to the fourteenth and fifteenth day when, with the patient *in extremis*, a crisis will occur, the temperature will drop and the patient take a dramatic change for the better, a crisis similar to that observed in typhus. Presumably some immunological reaction takes place, but serological investigations have not yet been done. The patient commences to take fluids and the dehydration is reversed. The lesions, rather copper-coloured, desquamate, but this is fine and flaky and not a true "scab". The classical "punched-out" pitted scar does not occur even on the face, but instead there is a fine tissue-paper scar, continuous over quite large areas, rather like that after a scald.

FIG. 41. Variola major, malignant confluent, eighteenth day, mortification.

Occasionally the patient does not die at about the twelfth to fifteenth day, but lingers on in a state so aptly described by the older writers as "mortification" (Figs. 40 and 41), and has the appearance of being mummified whilst still being alive; the skin of the face is fixed in a grotesque mask with the mouth permanently open, not unlike a ventriloquist's dummy. In spite of the really dreadful appearance the patient remains quite rational; hearing is acute, although vision may be impaired by keratitis. He remains alive for four or five days, but as in the severe burn, is just as unable to recover by reversing the destructive process in the skin, although by this time the smallpox virus has almost certainly ceased to have any effect on the tissues.

TYPE 3—MALIGNANT SEMI-CONFLUENT

A number of cases develop a type of smallpox malignant in character and otherwise identical with malignant confluent, except that the extent of the rash is less and satisfies our definition of semi-confluence. The prognosis is definitely more favourable, the mortality being of the order of 25 per cent rather than 70–80 per cent, and in this respect is in keeping with the view so often expressed that the extent of eruption determines mortality. It is important to differentiate this type from the malignant confluent, not only because of the patient's better chance of recovery,

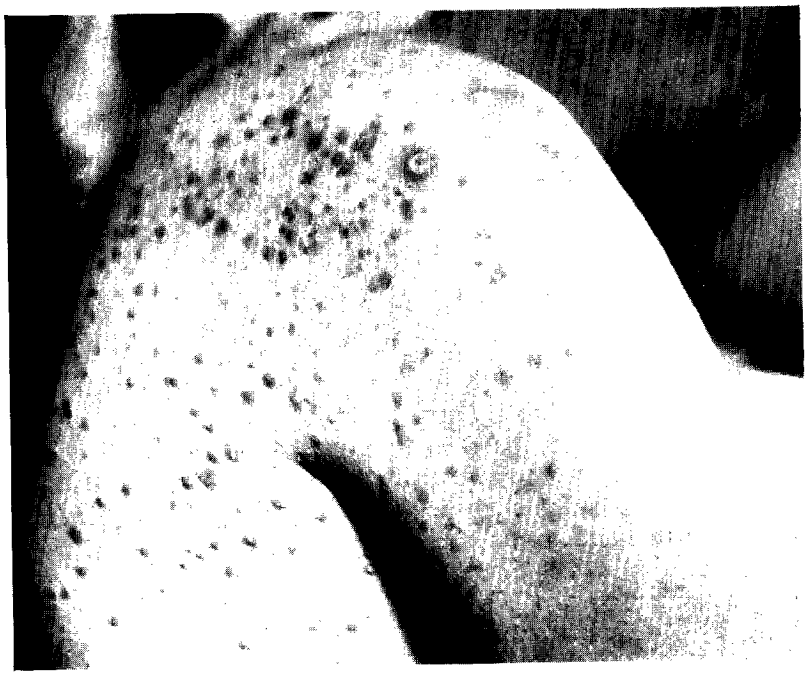


FIG. 42. Variola major, malignant semi-confluent, Type 3, rash at the sixth day. Note the lesions on the site of vaccination attempted late in the incubation period, (?) vaccinia, (?) variola.

FIG. 43. Variola major, malignant semi-confluent, eighth day. Although the eruption is not extensive the patient died.

but because this is the type of case which, although severely ill and with quite severe haemorrhages from the mucous membranes or the skin, may recover, apparently as the result of therapy. The recovery, however, is unconnected with treatment, being in keeping with the normal prognosis of this type of case.

The attack commences in the same way as type 2 with a sudden moderate rise in temperature, 101–102° F. (38·3–38·9° C.). The initial phase is the same as in type 2, but the remission of temperature and symptoms at the commencement of the eruptive stage is more marked, and may make it more difficult to classify the case until about the sixth day of the disease.

The elements of the rash show variation in size and rate of development, and because it is less dense the resemblance to "cropping" so characteristic of chickenpox is more obvious. However, the evolution is slow and the rash hot and tender. A diffuse erythematous base of a lobster-red colour may not appear until the tenth or eleventh day of the disease (Fig. 33), and deterioration in the general condition is less rapid. The most characteristic feature is the delay in the appearance of vesiculation, particularly on the limbs, shown in Figs. 42 and 43. Because the lesions are less concentrated, haemorrhages in the intervening skin may be more obvious than in type 2. Due to the absence of confluence on the limbs and trunk large areas of desquamation are less likely to occur. If death does not supervene between the twelfth and fifteenth day from toxaemia or haemorrhage, the lesions dry up at the vesicular stage without the formation of pustules. The absorption of fluid from the vesicles, without pus formation, is very similar to that seen in some of the benign types which have been treated with antibiotics, but the lesions themselves are more superficial and when separation has occurred the exposed dermis is copper-coloured (Fig. 31). Scarring is of the thin tissue-paper kind without sharp-edged pocks. Although the patient may well escape with his life, there is a risk of keratitis and corneal ulceration from about the twelfth day onwards. Loss of weight is considerable and convalescence may be protracted.

TYPE 4—BENIGN CONFLUENT

After the usual incubation period of twelve days the onset is sudden, with headache, vomiting, backache and general malaise. The initial temperature is likely to be higher than in the malignant types, usually 103–104° F. (39·4–40·0° C.) and occasionally as high as 105° F. (40·6° C.), but at the end of forty-eight hours the patient feels a little better and the temperature has dropped appreciably. By the third day the patient feels much better, the temperature may be practically normal and he may leave his bed. He does not usually feel well enough to work, but may do so for personal or economic reasons. At the same time the macular rash appears; the first few spots are very delicate (Figs. 49, 66 and 74), occurring on the face, particularly the forehead, malar region, bridge of the nose, along the sterno-mastoid muscles and over the trachea. There may be one or two on the chest, forearms, and particularly on the back, but frequently none are present on the abdomen or the legs. These early lesions show a great tendency to occur on particular sites so brilliantly described by Ricketts, and present a feature of smallpox of much diagnostic value. Within twenty-four hours many more macules join these original "herald spots", the rash becoming more profuse on the face and on the scalp, particularly if the hair is absent or thin. Papules rapidly replace the macules, and, in particular, the herald spots will feel deep and shotty even at this stage. This is due to vacuolation of the epidermis and the formation of fluid under pressure in what appears to be a papule but what is really an early vesicle. Patients sometimes complain of a pricking sensation in the skin. The

FIG. 44. Benign (in contrast) Type 6, discrete, early vesiculation, sixth day.

FIG. 45. Malignant confluent Type 2, eighth day.

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forearms will show macules and early papules especially over the "sites of election", over the head of the radius and ulna, across the wrist joints, along the extensor tendons and the head of the metacarpals and phalanges (Figs. 37 and 83). At this stage the lesions on the palms of the hands may or may not feel "shotty". The legs and feet are likely to show only one or two herald spots, whilst the back will show lesions more advanced than most on the arms, but less advanced than those on the face. The order of development of the rash is face and scalp, back, arms, chest, hands, legs and feet. This orderly progression of lesions is very characteristic and occurs in the majority of benign cases of this type, although in some instances of benign confluent, semi-confluent and discrete the eruption is uniform over the whole body and passes through each stage simultaneously (Fig. 46).

The most important feature of this type of rash is its adherence to a "centrifugal" distribution (Ricketts, 1908). If one examines each anatomical part separately, such as the face, arm, leg or trunk, there is seen a gradual change in the density of the lesions, the maximum being at the

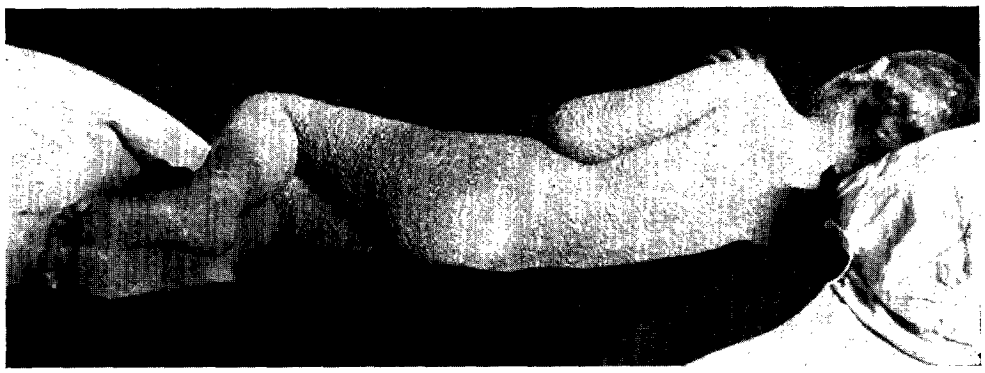

FIG. 46. Benign confluent, very uniform distribution. Even here some variation can be seen.

periphery, the minimum at the centre. For example, the upper face has more lesions than the lower face; the hand is more densely covered than the forearm; the forearm greater than the upper arm; the chest more than the abdomen. The back of the trunk is more affected than the front, and the extensor aspect of the arm more than the flexor.

The density will also be affected by other anatomical features. There will be increased density over bony prominences, points of pressure, or of mild irritation, and the converse; decreased density in areas subject to protection either because of anatomical configuration or from clothing. It should be noted, however, that even when the subject is habitually naked the rash is still centrifugal (Fig. 84). A knowledge of the occupation, peculiarities of clothing, social habits or early treatment of the patient will often explain an otherwise peculiar distribution. Unaccustomed activity on the feet will sometimes lead to a very early and extensive rash on this site. Tight corsets, or pressure on a fat abdomen whilst at work, may cause a dense rash on the abdomen compared with other parts. Severe trauma usually gives rise to no local increase in density, but trivial and invisible irritation is quite likely to. In Fig. 105 a group of lesions on the arm has occurred as a result of applying surgical spirit and rubbing the skin prior to venipuncture during the initial phase. It is important to recognize that smallpox lesions may appear

FIG. 47. Variola major. Herald spot on the internal malleolus and on a septic spot below.

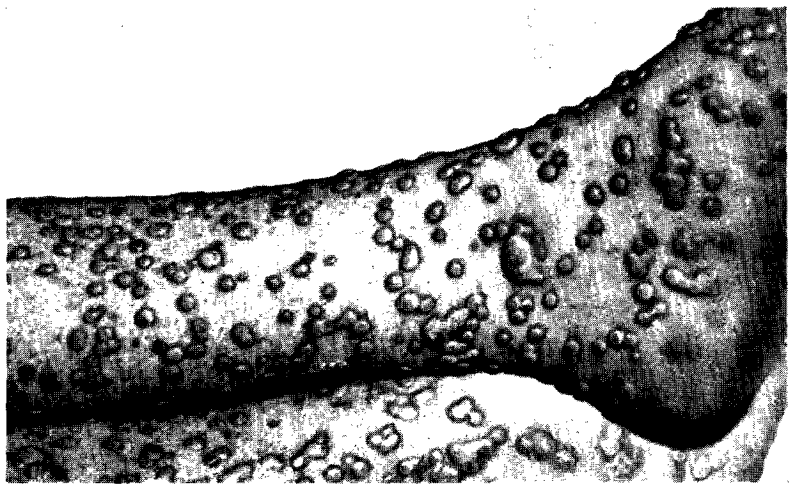

FIG. 48. Variola major, full vesicular eruption. The traumatised areas, which had the herald spots, show small confluent areas.

very early on the site of vaccination scratches done in the late incubation period, so giving rise to an apparently successful vaccination. One cannot help wondering whether some of the successful vaccinations claimed by Ricketts and others to have been obtained even as late as the second day of the eruption, may not really have been smallpox lesions on the vaccination sites. The laboratory can identify the virus from these doubtful lesions, but to date no results have been published.

At least by the end of the second day of the rash (about the fifth day of the disease), a confident diagnosis of smallpox should be possible. During the following days the small vesicular lesions

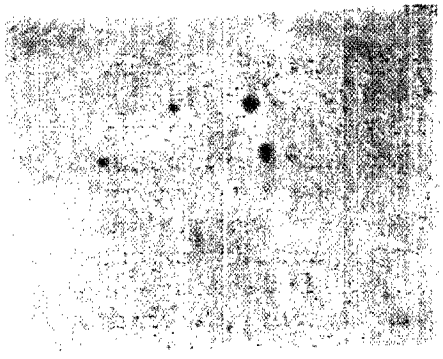

FIG. 49. Benign early herald macules on the third day of disease.

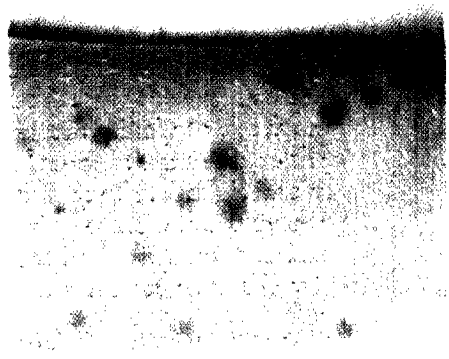

FIG. 50. Benign, papules twenty-four hours later.

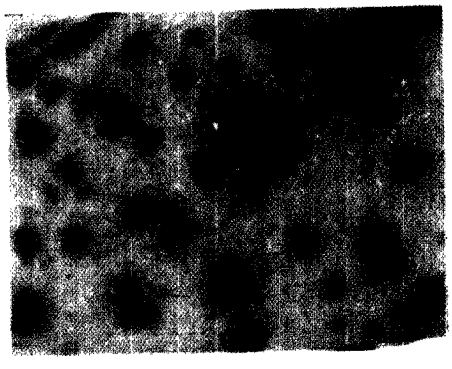

FIG. 51. Benign, papules and early vesicles twenty-four hours later.

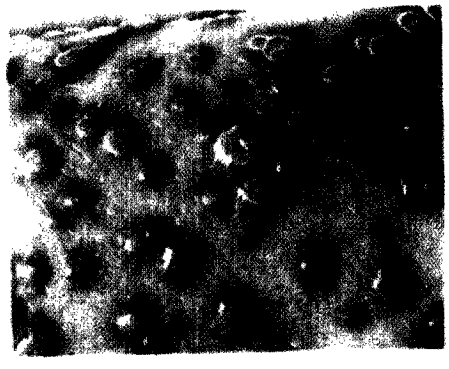

FIG. 52. Benign, early vesicle, sixth day.

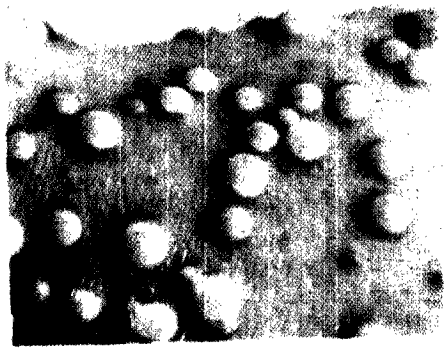

FIG. 53. Benign, mature 'pearls' deep-set in skin of forearm, seventh day.

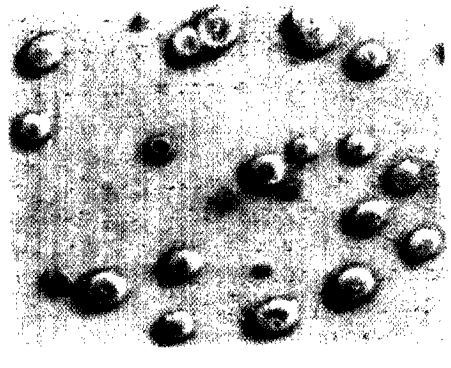

FIG. 54. Benign, secondary umbilication, lesions on abdomen commencing to dry up.

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FIG. 55. Benign, early scabbing abdominal wall.

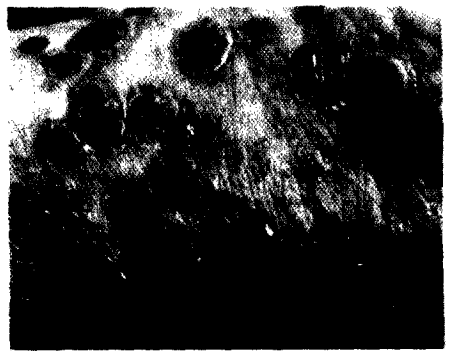

FIG. 56. Benign, scab separated from forearm. Seeds present on palm.

FIG. 57. Benign, maturation of seeds on palm, latest where skin is thickest.

FIG. 58. Benign, scars on hand, clustered round joints.

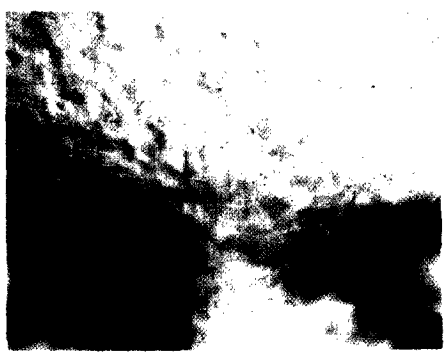

FIG. 59. Benign, scarring of forehead, two and a half years after attack.

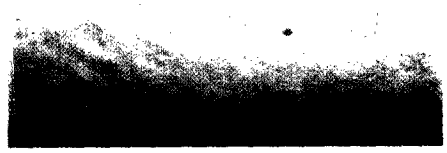

FIG. 60. Benign, very indefinite scarring on forearm, two and a half years after attack.

will grow in size so that by the fifth or sixth day of the rash (eighth to ninth day of the disease), a large part of the body will be covered with pearly vesicles some $\frac{1}{4}$–$\frac{5}{16}$ in. in diameter (7–10 mm.). Figures 49–60 show the development of the benign type of lesion. In the benign confluent the lesions coalesce on the face, the vesicles rapidly becoming pustular, and the face looks as if it is covered with a "mud-pack" (Fig. 63). As the lesions enlarge, there is considerable oedema of the skin and the normal facial expression is lost. The thickening and stiffening give rise to much discomfort, although the patient's general condition is quite good. The lesions on the rest of the body, particularly on the arms, are typical pearly vesicles set deeply in the skin with a sloping edge and a small red areola (Figs. 52 and 53). They feel hard, often described as shotty, are not tender to the touch and do not feel hot. They are multiloculated, in that when pricked only part of the vesicle collapses, but although the older writers made much of this

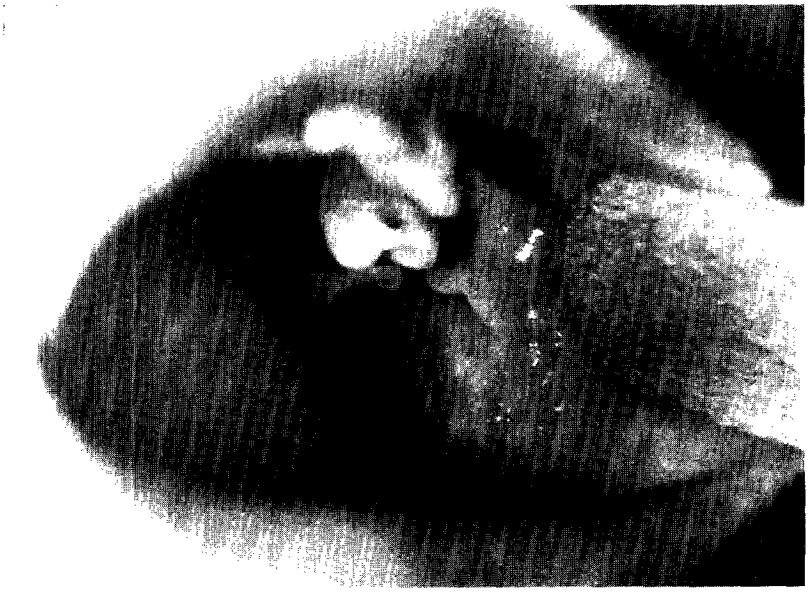

FIG. 61. Variola major, mucous erosions, sites of small vesicles in benign smallpox, third day.

as a diagnostic feature, it is of little value. As the vesicles mature, umbilication occurs with the development of a central depression, but this again may occur in other vesicular eruptions and is therefore not diagnostic of smallpox. The intervening skin remains normal.

Although the number of lesions in the mouth, particularly on the soft and hard palates, may be very variable, laryngeal, tracheal and oesophageal lesions are insignificant, and apart from the discomfort of the hard and inspissated serum on the face (Figs. 63 and 64) and mechanical interference with the movements of the mouth, there is no pain on breathing or eating and the appetite is usually quite good. The general condition of the patient is so different from that of the malignant case at the same stage. Whereas the latter has signs of a severe general infection but a relatively poor rash, the benign case has a spectacular eruption and relatively little evidence of toxaemia. In recognizing these two distinct syndromes in smallpox it can be seen

that it is not true to say that severity is directly correlated with the extent of the rash. Although the patient with benign confluent looks frightful, apart from the risk of broncho-pneumonia in young infants or the aged, which is less of a problem today, the prognosis is remarkably good and better than that of malignant semi-confluent.

At the stage of vesiculation and early pustulation the patient will have the very characterisic odour of smallpox. Although made worse by suppuration, it is distinct and is in no way dependent on this complication.

Cracking of the "mask" on the face and nose may give rise to bleeding (Fig. 62), but there is no haemorrhagic diathesis and no severe haemorrhages occur. Some secondary suppuration will occur, but the severity of this seems to depend much on the virulence of the prevailing secondary organisms, and the general hygiene of the patient. It should be controllable with current chemotherapy. In tropical countries one gets the impression that severe suppuration occurs more frequently. In some cases many of the lesions on the upper thighs and forearms, instead of becoming dry, remain "wet" and pustular for some days and are rather more offensive. This was described by the older writers as diphtheritic in type (Fig. 63), but there is no evidence that Corynebacteria are involved. Figure 64 shows that the rash that appears first matures first, and whilst the face may be pustular the arms may be at the vesicular stage. As mentioned before, sometimes the whole rash erupts at the same time, but the pustular stage is reached much sooner on the face than on the other areas.

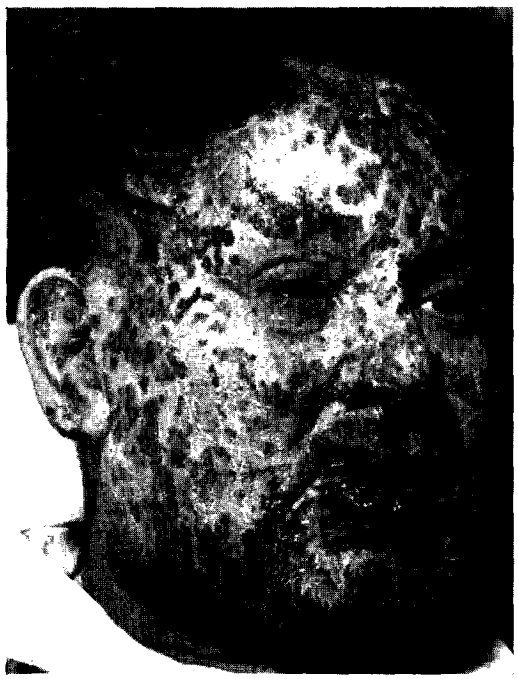

FIG. 62. Variola major, Type 6, twenty-first day. Most of the facial scabs have been shed. The scalp is still crusted, and some of the scabs on the nose and lips are firmly attached and very sore.

Lesions on the palpebral conjunctiva give rise to troublesome, but not dangerous, conjunctivitis. The lids are so oedematous that vision is only just possible. Keratitis of the type seen in malignant smallpox is not seen, but corneal ulceration may occur.

In Europe in the nineteenth century and in some countries today, this has been a fairly common and troublesome condition. However, each writer noted that it was rarer than in the days of his predecessors, and although it also occurs in variola minor it appears to be particularly common where there is eye disease such as trachoma, or where there is malnutrition. Vitamin deficiencies may be the determining factor. In European countries the change in the social class of those attacked may also affect the incidence (see Chapter 5).

With the maturation of the lesions the classical pustule is produced. Although it has been demonstrated that many lesions described as pustules do not contain pyogenic bacteria, when the lesions are profuse there is a great tendency for frank sepsis to supervene. When this occurs

FIG. 63. So-called 'diphtheritic' eruption. Offensive suppurating pustules.

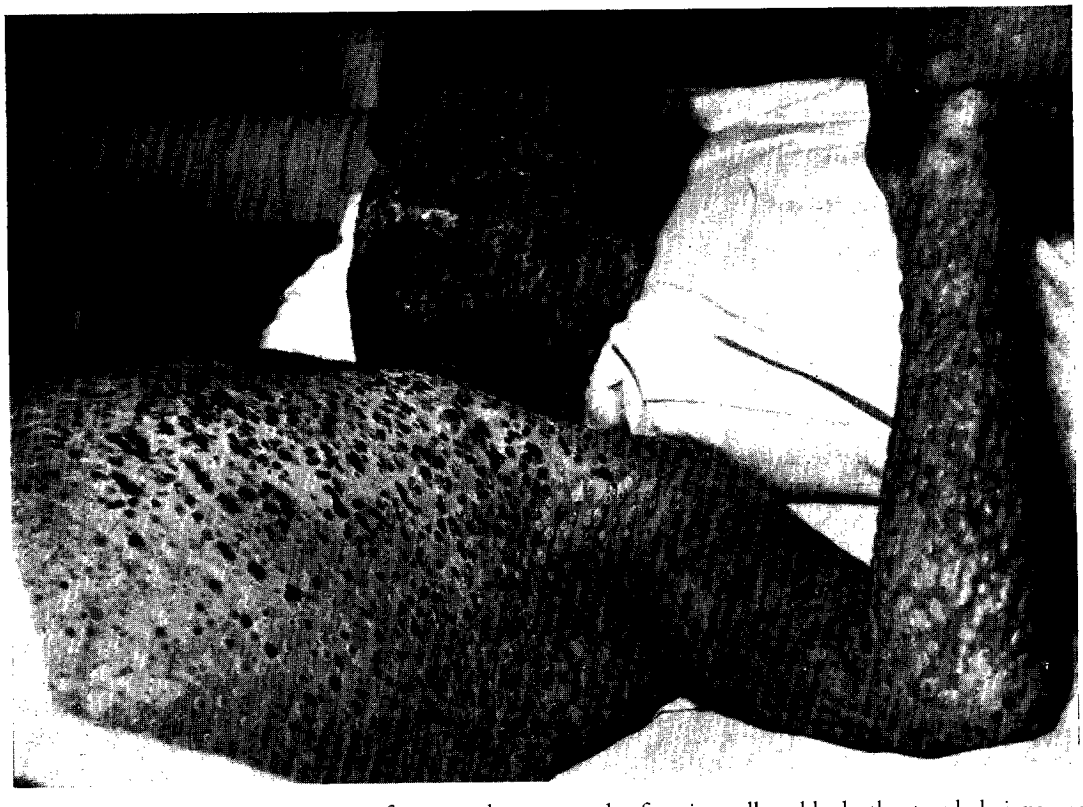

FIG. 64. Variola major, Type 4 at fourteen days; note the face is well scabbed, the trunk lesions are scabbing, but the lesions on the hand and arm are pustular.

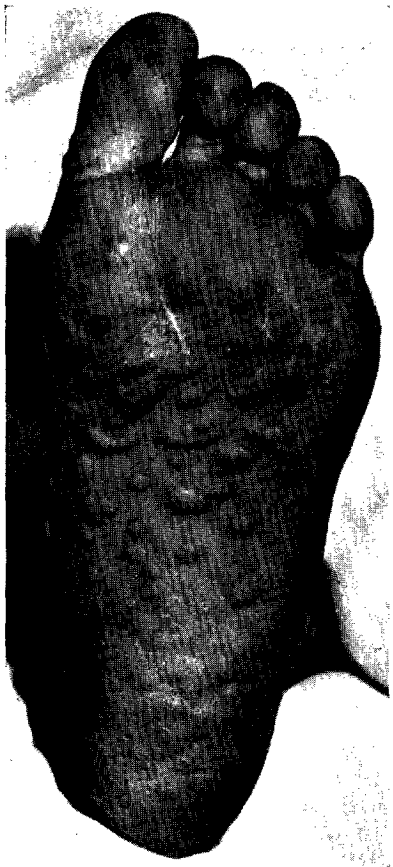

FIG. 65. Variola major, lesions on sole of foot. The appearance of the lesions varies with the thickness of the cornified layer.

pyrexia and mild toxaemia may develop and the fever in the past has been described as the secondary fever. However, my study of malignant and benign cases treated with antibiotics (Dixon, 1948) shows that a secondary fever is an integral part of certain types of smallpox quite independent of the development of frank sepsis. I suggest that it would be more accurate to describe three febrile states, primary fever of the initial stage, secondary fever developing from the fourth day onwards, and tertiary fever due to superadded sepsis (Fig. 3).

Although the development of sepsis and tertiary fever is closely related to the extent of the eruption in the benign case, it is also commoner where there is poor hygiene of the patient, particularly under tropical conditions.

By the fourteenth day of the disease many of the scabs will have come off the face and the patient will feel much more comfortable, and should be practically afebrile. Desquamation will be occurring from the trunk and upper limbs and hundreds of scabs can be brushed from the bedding every day. The process proceeds down the arms to the hands and down the legs to the feet. By the twentieth day nearly all the lesions will have cleared except those on the palms and soles. Here they are set beneath a thick horny layer, do not give raised vesicles, but mature by inspissation and gradual extrusion of the material as the skin wears away. The importance of these lesions, or "seeds" as they are called, is to prolong the patient's stay in hospital (Figs. 57 and 65).

TYPE 5—BENIGN SEMI-CONFLUENT

The relationship of this type to type 4 is exactly the same as that of type 3 to type 2. The initial symptomatology is similar to type 4, but the extent of the rash satisfies our criteria for semi-confluence. Compared with benign confluent there is a better prognosis (mortality about 12 per cent) and this is in keeping with the lesser extent of the rash. The semi-confluent nature of the eruption gives rise to a beautiful display of the distributional features of smallpox—centrifugal pattern, occurrence on pressure points and other sites of election. The development of the lesions and other features are the same as in benign confluent except that after the appearance of the rash the degree of pyrexia and malaise may be surprisingly little considering the presence of well over a thousand lesions. It is of interest that in this kind of case the secondary toxaemic element is completely absent, whereas in some of the discrete cases (type 6) where the rash is less, an element of secondary toxaemia may be present. Some lesions may be present in the mouth, but laryngeal lesions are absent.

Study of the clinical records of fifty years ago suggests that deaths from this type were

relatively rare except in young babies and old debilitated persons, or where secondary bronchopneumonia, erysipelas or pyaemia occurred. The situation is much the same today, although complications should respond better to modern treatment. In the period between 1880 and 1905 when much was written about smallpox, infant mortality was high. There was considerable mortality from scarlet fever and streptococcal fevers generally, and the risk of cross-infection in wards holding thirty or more patients of all ages can well be imagined.

The rash matures normally, pustulates freely, forms the classical smallpox scabs and leaves characteristic pitted scars. The facial scarring will cause considerable disfigurement.

TYPE 6—DISCRETE

This type is so named because in general none of the lesions coalesce. It must be appreciated that occasionally on sites of slight trauma or irritation small areas of confluence may occur and should not influence the clinician in assessing the case. When classifying, there is a tendency for the inexperienced to exaggerate the severity. An important feature of the discrete type is that in the early stages some of the cases present some features more like the malignant types, but the majority are consistently in keeping with other benign types.

The initial stage commences as usual, with a sudden, fairly severe pyrexia which declines during the next two or three days until by the time the rash appears the temperature is practically normal. The temperature then remains low and the general condition is very good until the termination of the disease, the patient feeling quite well, eating and sleeping fairly well, and the rash is the only problem causing considerable inconvenience and worry because of the probability of scarring. On the other hand, some cases will commence with only a moderate pyrexia of 101° F. (38·3° C.), and with the appearance of the rash the temperature may remain at about 100° F. (37·8° C.), increase while the rash appears and not decline until the fourth or fifth day of the eruption, when vesiculation has commenced. Although in the more usual discrete type the rash is typically pearly, not hot or tender, in some with greater toxaemia the eruption, at the fourth or fifth day of its development, may feel slightly warm, more than can be due to the normal areola, and may be just a little tender. The lesions are well formed, however, and quite unlike those in the malignant varieties which, of course, would not show any real vesiculation at this stage of development (fourth or fifth day of the rash). The mild toxaemia disappears by about the fifth day of the rash (eighth day of the disease) and from then on both variants pursue the same course. Lesions on the buccal mucous membrane may occur with some frequency, but are very variable in number (Fig. 70). Hoarseness and difficulty in swallowing are very rare. A further feature of the discrete case, showing this slight malignant element, is for small haemorrhages to occur in the skin or mucous membranes. There may be only a single haemorrhagic spot such as a sub-conjunctival haemorrhage (Fig. 90), but there is no tendency to serious haemorrhage as in the malignant case. Haemorrhages are more likely to be present on the legs where there is slight trauma, but they occur more frequently in the vesicles and not in the skin. It seems probable that, in the malnourished, vitamin C deficiency will increase this tendency. Some clinicians have, however, applied the term "haemorrhagic" to this type of case and have assumed that some particular treatment has affected the course of the disease which is essentially benign. It is for this reason that I firmly believe the word "haemorrhagic" should be omitted in the description of any type of smallpox.

Some of the lesions tend to dry up in the vesicular stage rather than forming definite pustules,

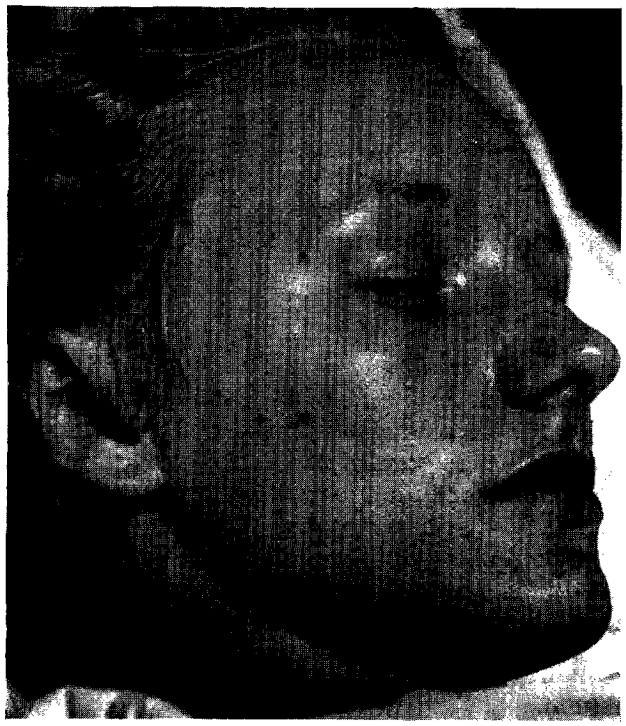

FIG. 66. Variola major, Type 6, early macules on the face. The two lesions on the cheek are acne.

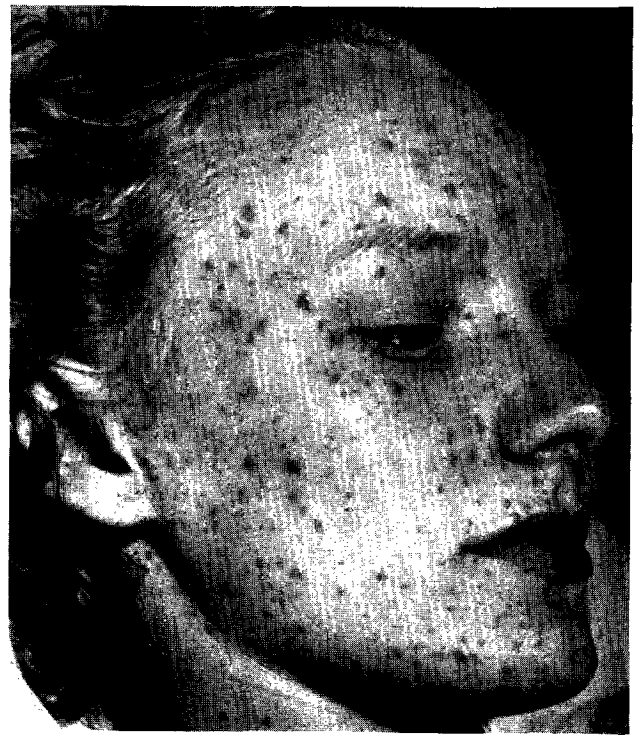

FIG. 67. Variola major, Type 6, early maculo-papular lesions, twenty-four hours later than Fig. 66.

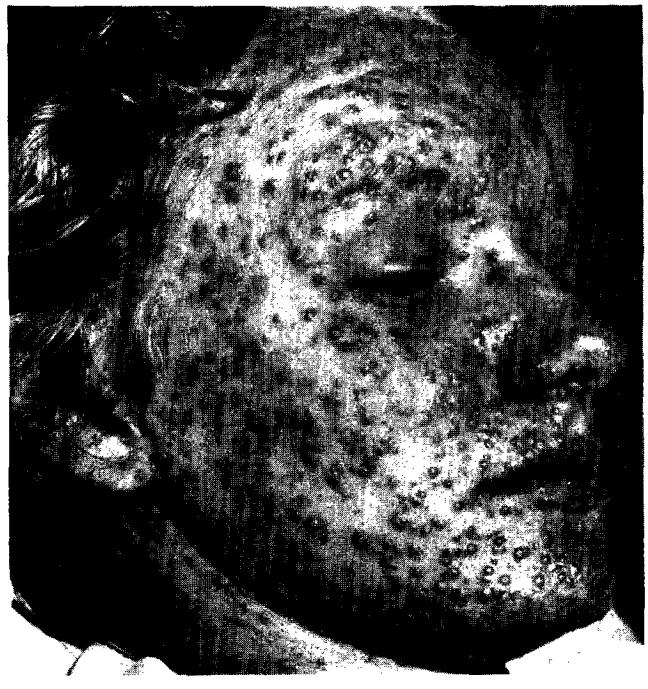

FIG. 68. Variola major, Type 6, early vesicular stage forty-eight hours later than Fig. 67, sixth day.

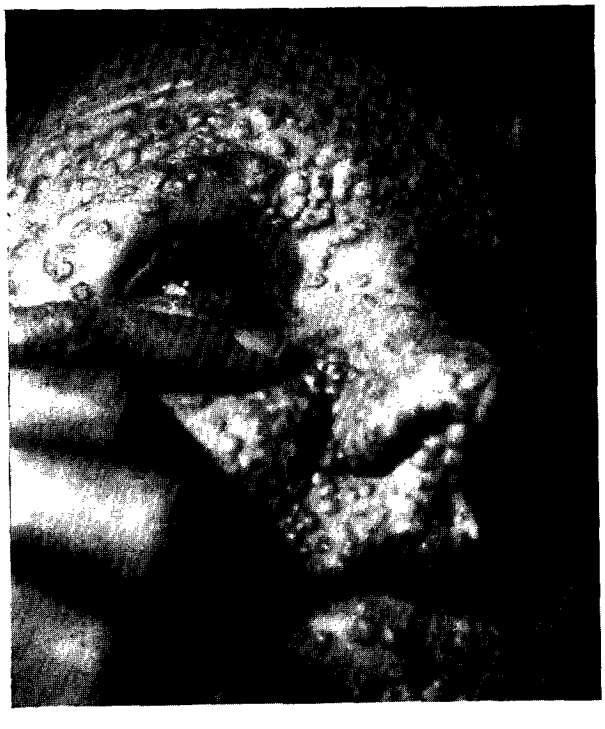

FIG. 69. Discrete, Type 6. Some lesions on forehead collapsing and drying up.

FIG. 70. Variola major, Type 6. Vesicular lesions on hard and soft palates. Note that skin lesions are partly papular, a few on the nose just becoming vesicular.

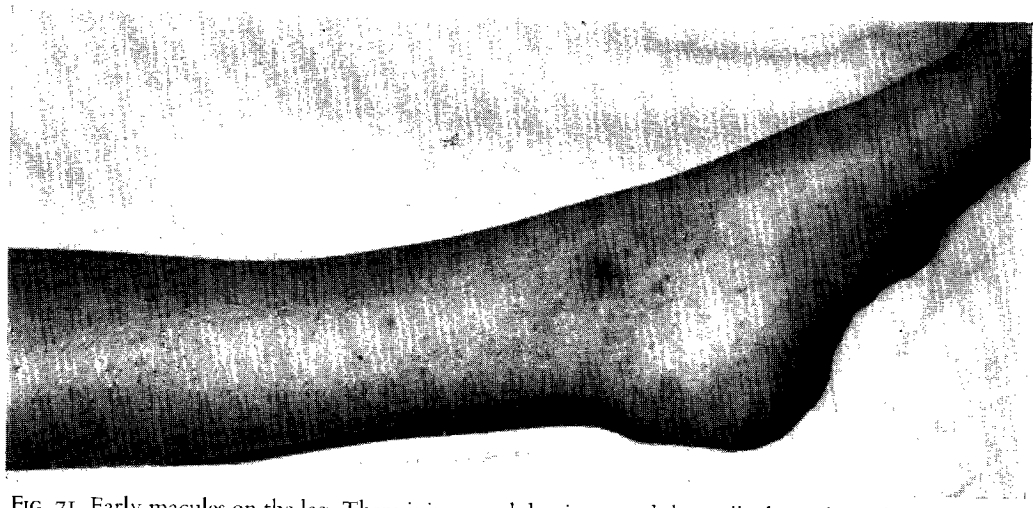

FIG. 71. Early macules on the leg. There is increased density round the malleolus, where the shoe presses.

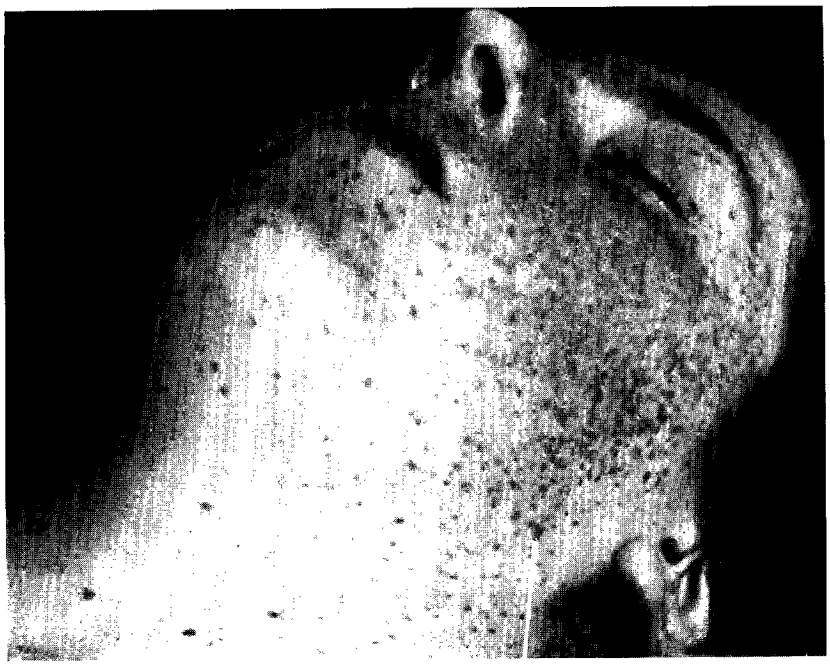

FIG. 74. Variola major, Type 6, early macular lesions over pressure points, angle of jaw A, trachea B, sternum mastoid muscles C. Many lesions on the face are unfortunately lost in a mass of freckles.

FIG. 75. Variola major, Type 6, early vesicular eruption sixth day. Some of the earliest lesions are larger. There is some vaccinomodification due to a successful vaccination performed in the incubation period.

D

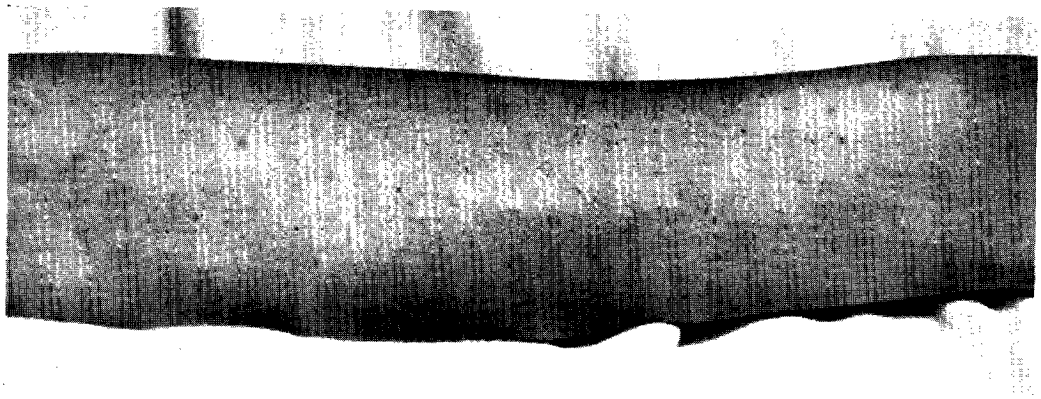

FIG. 76. Early macules.

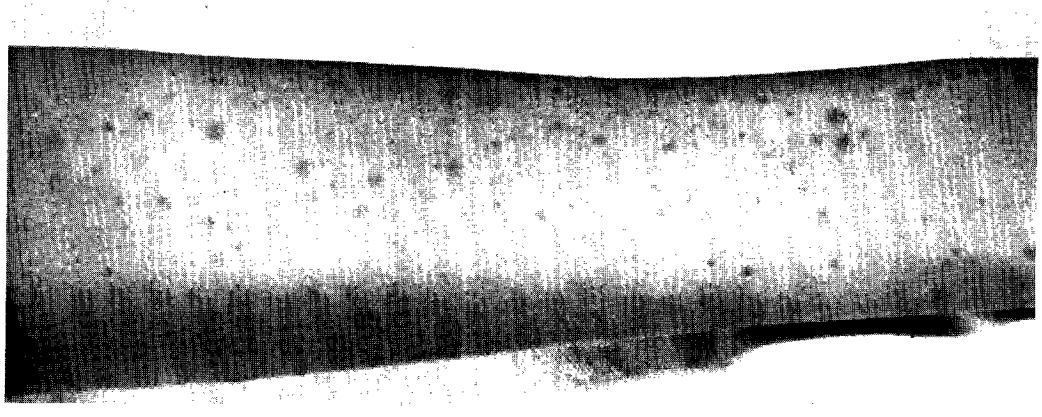

FIG. 77. Twenty-four hours later, maculo-papular stage.

FIG. 78. Forty-eight hours later, early vesiculation of herald spots, further increase in density.

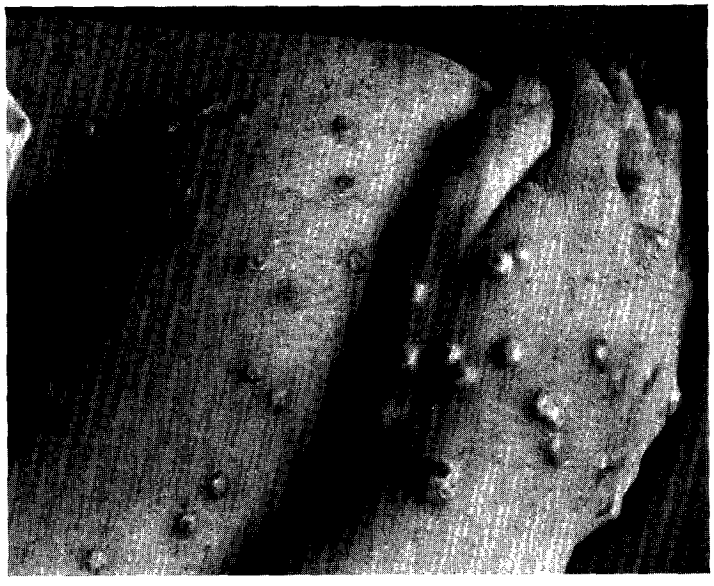

FIG. 79. Variola major, discrete. Lesions on the arm are more advanced than those on the hand.

FIG. 80. Variola major, Type 6, about the eighth day, centrifugal distribution. Compare with chickenpox.

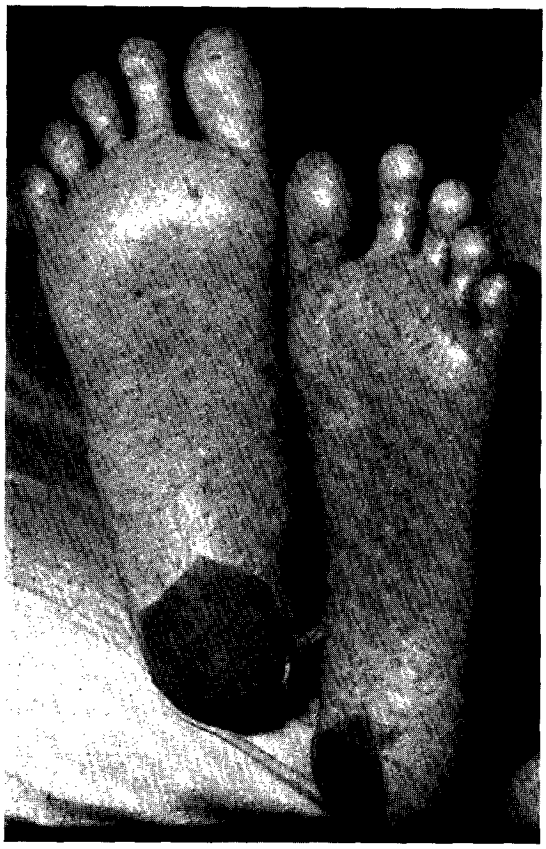

FIG. 81. Variola major, almost complete shedding of plantar cornified layer. This occurs after an extensive rash in a person who does not wear shoes.

FIG. 82. Discrete, Type 6, vesiculo-pustular stage. The pustules on the face, particularly on the cheeks and nose, are secondarily infected, which is common in tropical countries.

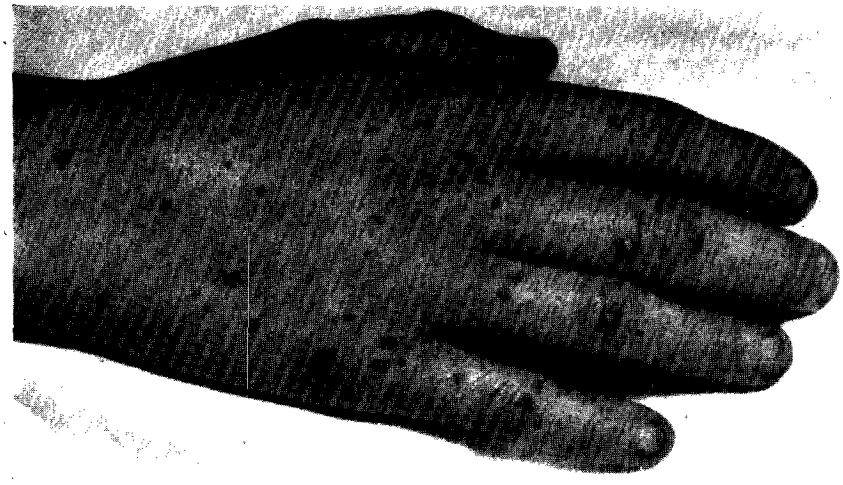

FIG. 83. Variola major, Type 6, sixth day, early vesicles on hand. Note lesions round the phalangeal joints.

FIG. 84. Discrete, Type 6. Scabbing is nearly complete on the limbs, showing depigmentation. Secondarily infected lesions are present on the face.

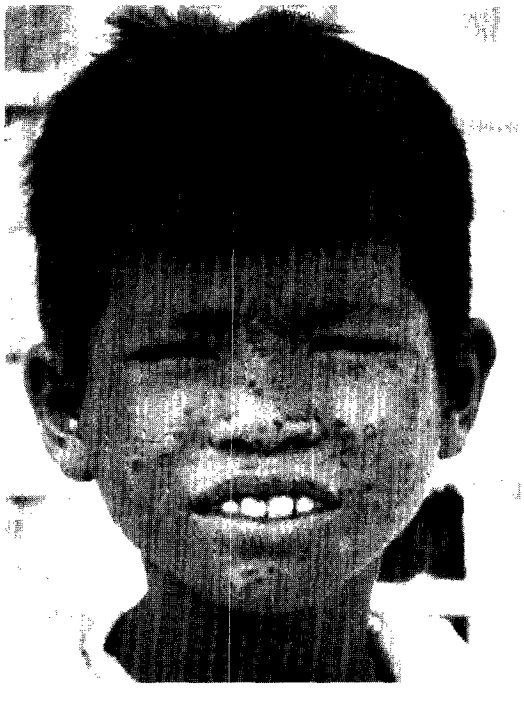

FIG. 85. Effect of chronic sepsis on smallpox scars. Keloid formation between the eyebrows.

but this varies considerably in different patients and on different parts of the body. Lesions on the face tend to pustulate more frequently than those on the chest or abdomen. Whether the lesions only vesiculate or go on to pustulate does not seem to make any great difference to the amount of the scarring which depends primarily on the depth of the lesions, the thickness of the skin and the site on the body. Severe secondary infection of these lesions will, however, increase the size of the scars (Fig. 85). Complications in discrete cases are relatively rare and, as the patient feels well after the first few days of the disease, he finds it very irksome waiting for desquamation to occur, particularly from the feet.

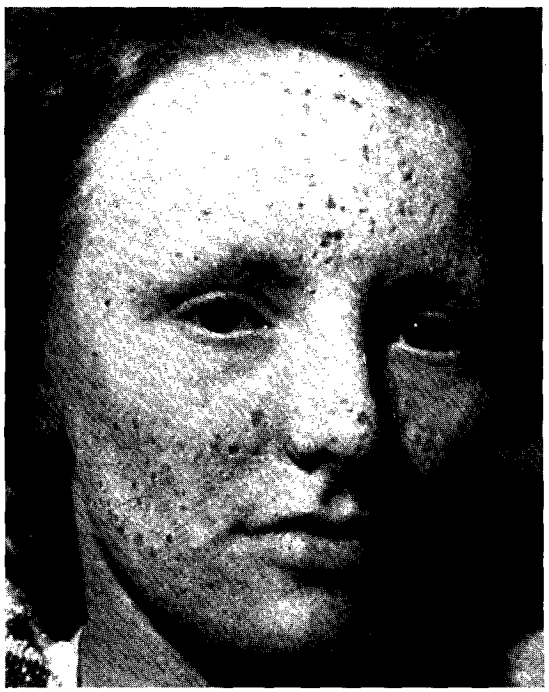

FIG. 86. Variola major, Type 6. Early scarring.

FIG. 87. Variola major, Type 6. All scabbing complete. Small septic lesion on forehead. Patient had treatment with antibiotics.

TYPE 7—MILD

The initial pyrexial syndrome is like that in other benign types. The temperature may be very high, up to 105° F. (40·6° C.), and initial malaise and headache and backache quite severe, but the temperature drops quickly, usually within forty-eight hours, and the patient soon loses the backache and often the headache as well; but on the third, sometimes fourth day, a sparse eruption appears with not more than 100 lesions. The distribution is characteristically centrifugal and very pretty patterns may occur on the face or arms in the usual manner. The lesions are hard, pearly and usually of normal size, but a few of the lesions may abort even in unvaccinated persons. The mortality from this type is very low (under 1 per cent), death only occurring in babies or the aged and debilitated. The disease itself produces less inconvenience

FIG. 88. Type 8
Variola major
in the unvaccinated.

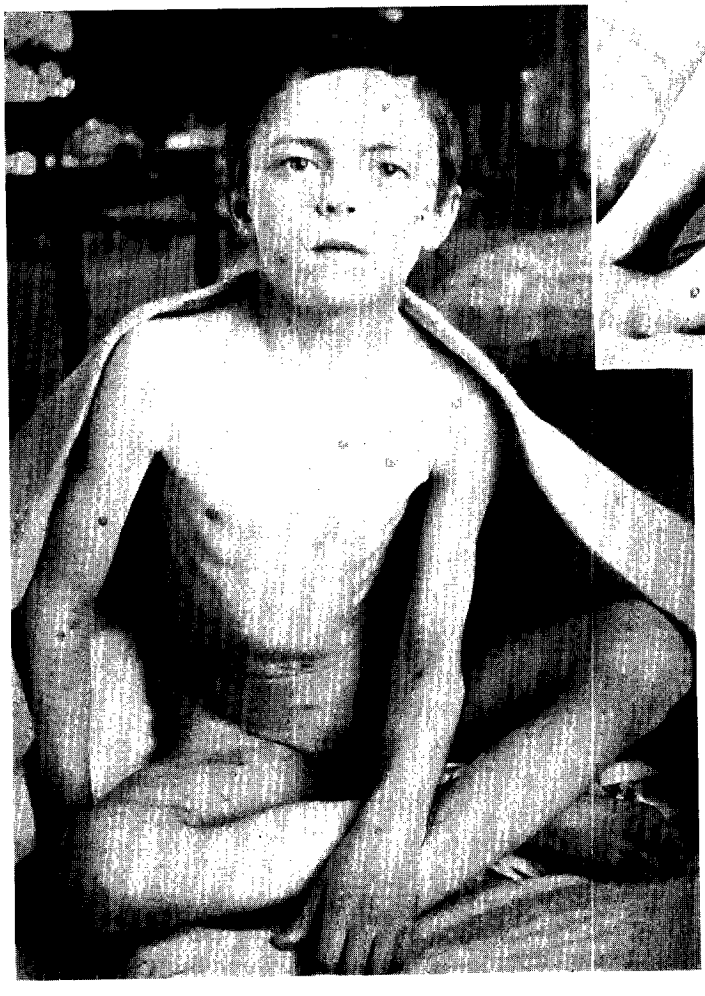

FIG. 89. Type 7
Variola major
in the unvaccinated.

to the patient than may an attack of chickenpox, the eruptive phase being wholly afebrile, but definite scars will remain, particularly on the face in the unvaccinated. These are very much less numerous than in the more severe benign types, but they are a serious blemish and important evidence in detecting missed cases.

Although mild cases (type 7) frequently occur in vaccinated subjects, it must not be forgotten that they can occur in the unvaccinated and the description given here applies to this type.

FIG. 90. Variola major, Type 6. Sub-conjunctival haemorrhage, not a bad prognostic sign.

TYPE 8—ABORTIVE

Type 8 (abortive) is an uncommon type in the unvaccinated. It frequently gives rise to difficulty in diagnosis. The pre-eruptive fever is of the normal type with quite a high temperature, up to 103° F. (39·4° C.), of sudden onset, short duration and declining to normal by the second day. Headache is common, but backache much less so. Although the rash may appear on the third day, sometimes only one or two lesions appear at this stage, followed, even as late as the fifth or sixth day of the disease, by a second crop of lesions, possibly only ten or fifteen in number, which are almost invisible in the macular stage because of their small size; most do not progress beyond the papular stage. The papule may or may not show an erythematous base and within forty-eight hours has formed a small vesicle which rapidly becomes a scab indistinguishable from many other scabby lesions which can occur on the skin from a wide variety of causes. Very occasionally in abortive types there may be quite a large number of lesions appearing simultaneously on the body at the third or fourth day and at first giving the impression that the patient is going to suffer from an attack of discrete smallpox, but the rash completely aborts at the papular stage. Flaky desquamation occurs leaving no scar and only a little transient discolouration of the skin. The patient's general condition is very good. There is no malaise at all after the initial syndrome. Lesions in the mouth are uncommon, but when they occur are small and not sufficiently characteristic to be of any diagnostic value.

TYPE 9—VARIOLA SINE ERUPTIONE

In this type, after an incubation period of twelve days the patient suffers from a pyrexial attack with sudden onset, a temperature of perhaps 102° F. (38·9° C.), with headache, occasionally a rigor and sometimes mild muscle pain or backache. At the end of forty-eight hours and often less the attack has subsided, the temperature is normal, the patient feels completely recovered, although sometimes a little weak and feeling "post-influenzal", and returns to work. Many persons, however, have a pyrexial attack only lasting for a few hours. Although this was noted by Byles (1843) and discussed more fully by Conybeare (1939), it has been called "illness of contact" by Boul & Corfield (1946). When such cases occur in doctors and nurses it may be an administrative advantage to use the term "illness of contact", but this and "variola sine eruptione" are really one and the same thing. Although this condition occurs most frequently in well-vaccinated persons, many cases have been recorded, and at least one confirmed by laboratory tests (Verlinde and Van Tongeren, 1952), in the unvaccinated. This type of infection is probably commoner than usually thought.

No macroscopic lesions appear in the mouth or throat which is understandable as, in general lesions occur more profusely on the skin than they do on the mucous membranes. It is considered by some that the patient with this condition is not infectious, because the viraemic stage is very limited. It seems more likely that the patient is infectious for a short time, probably for only a few hours; a view shared by Ricketts (1908).

Following this "influenza-like" attack, no focal rash of any kind appears. It must be remembered that unless the patient is examined very carefully on the sites of election for the odd abortive lesion, a case may be thought to be type 9 (*variola sine eruptione*) when it is really type 8. There are no complications and no sequelae after this type of attack. Presumably encephalitis is a possibility although, as far as I am aware, it has never been recorded.

Conybeare (1939) reported some cases in which a clinical syndrome not unlike a virus pneumonia occurred. Howatt and Arnott (1944) described some cases with X-ray evidence of some lung involvement. In many the incubation period appears to be about seven days (five to eight), but as this is measured from the contact to the onset of pyrexia a false interval may be due to concurrent vaccination which is present in many cases. In my own experience, "virus pneumonia" occurs surprisingly frequently among smallpox contacts, particularly doctors, but this may only be a diagnosis of convenience. It is surprising that this syndrome gives rise to "off-duty" for at least fourteen days, in contrast to classical type 9—a few hours. Even in cases with X-ray findings it does not seem likely that the lung condition is due to smallpox virus, as there is no epidemiological evidence that this type of patient is infectious. There is always the possibility of concurrent infection with some other virus and an increase in the susceptibility of the patient induced by the febrile attack. It is to be noted that in general the lung escapes clinical attack in all other types of smallpox. This is discussed further in Chapter 9 where I have suggested it is a form of "pulmonary allergy". This is the type of case in which laboratory investigations are urgently required to elucidate a rather confusing picture; what part the concurrent vaccination plays is difficult to see. Although many cases occur in those whose immunity is high, as judged by the revaccination result, and one occurred in a virologist who had much contact with vaccinia, some have occurred in those whose immunity is low as judged by the primary-like appearance of revaccination.

It is perhaps significant that in the last ten years increasing attention has been given to "virus pneumonia" accompanying chickenpox.

MISCELLANEOUS RASHES

Under the title of "initial rashes" the older writers described a wide variety of eruptions usually occurring before the focal rash was identified, but sometimes occurring at the same time. Ricketts called them "toxaemic eruptions" whether they occurred in the initial stage or later.

It can be seen from descriptions in the older books that the purpuric and petechial and some of the erythematous rashes are merely the normal in fulminating cases or the early stages in the development of the malignant focal eruption. Examination of the coloured illustrations will show many of the features described, such as the astacoid rash of Roger and Weil (1901) (Fig. 35), the toxaemic erythematous rashes of Ricketts (1908) (Fig. 15), and petechial and purpuric rashes (Figs. 11, 12, 19 and 32).

The captinoid rash of Thomson and Brownlee (1909) described as a "pale sepia or smoky rash confined to the bathing-drawers" area but of good prognostic significance, does not seem to have been recognized very much except by the original observers. It is to be distinguished from the petechial rash, pathognomonic of smallpox, affecting the "bathing-drawers" area, but this may invade the flanks and axillae.

Many of the early writers give accounts which tend to confuse the reader. Great emphasis was placed on the prognostic significance of these rashes, and hence the difficulty. When one appreciates that the purpuric, petechial and some erythematous rashes are part of fulminating or malignant smallpox, then these will be bad omens, but in a proportion of cases of smallpox in the vaccinated, transient erythematous or morbilliform rashes occur which the older clinicians recognized foretold a good and not a bad outcome, simply because much of the smallpox in the vaccinated is very mild. These erythematous and morbilliform rashes, particularly the former, appear before the focal eruption, although occasionally they may occur at the same time. They tend to occur in the flexures, those areas where the focal smallpox eruption appears least, and are only important in that their presence tends to confuse the diagnosis in the early stages.

Although the petechial rash in the groin is pathognomonic, I think it is undesirable to give special names to any rashes which are an integral part of the development of the fulminating or malignant smallpox syndrome. In my opinion, the transient erythematous or morbilliform rashes are the only true "initial" rashes. Their fleeting character and limited involvement of the body suggest that they are allergic in character. They disappear without leaving any staining. Although they have been mostly observed in the vaccinated, and this supports the idea of allergy, they are not unknown in mild cases in the unvaccinated.

Their frequency is difficult to estimate. Earlier writers (Boobbyer, 1894) have assessed this at about 10 per cent, and this is the figure given by Japanese (Uchida, 1954; Ueda, 1954) and Malayan observers. In the case of the English figures this includes all "pre-focal" rashes and obviously includes many petechial and erythematous rashes in the early stages of malignant cases. Examination of a book by Uchida (1956) shows that he also includes these in his use of this term. Some local rashes around the site of vaccination lesions (presumably in contacts) are also regarded as initial rashes of variola sine eruptione, although they might equally well be secondary to vaccinia. On the other hand, Ueda (1954) assures me that in his experience

the 10 per cent represents true initial rashes allergic in nature and not confused with the early stages of the malignant type. In Japan in recent years and in England at the turn of the century much of the smallpox occurred in the vaccinated and this would obviously affect the figures and be likely to increase the initial rashes of good prognosis. As these rashes occur before the focal rash, they are frequently not observed by any doctor and least of all by hospital staffs who have written so much on smallpox. Marsden (1936) saw thirty-seven such rashes, mostly blotchy or macular erythemas, amongst his 13,000 variola minor patients, but, as he pointed out, less than 1 per cent of admissions to hospital occurred at this early stage. This represents an incidence of about 0·3 per cent, but no information is given as to whether these were predominantly in the vaccinated or not. Similar rashes—sometimes only local—occur as complications of vaccination, but I am of the opinion that, in England at any rate, this type of rash is less common today as an accompaniment of either vaccinia or smallpox.

A rare variety of smallpox which is difficult to classify is that known as *variola corymbosa* (Figs. 91 and 92). During thirty years' experience at the London Smallpox Hospital between 1836 and 1866, Marson saw about 15,000 cases, amongst which 104 were of this type. The name is given because the lesions occur in clusters. The peculiar feature of these cases is that although the number of lesions puts it in the discrete or semi-confluent class, the prognosis is bad: 44 per cent mortality in the unvaccinated and 32 per cent in the vaccinated. Marson describes the condition as follows: "The disease appears in clusters or it may be that only a single cluster is formed and yet the fatal character before alluded to is given to the disease. In other parts of the body, the eruption is perhaps but sparsely scattered, and we might expect the disease to rank in danger with a common semi-confluent case; such, however, is not the practice. It generally happens that there are two or three patches about the size of the palm of the hand in different parts of the body, in which the pimples are as closely set as could be and in the immediate neighbourhood of each patch the skin is free from eruption or nearly so, a few spots only of the disease being formed. There is a great tendency to symmetry in this form of the complaint.When a patch is formed on one arm or leg it often happens that a similar patch is formed on a corresponding limb on the opposite side. In some instances there are numerous corymbose patches on different parts of the body about the size of a half-crown or five-shilling piece" (32 mm. or 37½ mm.).

I have no experience of this type of case, and MacCombie (1906), who was Medical Superintendent of the South Eastern Smallpox Hospital, London, for many years, stated that he had never seen a case. The high mortality may obtain because many of these cases are really malignant semi-confluent in type, or the aggregation of lesions may be a sign of some deeper constitutional factor or concurrent disease which accounts for the mortality. This form does not occur in variola minor.

For long it has been recognized that it was unusual for smallpox to occur concurrently with other infectious disease, although it could and still does attack patients in hospital with a wide variety of conditions. Concurrent scarlet fever, measles and chickenpox have been described, the first two often in mistake for the early stage of malignant smallpox, the last one in mistake for variola minor, or smallpox modified by vaccination. Concurrent vaccinia is of course very common, and herpes simplex, infective hepatitis and secondary syphilis may also occur. Apart from vaccinia, there seems no reason to suppose any interference, and the clinician must be prepared for the bizarre clinical picture of the simultaneous presence of two or even three diseases (Fig. 93).

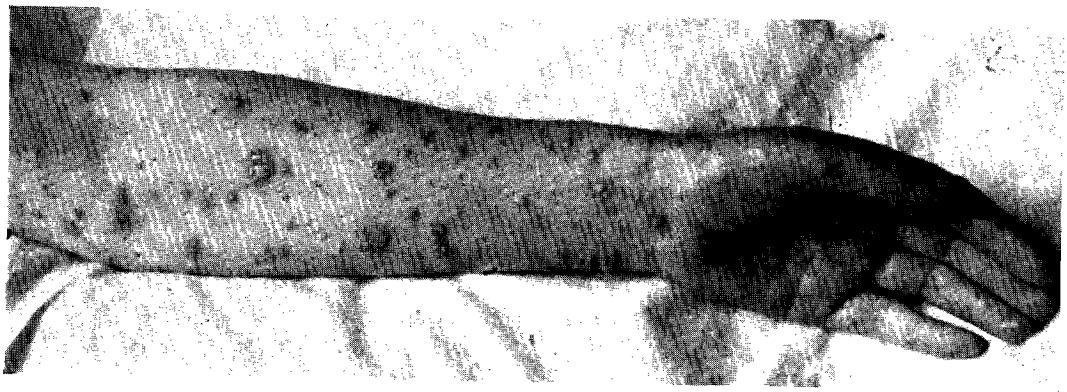

FIG. 91. Variola major, variola corymbosa, small lesions.

FIG. 92. Variola major, variola corymbosa, large lesions. This type of case was frequently fatal.

VARIOLA MAJOR IN THE SUCCESSFULLY VACCINATED

Confusion sometimes arises over the description of smallpox in the vaccinated due to differences in interpretation. Vaccination literally means "to inoculate with virus"; it is the operation only and does not mean the automatic attainment of immunity against smallpox.

The cases referred to in this Chapter are those where successful vaccination has been performed some time, usually many years, before contact, and where the resultant immunity has waned, and cases where successful vaccination has been performed after contact—during the incubation period—and in which some alteration in the severity of the disease can be properly

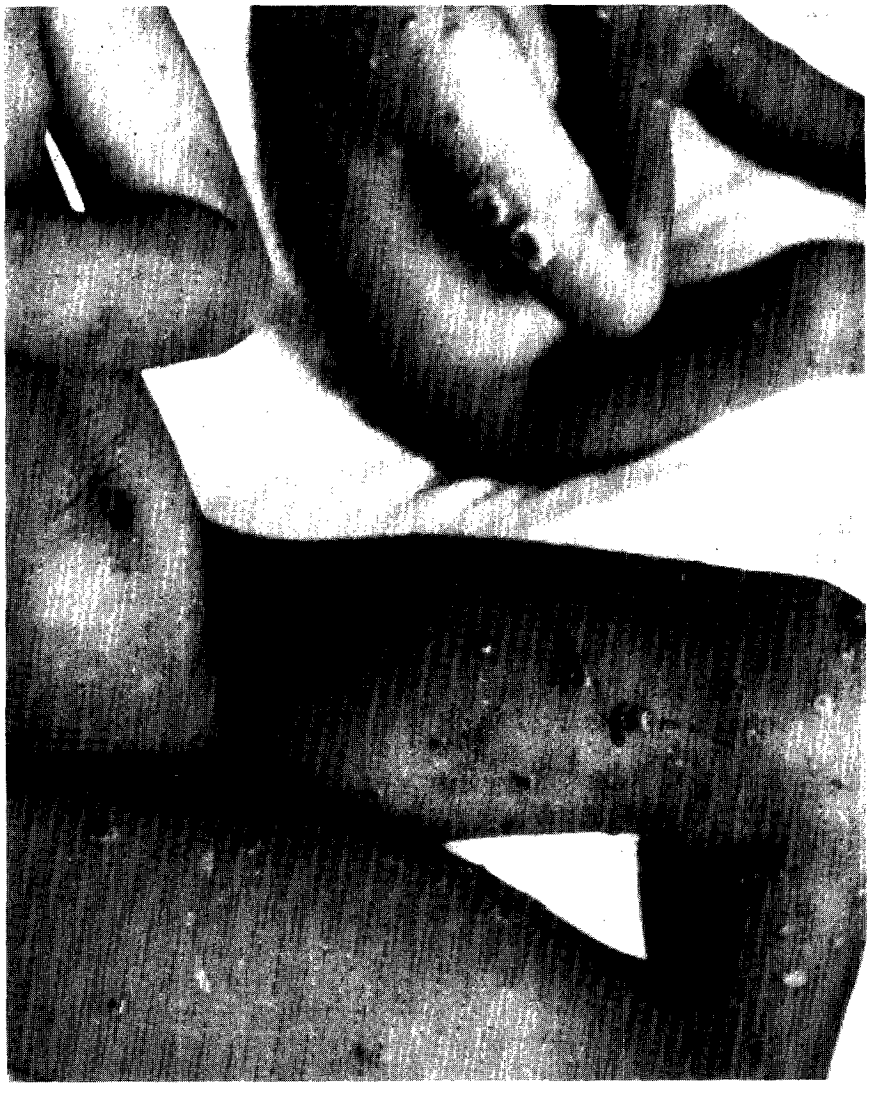

FIG. 93. Vaccinal infection of secondary impetigo from scabies—lesions are scabbing. Vesicular lesions are concurrent smallpox. The child in the foreground has vaccination lesions similar to the child in the background.

credited to that operation. In the latter group it should be noted that many patients, who have a successful vaccination after contact, show nothing in their clinical condition to indicate that the vaccination has had any effect on the attack of smallpox. It is sometimes forgotten that a mild case of smallpox may occur due to natural constitutional factors in the individual or is related to the size of infecting dose and not the result of vaccinial immunity. In persons vaccinated during the late incubation period the vesicle which occurs is, in some instances, probably variolous rather than vaccinial.

The immunity induced by successful vaccination gives rise to three different effects (see Chapter 9), but we are concerned here with the effect of two components; an anti-dissemination factor which affects the number of lesions and a skin immunity factor which affects the characteristics of the individual lesion. The combined effects are quite distinct and are called "vaccino-modification", and in their absence we should not assume that the precious successful vaccination has had any effect.

As in revaccination a characteristic of the smallpox lesion in the partially immune skin is for it to mature more quickly and to be situated more superficially, so much so that it does not feel "shotty" and little or no scar will result even on sites normally liable to scar. The circular shape of the smallpox lesion is less constant; it may be oval or even crenated and have an appearance very similar to some chickenpox lesions. Instead of all, or nearly all, the lesions on each anatomical part appearing more or less simultaneously, they may appear over a number of days, even as much as five or six days, so that the early lesions may be pustular or scabbing,while alongside are papular or early vesicular lesions. This "cropping" is very characteristic of vaccino-modification. There is also considerable variation in the size of lesions, later crops in particular being small, maturing rapidly without even the appearance of a pustule, let alone any tendency to frank sepsis. Although the large lesions tend to occur on the usual sites of election (Fig. 135), later lesions, particularly in those patients with very few lesions, may occur on quite unexpected sites. There is a greater tendency for the areola to be conspicuous around the early lesion, which the older clinicians regarded as a good omen, although it is the case, the vaccinial state of the patient, which is the determining factor.

When a successful vaccination has been performed more than twenty years before the attack, the residual immunity may be nil; this is shown by the not infrequent occurrence of type 1 (fulminating). The clinical appearance is no different from that in the unvaccinated. The point to emphasize is that the presence of scars from vaccination done as recently as twenty years before, does not rule out the possibility of fulminating smallpox. Cases have been reported where the interval is less but the date and success of the vaccination is not always certain. A history of vaccination without evidence of a scar should be ignored. The interval is often longer; in the case illustrated in Fig. 6 there are four scars from a vaccination done some sixty years earlier.

In persons possessing negligible residual immunity types 2 and 3 occur with no tendency for the rash to be any different from that in the unvaccinated. The development of a semi-confluent attack does not mean that in the absence of past vaccination the individual would have had a more severe attack. However, many clinicians have extraordinary faith and the literature abounds with statements that a vaccination done even fifty or sixty years previously *must* have had some effect on the clinical condition, although differences in severity can be accounted for by the unknown constitutional factors and possibly the size of the infecting dose which, presumably, must be one factor in determining type in the unvaccinated.

FIG. 94. Vaccino-modified vesicles, variation in size although mature.

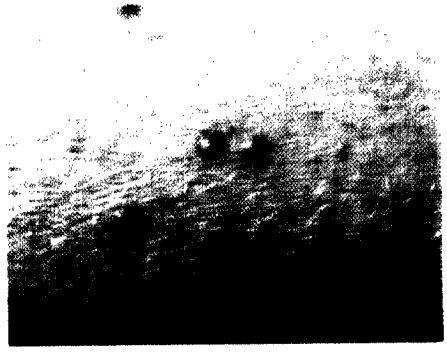

FIG. 95. Vaccino-modification, miniature mature vesicles.

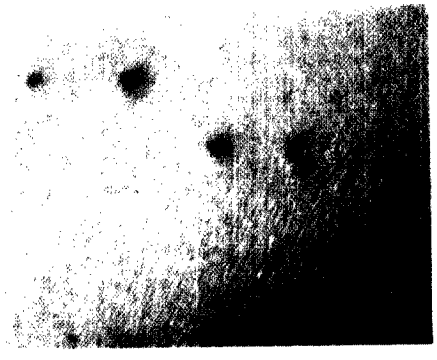

FIG. 96. Vaccino-modified, small scabs, third to fourth day, sixth or seventh day of the disease.

FIG. 97. Vaccino-modified, single scab, three days from macule to this appearance.

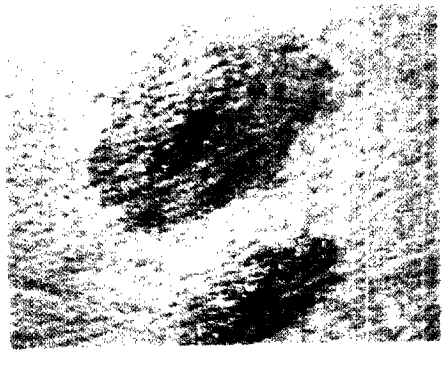

FIG. 98. Vaccino-modified, extensive erythema, urticarial type of lesion.

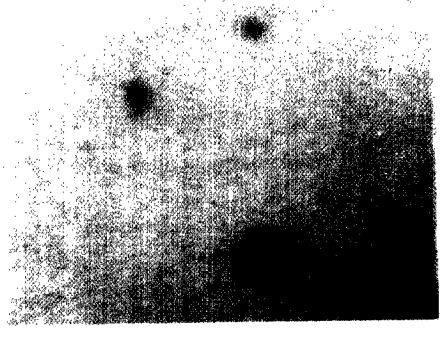

FIG. 99. Vaccino-modified, mixed small papules and "mosquito bite" type of lesion.

To face p. 46

FIG. 100. Vaccino-modified, transient scarring on hand 14 days from onset of attack.

FIG. 101. Variola inoculata. Infection of pulp of finger from needle prick, small secondary lesion at tip.

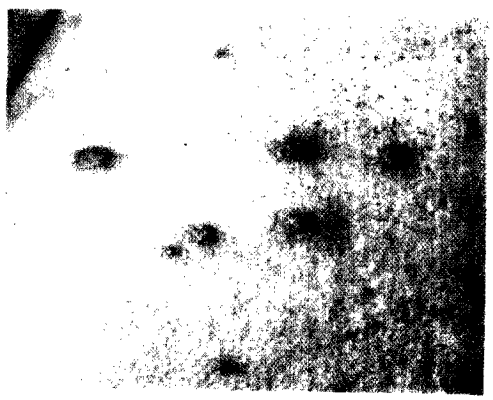

FIG. 102. Chickenpox lesion.

FIG. 103. Chickenpox, early scar.

Type 4, benign confluent, occurs in the vaccinated, but is less common than the semi-confluent, type 5. In type 4 the clinical condition is usually indistinguishable from that in the unvaccinated subject and the features of vaccino-modification so characteristically seen in types 5–8 are rarely seen. The initial fever is entirely normal for a benign type, the rash develops as in the unvaccinated with large pearly vesicles, and with very few exceptions all

FIG. 104. Variola major, vaccino-modified, Type 6, tenth day of disease. Thought to be chickenpox. Note distribution, avoidance of soft tissues, increase over pressure points.

are at the same stage of development on each anatomical part. In some cases there is a slight speeding up of the rate of maturation and a little less tendency for suppuration. It should be emphasized that in spite of the previous successful vaccination the level of immunity in this type of case is so low and apparently incapable of rapid stimulation, that the evolution of the rash is usually the same as in the unvaccinated. Very occasionally, although the macular and papular stages are profuse and herald a confluent attack, the rash suddenly regresses and within twelve to fourteen hours the papules disappear, leaving a little branny desquamation. There is no residual scarring and the patient feels perfectly well. This suggests a sudden immunity

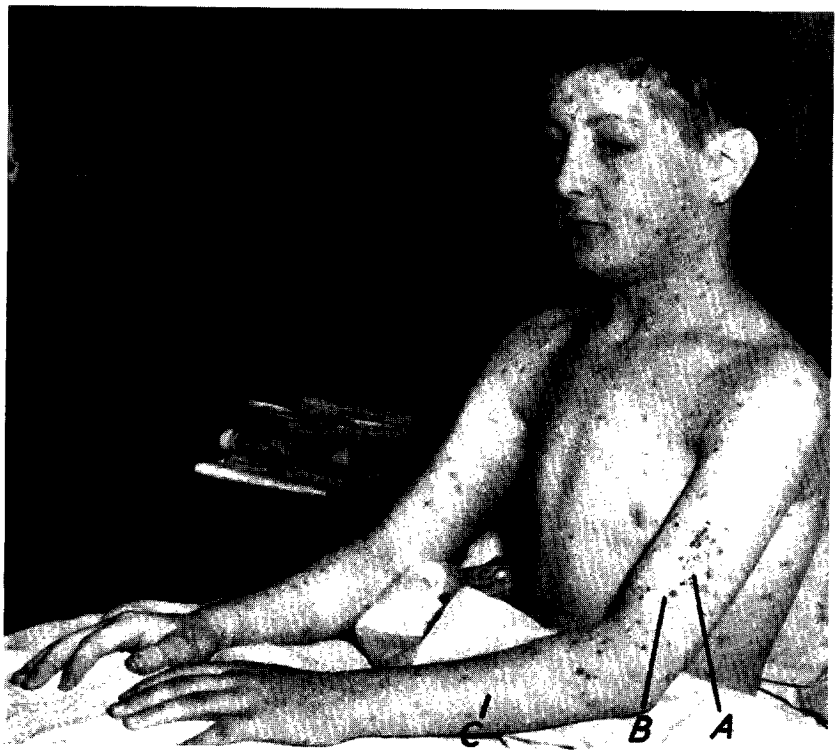

FIG. 105. Variola major, vaccino-modified, Type 7. Vaccinated on day of contact at A; secondary vaccinial lesions round the primary are at scabbing stage, B; early maculo-papular smallpox eruption, C.

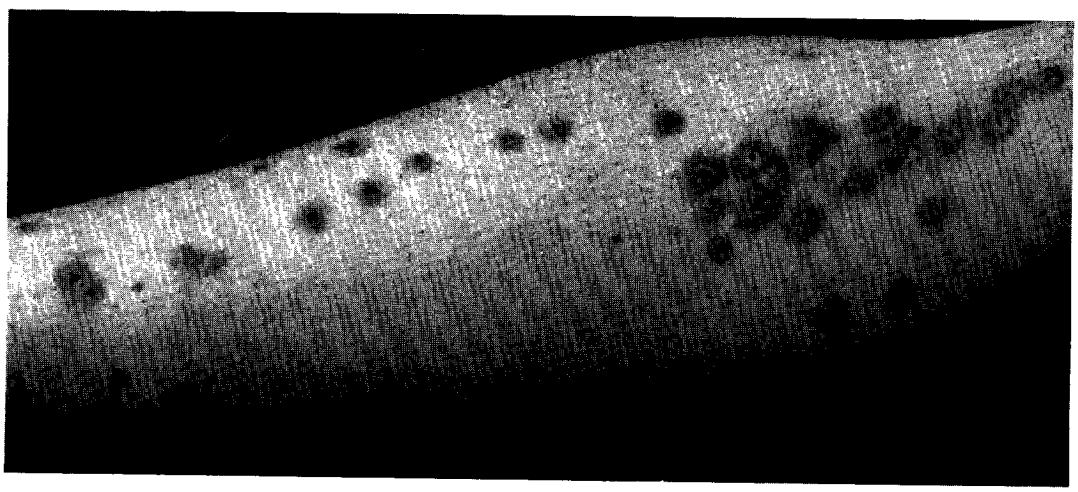

FIG. 106. Variola major, vaccino-modified, Type 7. Effects of trauma. Skin has been rubbed with spirit and a vein puncture performed at the end of the initial stage.

response in an individual sensitized by a previous vaccination, but whose original level of immunity was insufficient to prevent both the infective and invasive stages of the disease. It would, however, be more correct to call this abortive, type 8, vaccino-modified, rather than benign confluent vaccino-modified, as the clinical condition and prognosis are best suited to this description.

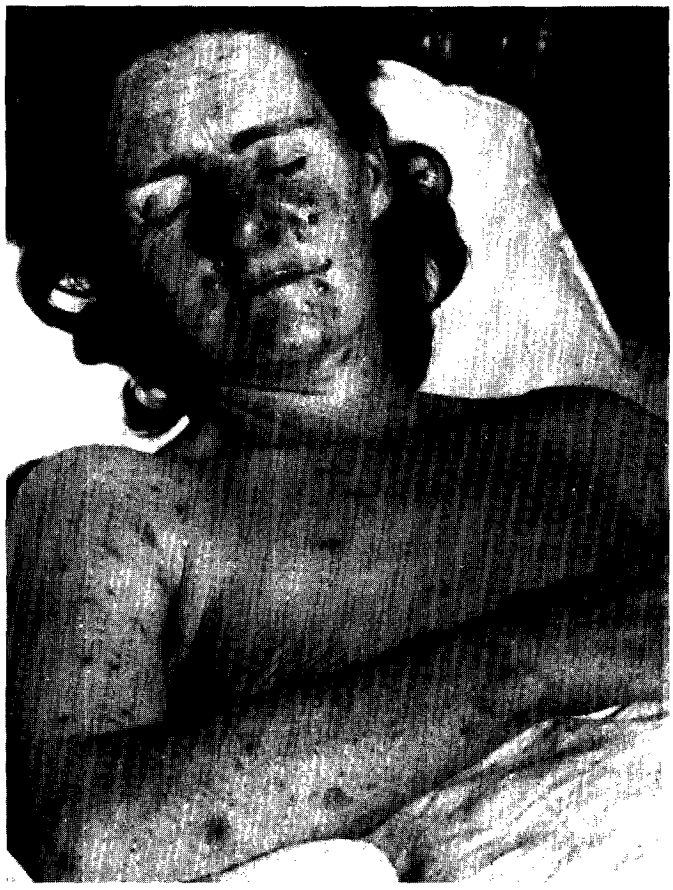

FIG. 107. Variola major, vaccino-modified, Type 7. Typical distribution.

When we come to consider benign semi-confluent (type 5) in the vaccinated who have partial immunity, we have the first type where there is a considerable difference from the disease in the unvaccinated. The initial syndrome is identical, with severe prostration, headache, backache, etc.; vaccination even a relatively short time before does not modify this phase; it either occurs in the normal way or there is no infection at all. The rash appears in the usual way about the third day, but at first it may be very sparse. Instead of a few herald spots there may be quite a number, often on pressure points. These early lesions will grow rather

more rapidly than in the unvaccinated and often to a larger size, particularly on the limbs. While this has been occurring, further macules will appear in between these growing lesions and these will vesiculate over the following two to three days. Further macules may appear

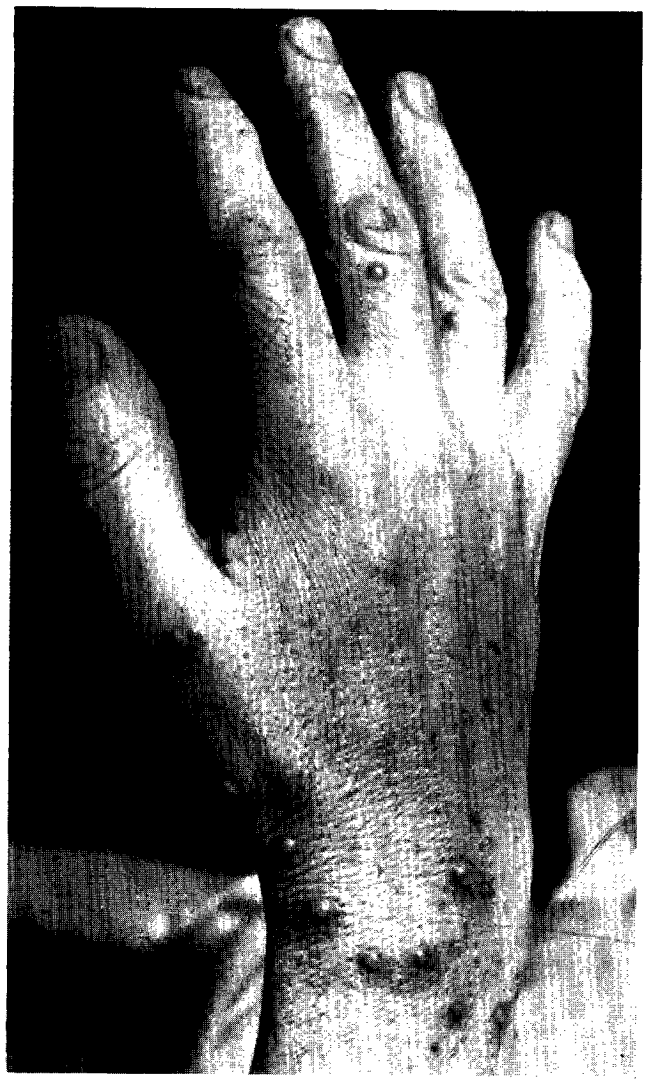

FIG. 108. Variola major, vaccino-modified, Type 7. Variation in size of lesions. Lesions over back of wrists, very small lesions along extensor tendons of the hand.

over a period of three to four days. Although lesions will be seen at various stages of development giving the appearance of cropping, the later lesions mature more rapidly so that, as the rash develops, it tends to become more homogeneous. Development of the later lesions is poor,

and small papules and abortive vesicles may be seen. These effects are particularly noticeable on the limbs and trunk; on the face, the lesions being earlier, show little modification and the resulting confluence obscures the process to some extent.

By the ninth or tenth day of the disease the elements of the semi-confluent eruption will show variation in size and stage of maturation, and although many of the lesions will have felt

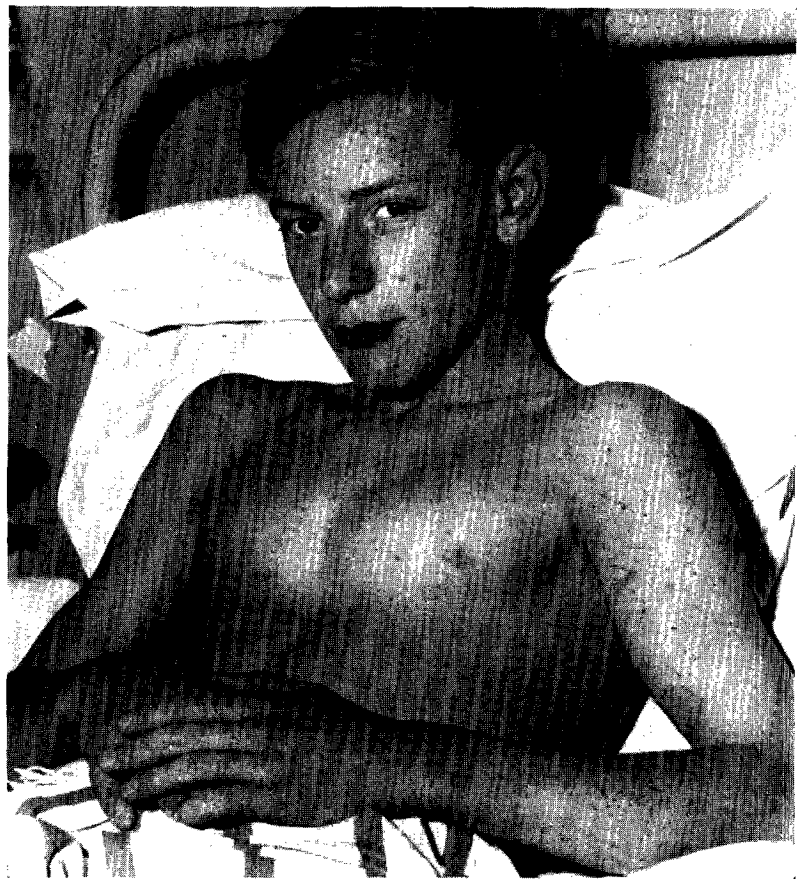

FIG. 109. Variola major, vaccino-modified. Third day, early maculo-papular lesions on the face, forearms and hands.

shotty in the early stages and will develop into typical deep-seated vesicles, others will be more superficial. The degree of modification of the rash will vary considerably in different individuals; it must be remembered that in some persons who have been vaccinated, the appearance may be the same as that in the unvaccinated. When evidence of vaccino-modification occurs, as shown by changes in the development of the rash, the rapidity of evolution lessens the chance of septic complications. The more rapid amelioration of symptoms, although of less importance to the fit adult, may be vital to the aged or infirm. A further benefit will be a reduction in the

number of scars due to some of the lesions failing to mature and to the more superficial nature of many of them, but it must be realized that it is on the face that modification is least, and quite severe scarring will result.

In the large outbreaks in the past, type 6 discrete was the commonest type of smallpox in young adults who had not been vaccinated since infancy.

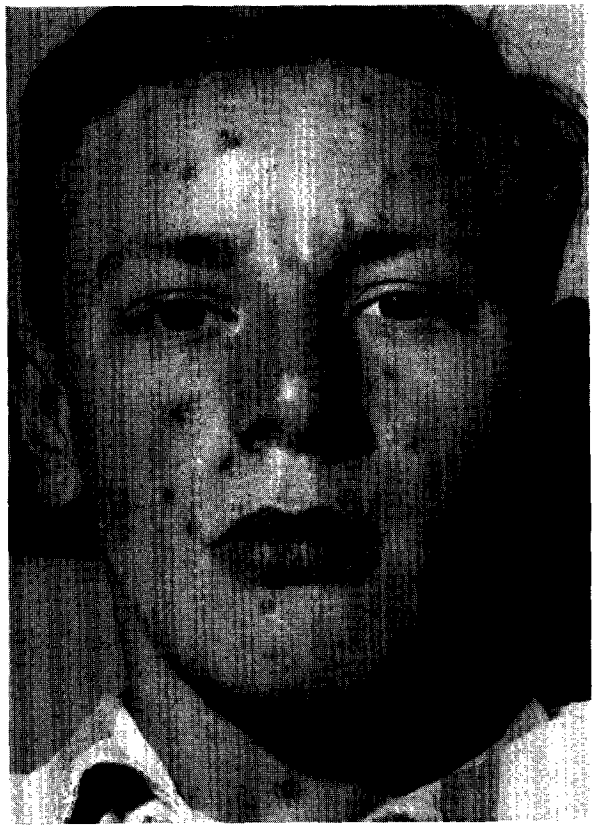

FIG. 110. Variola major, vaccino-modified, Type 7. Typical vesicular stage on the face, sixth day. Note distribution, lesions on the forehead, cheeks, over trachea, and absent from orbital fossae.

The initial phase is quite severe and is the same as in the unvaccinated, with sudden onset, temperature up to 103° F. (39·4° C.), headache, backache, general malaise. Fleeting erythematous rashes may occur—the so-called initial rashes—particularly affecting the flexures. Although there is some confusion over the nomenclature of these rashes, this type is more common in smallpox in the vaccinated than in the unvaccinated. They are probably allergic in origin and are not to be confused with the early stages of the malignant eruption.

The focal rash appears on about the third day, but there is greater variation in the time of its appearance. In some cases some elements of the rash appear on the first or second day, and in

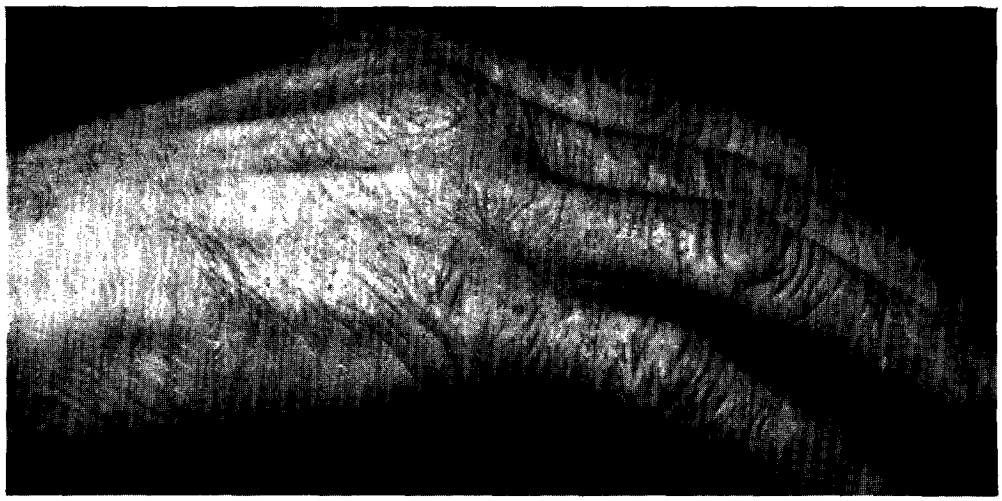

FIG. 111. Variola major, Type 7, vaccino-modified. Small scabs on hand at fourteen days. Patient diagnosed as chickenpox.

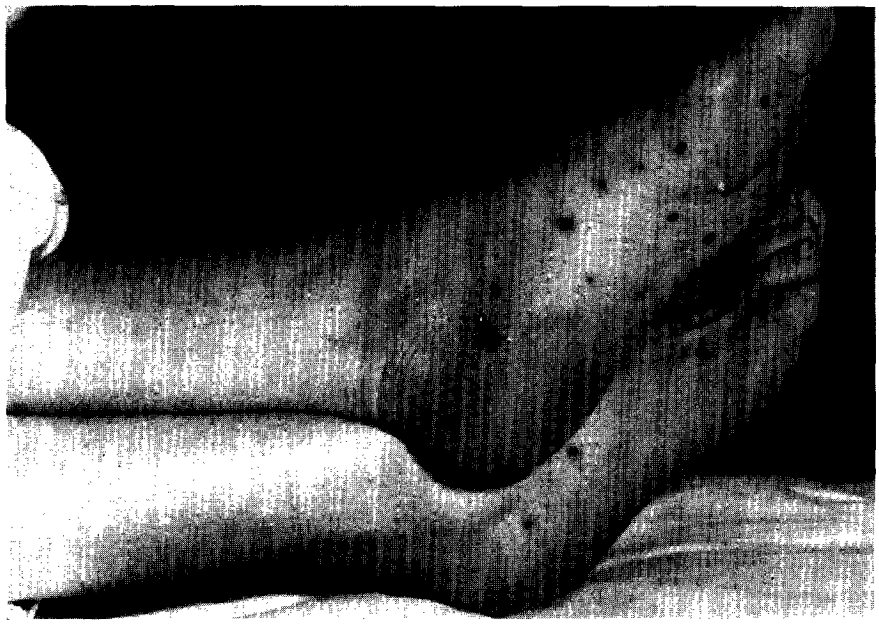

FIG. 112. Variola major, Type 7, seeds on the feet, present along pressure zones of the shoe. No lesions are visible on the legs at this stage.

others there are no signs of any rash until the fourth or fifth day. It seems probable that in some instances the real course of events is more constant than the patient's own story would have one believe as the orderly appearance of the rash seen so characteristically in discrete cases in the unvaccinated does not hold true in the vaccino-modified case. Not infrequently the earliest elements of the rash appear on the chest or back or even the abdomen and not on the face. Although lesions may appear early on the face, the time interval between their appearance on the face and upper arms and on the hands and legs is extended. Combined with the more rapid maturation of the lesions this leads to the appearance of scabs on the face and quite early papules on the limbs at the same time. This would not matter so much, but even on each anatomical part some lesions are much later than others, giving the appearance of cropping (Figs. 104 and 138).

The character of the individual lesions gives one little help in differentiating from chickenpox. Many are very superficial, are not shotty and scab rapidly. Although not quite so irregular in shape as a typical chickenpox lesion, most of the superficial lesions are not strictly circular. Careful study, even to counting and plotting of lesions, will show that the eruption is centrifugal in distribution (Fig. 138).

Once the rash appears the general condition of the patient rapidly improves. The acceleration of maturation decreases the liability to scarring and shortens the stay in hospital. Many of the later lesions will abort and produce very superficial lesions giving scarring no worse than chickenpox; some, particularly the very large ones on the nose (Fig. 107) and forehead, produce scars similar to those in the unvaccinated, and in the assessment of the value of vaccination both before and after contact this point should not be ignored. The "malignant element" sometimes present in this type (6) in the unvaccinated, is never present when vaccino-modification occurs.

Type 7, or mild, is very common in a vaccinated but only partially immune population. The initial syndrome is normal, with sudden onset, pyrexia, headache and malaise. The temperature drops to normal by the second to third day and the patient feels well enough to go to work. The rash first appears as a few macules on the face and arms. A few papules may form normal vesicles and often grow to a very large size; a full, tense, pearly lesion. Many, however, appearing later, may not progress beyond the papular stage, changing into a dry "spot", a feature illustrated in Fig. 108. In spite of this obvious cropping and variation in character and depth of lesions, the rash generally shows the centrifugal feature of smallpox and occurs on the sites of election, illustrated in Fig. 110. The diagnosis is likely to be missed because of the sparse nature of the lesions and because the patient feels so well. Even the large vesicular lesions will dry up rapidly and many of the papular lesions will abort so that by the fourteenth day of the disease all the scabs will be detached and only a few seeds may remain on the hands or feet (Figs. 111 and 112). Scarring is very slight, limited to the nose or forehead; this is shown in Fig. 158, two and a half years after the attack. It is this type of case which is so often missed and is the source of infection to others. It is difficult to make a clinical diagnosis retrospectively when seen more than twenty-one days after an attack.

Type 8. Individuals whose immunity is relatively high, or whose immunity mechanism reacts late to the stimulus of infection, suffer from type 8, abortive attacks. The initial symptoms may be quite severe. There is sudden fever with headache and malaise, but backache is more rare. Improvement may be equally rapid, so that within twenty-four to thirty-six hours the patient feels well again. Apart from the exceptional cases with a late-acting immunity mechanism previously described, the rash is usually very scanty and may consist of only one

lesion; normally there are under ten. These lesions may be anywhere on the body and unless some traumatic localization factor has been present are usually well scattered, e.g. one on the face, one on the lower arm, perhaps one on the back and one on the leg. Occasionally all the lesions may be on the face or all on one anatomical part, even on the back, sometimes determined by the presence of acne. As the lesions are so few it is difficult to decide whether there is a centrifugal distribution or not. The preference for certain pressure points may be a help, at

FIG. 113. Variola major, Type 7. Late dome or sentinel vesicle on the hand, other lesions more superficial, and have already scabbed. The patient had chronic eczema.

any rate it should make one wary of giving a negative diagnosis without further observation or laboratory tests. Common sites for single lesions are between the eyebrows, on the nose, the ulnar styloid process, the external malleolus or over the tendo Achilles. The character of the lesions does not give one much help. The macules are very indefinite and become minute papules which are not shotty or deep-set in the skin. The summit of the papule is dry and keratinized and is indistinguishable from the many papular conditions seen from time to time on almost any skin (Figs. 95, 96 and 97). A few lesions of this kind on the skin of an Asiatic seaman or on the back of a youth with mild acne, represent a diagnostic problem impossible to solve

clinically except in known smallpox contacts. Scabs from these lesions should yield smallpox virus if sent to a suitable laboratory, but a negative report on such small amounts of material is not conclusive. Unless a smallpox contact, the suspicion is not likely to be entertained and the availability of laboratory services will not affect the problem. The lesions are present for only two to three days and a very tiny "scab", just a flake of skin, will separate leaving a small mark, a little more easily seen on the pigmented skin, but possessing no characteristic features. The patient is unlikely to remain off work for more than the one or two days of the initial syndrome and no permanent scarring results.

Type 9. Finally, one has to consider variola sine eruptione and "illness of contact" in the vaccinated. It had been noticed by Byles even as early as the time of Chadwick (1843) that vaccinated persons coming in contact with cases of smallpox might develop a sudden febrile condition about twelve days later with headache and malaise. The attack lasts only a few hours or the full twenty-four to forty-eight hours of a smallpox initial syndrome of moderate severity, but is not followed by any rash. On clinical grounds and in the absence of smallpox contact, it is impossible to distinguish this from many other acute virus infections. There is a virus "shower" and it should be possible to grow virus from the blood, if it is taken at the right time. It is likely to be difficult as the clinical syndrome suggests that viraemia would only be present for an extremely short time. Although in the unvaccinated a positive complement fixation test would strongly support a diagnosis of variola sine eruptione, in the vaccinated evidence must depend on the titre. Although Downie and Macdonald (1953) claim that a high titre when successful vaccination was done more than a year before denotes a new infection, experience of this test is as yet insufficient to exclude the possibility of a high titre in some individuals vaccinated or revaccinated many times where the interval since the last vaccination is more than a year, or who have been in contact with smallpox previously. There is also the possibility of some rise in titre as a result of some other viral or bacterial stimulus.

CHAPTER 3 | *Variola Minor*

Epidemiological experience shows that variola minor is a permanent variant of the smallpox virus giving rise to a disease that only differs from variola major in its spectrum of severity. It is particularly important to appreciate that variola major in the unvaccinated, and more frequently in the vaccinated, can give rise to an attack which is impossible to distinguish clinically from variola minor. Until recently it has not been possible to differentiate between the two viruses with certainty. Following Dinger's (1956) and Helbert's (1957) work, Nizamuddin and Dumbell (1961) report a simple test based on the temperature of growth in the chorioallantois.

Variola minor can be classified, using the author's classification, in the same way as variola major. The most important authority on this form of smallpox is J. Pickford Marsden (1936), whose account of the clinical features of 13,686 cases remains the standard work on this subject, and to whom I am indebted for a great deal of information. Marsden, using Ricketts' (1893) classification found only 0·2 per cent of "toxic" cases (type 1), 0·01 per cent confluent on the face in the papular or vesicular stage (type 2), and 0·12 per cent confluent at maturation (type 3). The remainder 2·16 per cent were classed as discrete with more than 500 pocks on the face, leaving 97·6 per cent being discrete with less than 500 pocks on the face. The epidemiological aspects of severity are discussed in Chapter 14.

TYPES 1, 2 AND 3

From the figures quoted above, it is seen that toxic cases (Ricketts) which would include types 1, 2 and 3 (Dixon) are exceedingly rare in hospital statistics. Figs. 114 and 115 show two fatal cases in the outbreak in New Zealand in 1913, which have the appearance of malignant confluent attacks. Robertson (1913) had one death in the Australian outbreak. Although the case was complicated by pregnancy, he did not think this contributed directly to the fatal outcome.

It seems probable that type 1 (fulminating) can occur in a particularly susceptible individual with early death, with or without purpuric manifestation. Although no cases of this description occurred in Marsden's series, comparison of events in outbreaks of variola major leads one to believe that cases might occur and not be recognized or admitted to hospital. The universal belief that variola minor never kills doubtless leads clinicians to dismiss entirely the idea that variola minor could be a possible cause of sudden death. From the description given by Marsden it would appear that two of his cases might be described as malignant, types 2 or 3. One, however, was in an infant twelve days old, and the other in a man of fifty-six who also had uraemia. These possibles in a series of over 13,000 cases only serve to emphasize the rarity of such types of variola minor. When they do occur the signs and symptoms are essentially similar to those of variola major.

TYPES 4 AND 5

Marsden records nineteen cases which fit into the author's classification with confluence on the face. Apparently Killick Millard (1925) did not see any such cases during the Gloucester outbreak of 1925, but I was able to photograph one, shown in Figs. 117 and 122, in the Rochdale outbreak of 1951–2.

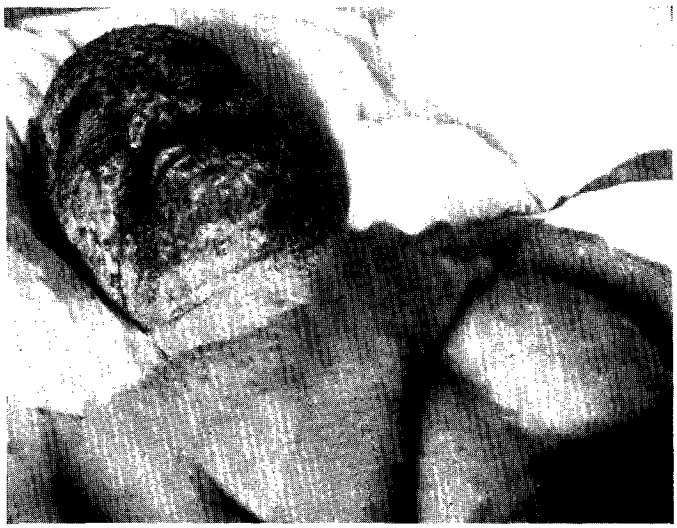

FIG. 114. Fatal case of variola minor, probably malignant confluent.

FIG. 115. Fatal case of variola minor.

The incubation period is the same as in variola major (Marsden, 1936; de Jong, 1955), although it is frequently stated to be lengthened. The onset of fever is sudden, there is malaise, and there may be headache, backache and vomiting. Abdominal pain leading to a diagnosis of appendicitis perhaps seems more frequent than in variola major. Marsden noticed that "bronchitic cough" was a frequent manifestation, although in variola major respiratory

FIG. 116. Early maculo-papular rash on the scalp, variola minor.

FIG. 117. Vesicular stage, severe variola minor Type 6.

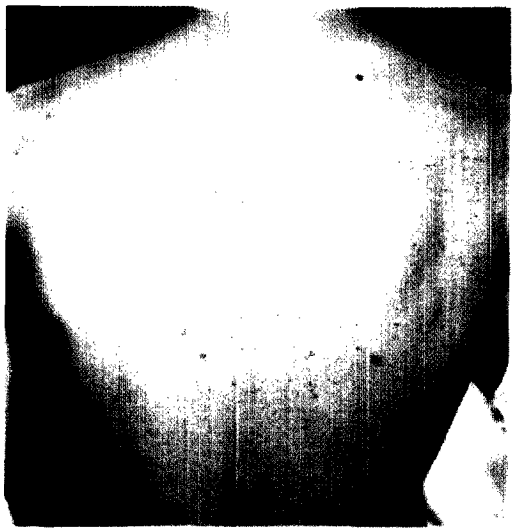

FIG. 118. Early maculo-papular rash, variola minor, rather irregular distribution.

FIG. 119. Typical large pustular lesions, variola minor Type 7.

To face p. 58

FIG. 120. Variola minor scars. Reverse distribution, centripetal. The face is shown in Fig. 119.

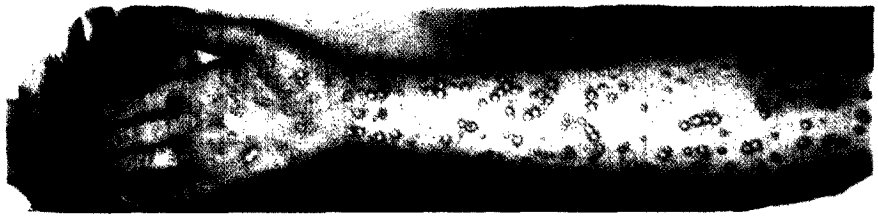

FIG. 121. Variola minor Type 6.

FIG. 122. Variola minor Type 6. Note distribution over muscles of the neck, and angle of jaw, and the facial oedema.

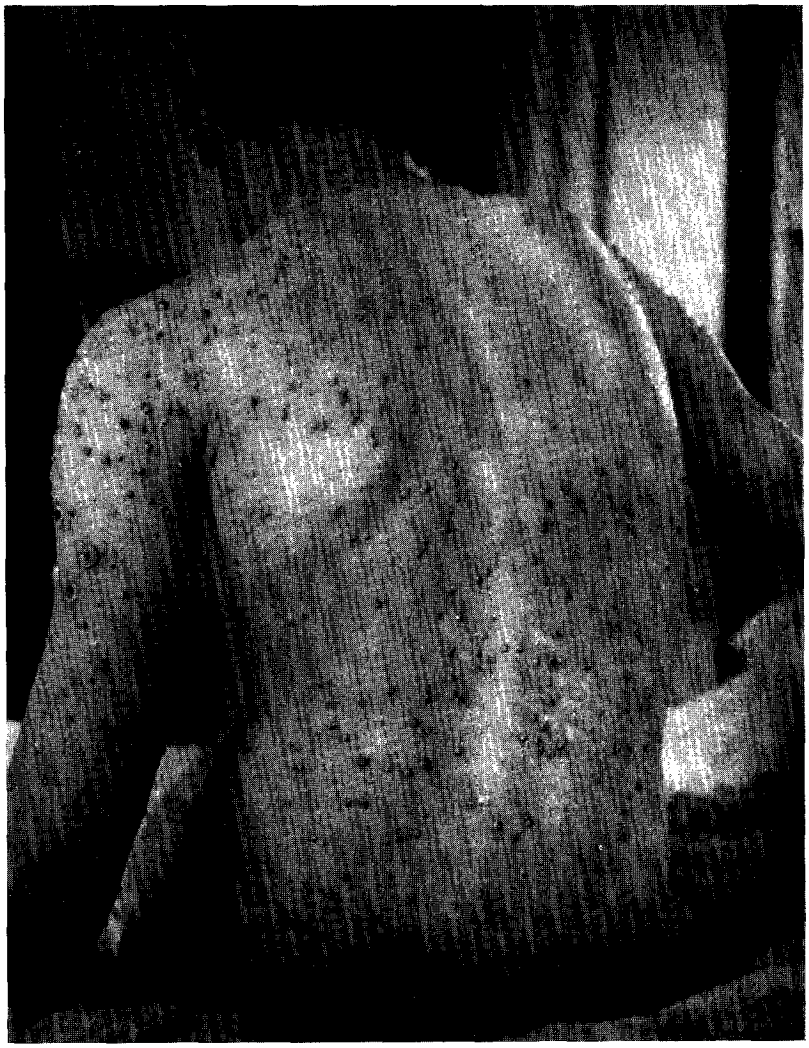

FIG. 123. Variola minor, typical rash, discrete, Type 6. Increased density can be seen due to pressure of the belt. Successful vaccination performed after contact.

symptoms in the initial phase are conspicuous by their absence. There are possibly a greater number of cases in variola minor where the initial stage is vague or indefinite. Marsden (1936) records that 8 per cent of his cases had no history of an initial stage, and Innes (1953) recorded that of 120 cases only 21 had a severe initial stage. However, it is particularly difficult to get accurate details of the initial stage of the attack in variola minor. It must be remembered that in most series of hospital cases the patients are only admitted in the eruptive stage. There is also

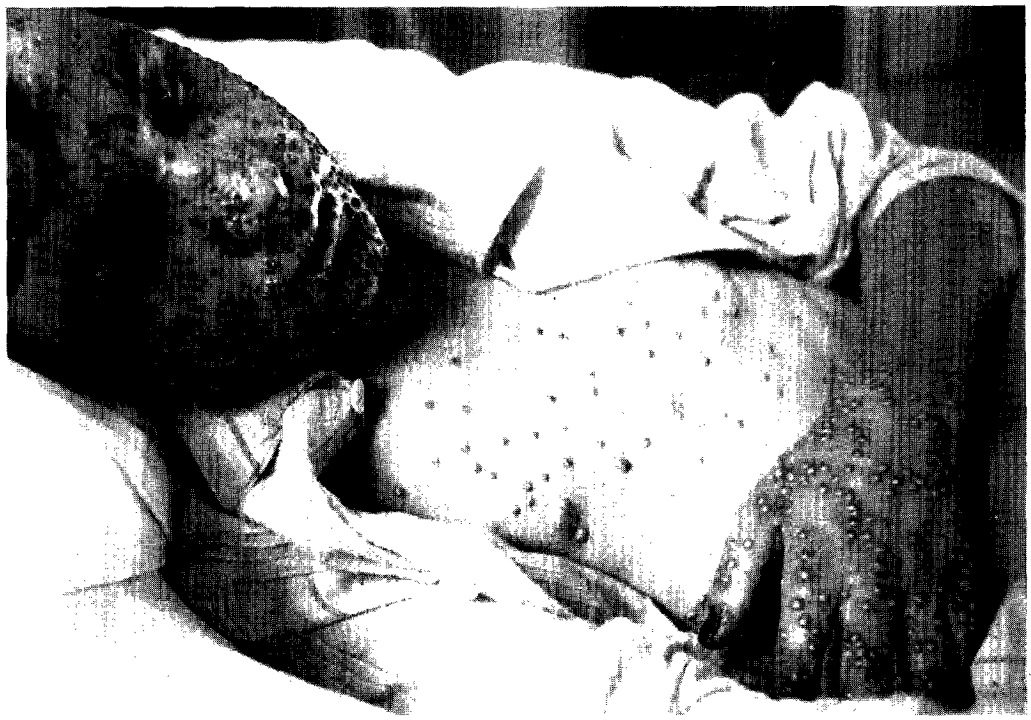

FIG. 124. Variola minor, Type 6, typical distribution.

a tendency to minimize the initial stage in variola minor as it provides an excuse for late diagnosis. The photographs, Figs. 117, 121 and 122, show various aspects of a patient, a young woman of twenty-three, suffering from type 5 variola minor. The characteristic size, rate of maturation and distribution are in no way different from the same type of variola major. The oedema of the face is very typical, obliterating the features and making the patient look twenty years older. Lesions occur in the mouth as in types 4 and 5 in variola major, but may be quite few, and lesions on the larynx and trachea are uncommon. In this type of case normal vesiculation occurs which pustulates, and leaves scars just as severe as in variola major, which remain to remind the patient, at least, that variola minor can be of more than minor importance.

TYPE 6

The initial stage is normal and the rash may be the same as in variola major with large even-sized pearly lesions—hard to the touch and deep set in the skin. In others the lesions are all very much smaller, tend to be more superficial and mature to a "granuloma" rather than a pustule.

FIG. 125. Variola minor, discrete, Type 6. Fatal attack in an infant six weeks old. From the appearance one would imagine broncho-pneumonia supervened.

In some, and in my opinion these are rare in this type in the unvaccinated, there are mixed large and small lesions, the large ones being the earlier and the smaller ones later crops. As in variola major, single large lesions (sentinels of Marsden) (see Fig. 113) may occur on the hands

or feet. With the development of the eruption there is a relief of general symptoms and a decline in temperature. Prior to the use of antibiotics it was the discrete case that developed pyogenic complications such as boils, or even occasionally a fatal pyaemia.

This type of case constitutes about 5 per cent of cases of variola minor, but these will have some permanent scarring on the face as in variola major.

FIG. 126. Variola minor, severe Type 6 case. Typical distribution, particularly on the dorsum of the hand.

TYPES 7 AND 8

In type 7 some of the lesions are of normal size or even larger, but smaller abortive lesions may also occur, although not to the same extent as in the vaccinated. These large lesions will leave scars on the face.

The initial attack is of the usual kind: sudden onset, with pyrexia, headache, backache, pains in the abdomen or limbs, and vomiting. Lesions in the mouth may occur, but are likely to be very few, and with the onset of the eruption, when diagnosis is most likely to be made, will be absent. The attack is very like influenza. The initial phase is short, twenty-four to forty-eight hours, and the patient has completely recovered, feeling quite well, before any eruption appears. It usually appears on the third day, but may be delayed to the fifth or even sixth day.

The eruption, scanty though it is, has a normal centrifugal distribution and predeliction for pressure points. In abortive type 8, the lesions are small, passing from macule to a miniature vesicle and "granuloma" stage in two or three days. The lesions are superficial (Fig. 131) and do not feel shotty at any stage of their development. The appearance is similar to variola major, but unlike the usual appearance in modified variola major, all the lesions may be of this type. These forms, type 7 and abortive type 8, have been described as "influenza with spots", or more

FIG. 127. Variola minor, late discrete case. Mother nursing successfully vaccinated and unaffected baby.

accurately as "influenza followed by spots", and as Marsden (1936) points out, the two events are frequently unrelated in the minds of patient or medical attendant.

Figs. 114–129 show cases of variola minor. It should be remembered that, being taken in hospital, these are of the more severe types. Many cases of types 7 and 8, are not discovered.

TYPE 9

Variola minor sine eruptione would appear to have nothing to distinguish it from the similar syndrome occurring in variola major. No cases of "pulmonary allergy" syndrome appear to have been recorded but they may well occur.

FIG. 128. Variola minor. The mother, successfully vaccinated in infancy thirty years before, has a moderately severe attack. The child, unvaccinated, has an exceedingly mild attack.

VARIOLA MINOR IN THE VACCINATED

The effect of vaccinial immunity in variola minor is similar to that in variola major, bearing in mind the different spectrum of severity.

The duration of immunity following successful vaccination appears to be longer for variola minor than for variola major (Marsden, 1936) (see Chapter 14). Although it is extremely rare, severe variola minor may occur in the aged not vaccinated since infancy.

Even slight residual immunity appears enough to shift the severity of attack to the mild

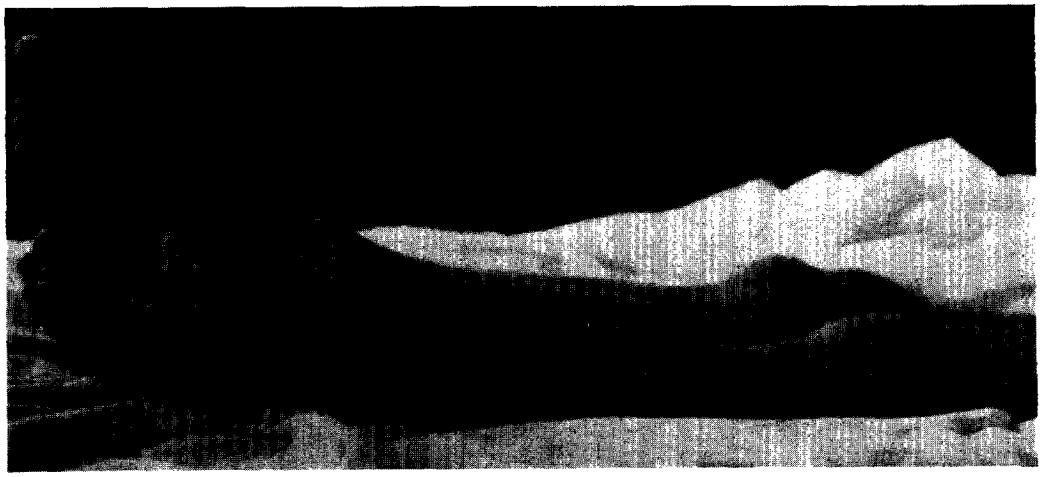

FIG. 129. Variola minor, severe rash on the feet in a discrete case, the effect of trauma.

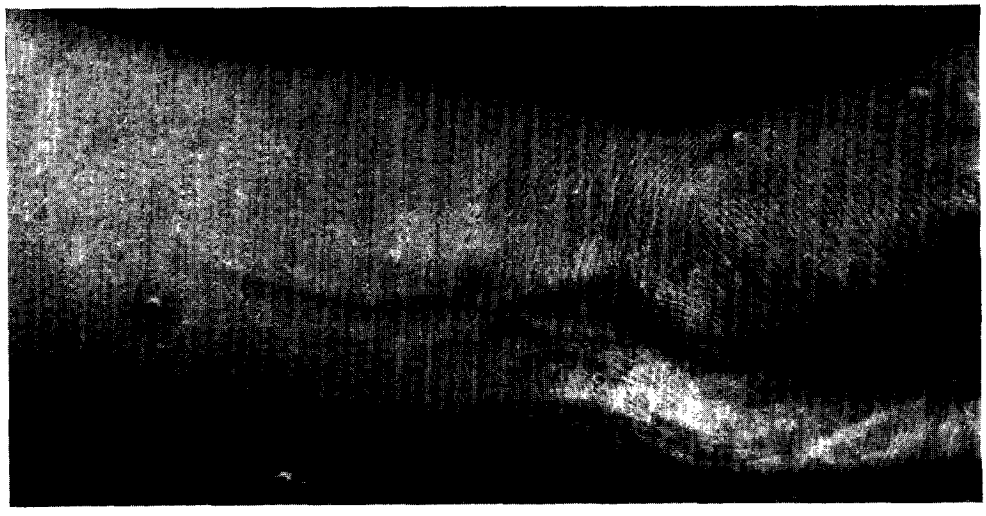

FIG. 130. Variola minor, small abortive type vesicular lesions, frequently seen.

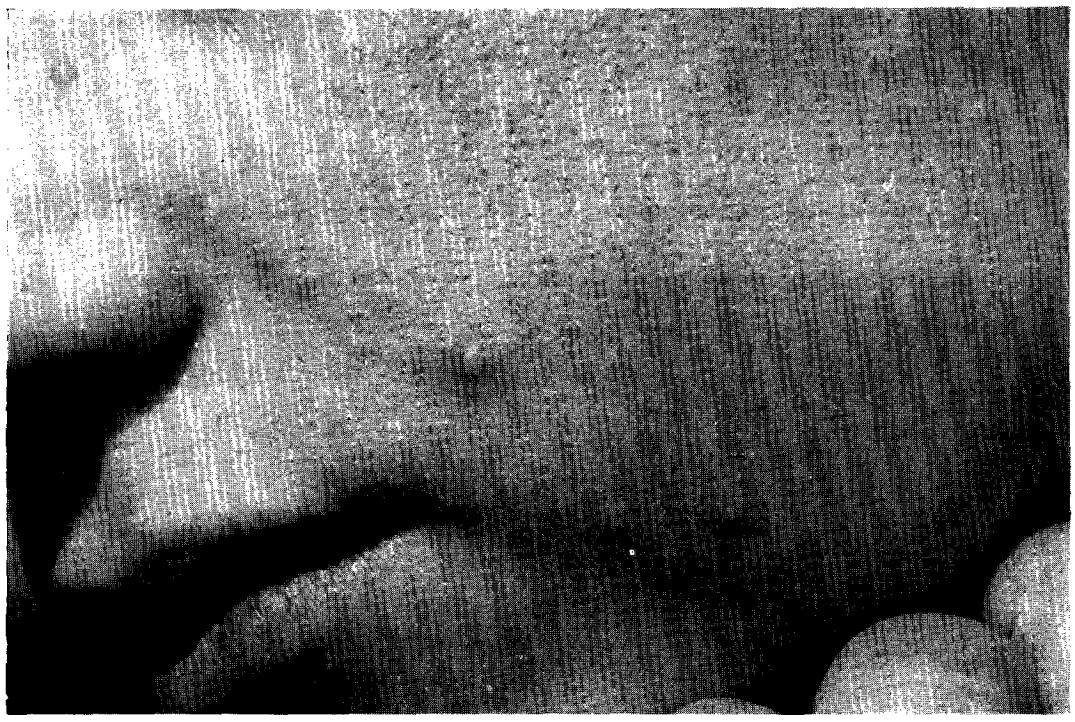

FIG. 131. Variola minor, lesions of the face. Some are very small.

end of the scale, with the result that types 4 and 5 are rare. Type 6 will occur (Fig. 128), but vaccino-modification, although not affecting the initial and early eruptive stages, will often cause extreme variability in the character of the elements of the rash and acceleration of maturation as in variola major.

Type 7 will occur frequently and will show the usual features of vaccino-modification with superficial lesions, cropping and more bizarre distribution. Occasionally—for example, on a limb (Fig. 120)—the distribution may be centripetal as in chickenpox. The acceleration of maturation still shortens the "illness" so that the patient will be quite well after the initial phase.

TYPE 8

These occur in the vaccinated as in variola major.

TYPE 9

There are probably a very large number of cases of variola minor sine eruptione in the vaccinated, but most of these remain undiagnosed.

CHAPTER 4

Differential Diagnosis
Laboratory Diagnosis
Post-mortem appearances

DIFFERENTIAL DIAGNOSIS

"It is perhaps of all diseases that in which a certain diagnosis can be arrived at in every case" Ricketts, 1900).

Before discussing the differential diagnosis it is of interest to briefly review the overall accuracy of the diagnosis of smallpox. Today few would agree with the confident statement above, made by one of our Victorian forebears. Many of the older writers describe smallpox but pay relatively little attention to the differential diagnosis. This may have been due to their great familiarity with the disease or faith in their clinical diagnostic ability unchallenged by laboratory techniques available today.

Cameron, writing in 1905, stated that of 7,842 patients sent to the smallpox receiving station in London, presumably by general practitioners, in only 607 was it necessary to correct the diagnosis, an accuracy of about 90 per cent. Of 7,235 cases seen by the fever hospital staff and sent from the receiving station to the smallpox hospital, only two were found not to have smallpox. This gives an accuracy of about 99·9 per cent. It must be remembered, of course, that most of these cases would be seen at some stage of the focal eruption. In Marsden's (1936) series of variola minor in London, 92 per cent of the cases seen at the receiving station had the correct diagnosis. However, we have no knowledge of how many cases were missed and therefore not sent to hospital.

In 1954 I visited a number of countries in the Western Pacific region of the World Health Organization. In those countries where smallpox was endemic a similar confident attitude prevailed. It was noticeable, however, that in these countries medical practitioners had little knowledge of the fulminating or the very mild cases. As in Europe fifty years ago, I have no doubt that the apparent high degree of accuracy of diagnosis was partly due to only recognizing the cases easy to diagnose from the middle part of the spectrum of severity.

There is little doubt that we are more critical in our diagnosis today than were our predecessors fifty or a hundred years ago. This is in keeping with trends in medical diagnosis: the aim to detect sub-clinical and abortive attacks of classical diseases. Cameron, writing in 1905, rather doubted the existence of *variola sine eruptione*, which is perhaps not surprising from his hospital experience, and he stated quite definitely that without any lesion on the face a disease could not be smallpox. Bancroft (1906) included under sine eruptione cases in which "a few definite pocks occasionally appeared". Even Ricketts (1908) gives one the impression that *sine eruptione* could include patients with a few "spots". In those days a rash had to

be a real rash, something very definite, and a few "spots" did not come into this category. We are more aware of the very mild and abortive cases, and doubtless our experience of variola minor has gone a long way to reinforce this appreciation.

Today in those countries where smallpox is a rare imported disease, most general practitioners would obtain a far worse score for diagnosis than was the case in 1905. However, observations in many countries convince me that experienced clinicians have all made mistakes and will continue to do so. From the public-health point of view referred to later, we must ensure as far as possible that the mistake is always on the side of public safety. The very infrequency of the disease, the lack of clinical experience so necessary, and the publicity over a missed case, produce a situation and problems for the doctor which would not have occurred fifty years ago when the disease was common. This does, however, put greater emphasis on the problems of differential diagnosis and of assessing the relative value of clinical and laboratory findings.

Smallpox has been confused with many diseases; the chart below (Fig. 132) gives the more common ones. It is convenient to divide the problems of the differential diagnosis into those of the initial stage, the early macular and papular stage, and the late vesicular and pustular eruptive stage.

Initial stage

Influenza	Acute purpura
Acute septicaemias—streptococcal, meningococcal	Acute leukaemia
Toxic scarlet fever	Lumbago
Meningitis	Encephalitis
Appendicitis	Enteric fever
Pneumonia	

Early: Maculo-papular and erythematous stages

Measles	Erythema multiforme
Rubella	Acne (modified cases)
Drug eruptions	Insect bites
Papular syphilide	

Late: Vesicular and pustular stages

Chickenpox	Impetigo
Vaccinia (generalized)	Drug eruptions
Erythema multiforme	Pustular syphilides
Stevens-Johnson syndrome	Pemphigus
Scabies	Bullous impetigo

FIG. 132. Chart of diseases confused with smallpox at different stages.

INITIAL STAGE

The initial stage is the illness due to the "virus shower" commencing suddenly at the end of the incubation period. It therefore closely resembles the onset of many virus diseases, particularly influenza, or of some acute bacterial disease such as meningococcal infection or pneumonia. The degree of fever is not of any great help as it may range anywhere between 100–106° F. (37·8–41·1° C.). In the fulminating case we have a moderate pyrexia, 100–102° F. (37·8–38·9° C.), associated with a profound shock-like condition of the patient. The loss of

muscle tone of the face (Fig. 8), coupled with the peculiar apprehension and mental alertness, is unlike any other acute infectious disease. The pulse rate is raised and also the respiration rate, although there are no physical signs in the chest.

In other types the similarity to influenza is very close. The temperature is raised to 103–105° F. (39·4–40·6° C.), with corresponding rise in pulse rate and little change in respiration rate. General weakness of the limbs is similar to influenza, but the headache is usually much more severe. This fact is of little help as this symptom is capable of such varied interpretation.

The occurrence of fever and prostration is against a diagnosis of severe migraine. Maniacal symptoms occur, and suicidal attempts have been made, but it is doubtful if these have much diagnostic significance. Extreme drowsiness or even coma may suggest infective encephalitis, but in smallpox the cerebro-spinal fluid is normal.

Muscle pains occur all over the body. If they are localized in the back to give that peculiarly severe backache of smallpox, the symptom may be diagnostic. Unfortunately, as I have been at some pains to point out before (1948), and as was previously stated by Wanklyn (1913*a*), "it may be emphatically said that the statement 'no pain in the back' does not exclude smallpox". He enlarges on this point to write: "pain in the back seemed to be responsible for misdiagnosis on a good many occasions". In view of the fact that one still reads statements that intense backache is present in all severe cases of smallpox, it seems necessary to emphasize that slight backache, plus other symptoms, may also be suggestive of smallpox, but the symptom may be absent altogether and it may be present to some degree in influenza or other febrile conditions. As mentioned before, the frequency of this symptom seems to vary in different parts of the world, and in different races.

It is not uncommon for the muscle tenderness to affect the abdominal muscles and, coupled with vomiting, a common symptom, a diagnosis of acute appendicitis is made. In Marsden's (1936) series of variola minor, this was the commonest cause of wrong admission to a general hospital. A more careful examination of the patient, the absence of deep tenderness and the rather high temperature should eliminate this mistake. After a short period of observation the white count may be raised in appendicitis, but it will be normal or reduced in smallpox.

The tendency to haemorrhage is a feature of fulminating and malignant smallpox, and the occurrence of a petechial rash, especially in the groins and along the flanks to the axillae, is diagnostic of smallpox. Other forms of febrile purpura due to meningococci or other organisms do not have such local distribution or symmetry. When only a few small haemorrhages are present no definite opinion can be given. The appearance of the catamenia is very common in the initial stage of smallpox.

A diagnosis of acute leukaemia is sometimes made because of the presence of haemorrhages and because of the leukaemic blood picture, but the abrupt onset, pyrexia, apprehension, and rapidly fatal termination is unlike that disease.

Fleeting erythematous rashes may occur during the initial phase, particularly in the vaccinated, and together with the vomiting give rise to a diagnosis of "food poisoning". The fever, however, is rather high for this condition and the erythematous rash rather more symmetrical than in allergic food rashes.

Erythematous rashes on the face and later on the arms and trunk occur in the fulminating and some malignant cases and sometimes give rise to the diagnosis of toxic scarlet fever. The rash is a diffuse not a punctate erythema, the temperature is much lower (malignant type) than in severe scarlet fever and the tongue and fauces are practically normal.

Unfortunately in the most common types of smallpox the initial phase has nothing to distinguish it from other febrile conditions. Without any epidemiological pointer, clinical diagnosis is impossible. If the person is a contact of a known case and the pyrexial attack occurs within the normal limits of the incubation period, it should be regarded as the initial phase of smallpox until proved otherwise. If smallpox is suspected, then this is the time to attempt blood culture as the chance of it being positive even in the mildest case is greatest at this stage of attack. Many years ago the leucopenia developing at this stage was thought to be of diagnostic value, but owing to its frequent occurrence in other virus infections its value is only negative.

EARLY ERUPTIVE STAGE

Because of the different appearance and development of the rash in the malignant and benign types it is necessary to consider these separately.

The early malignant rash is morbilliform in type. There may be erythematous areas just raised above the level of the skin between which there may be simple macular or papular elements and minute petechiae. The rash is soft, there is no shottiness, and it feels superficial. Severe measles may be the first diagnosis, and the resemblance to the early malignant rash is very close (Fig. 21). In measles the temperature will be higher at this stage. Although the appearance of the face will be quite like early malignant smallpox, examination of the chest and back will show typical measles lesions. The development of the measles rash over three days is also quite characteristic. Haemorrhages may occur in the mouth in both conditions, but are very much commoner in smallpox. There will be no Koplick's spots but smallpox lesions may be present on the buccal mucous membrane more particularly on the soft palate, and should not lead to confusion. Although there may be some laryngitis and redness of the conjunctiva, respiratory and eye symptoms of the kind seen in measles are absent at this stage.

Occurring in an adolescent or an adult the first diagnosis may be rubella. It is here that the classification into malignant and benign, and a sound knowledge of the various features in smallpox, are of such value. Confusion between the rashes is only likely to arise between malignant smallpox and rubella. In severe rubella in adults the temperature may be high with a fair degree of malaise. The rash, however, comes out quickly and is followed by an improvement in the general condition. In malignant smallpox the slow evolution and moderate temperature is quite different and the patient is very ill. Enlarged glands do not occur in this type of smallpox.

Maculo-papular drug eruptions may be confused with the early eruptive stage of malignant smallpox. They cause particular difficulty if the drug has been given for a pyrexial condition as the eruption may well appear about the third day of the disease. This is particularly true of some sulphonamide rashes where the papular elements may be quite distinct and the rash have a centrifugal distribution, even picking out pressure points along tendons. It tends to be photosensitive, but the rate of development is very rapid compared with the slow progress in malignant smallpox where the patient would have had to be ill for seven or eight days for a similar appearance. There are abrupt changes in density quite unlike smallpox. The patient should also have signs of the disease for which the drug was prescribed as well as the history of its use.

In the benign types the earliest lesions are discrete macules usually on the face and arms.

They rapidly become papular and when profuse appear early on the face and scalp (Fig. 67 and 77). In these benign rashes the shottiness of the lesions is apparent whereas the rosealar and papular syphilitic rashes are soft and lack uniformity in size and distribution. In syphilis a profuse rash on the face would be accompanied by a rash on the chest and abdomen of equal or greater density and the general symptoms are likely to be less severe.

When the lesions are accompanied by a large erythematous base as in mild attacks of variola major in the vaccinated and also in variola minor, the diagnosis may be papular urticaria (Fig. 98). This will only occur if the lesions are extremely scanty or examination of the body as a whole has been neglected as it is exceptional not to find some lesions more typical of smallpox. However, such "papular urticaria" following vomiting has not infrequently given rise to a diagnosis of "food rash", particularly in outbreaks of variola minor.

Occasionally multiple papular lesions due to insect bites may have to be considered, particularly in smallpox contacts. The history of possible exposure and the absence of an initial phase will go a long way to establishing the diagnosis, but the linear arrangement of the lesions so frequently seen in insect bites also occurs in mild smallpox along the site of trauma from scratching.

In extremely mild smallpox where the lesions pass imperceptibly from papule to small granuloma the similarity to acne may be very close. When the lesions occur on the arms and parts of the trunk not usually affected by acne the mistake is not likely to be made. Unfortunately, in some of the mildest smallpox cases only a few lesions may occur on the face and on the back, common sites of acne, and may be interspersed with genuine acne lesions. On the other hand, a contact who has never had acne and who suddenly develops this type of lesion should be regarded with suspicion. In a smallpox contact even with a history of previous acne, a typical initial phase will require explanation if the diagnosis is to be discounted.

Any of the elements of the focal rash may be scraped and examined for the presence of virus particles, but it is in the "difficult" cases that these are likely to be few and the result can at the best only be described as suggestive of smallpox and not conclusive. Scrapings can be cultured for virus and, if positive, establish the diagnosis. A complement fixation reaction may also be done using this material as antigen. If this is positive the diagnosis is between variola and vaccinia. A case of erythema multiforme gave a positive serological reaction (C.F.T.) for smallpox on two separate occasions (Marsden, 1954), so that caution should be exercised if the clinical progress is unlike smallpox. Blood culture should still be positive at this stage in malignant cases, but not in benign, and a negative result should not be regarded as of any significance. In malignant cases soluble antigen may also be present in the blood for the first five or six days (Downie *et al.*, 1953).

VESICULAR AND PUSTULAR STAGE

When the lesions are frankly vesicular the disease which gives the greatest trouble is chickenpox. There is generally no pre-eruptive phase in chickenpox, but when present it only lasts twelve to twenty-four hours. When the rash appears, the temperature does not drop as is usual in benign smallpox, the type most likely to be confused with chickenpox. Lesions may be quite profuse in the mouth, if anything more so than in smallpox with skin lesions of comparable density. In chickenpox these occur concurrently with the rash, whereas in smallpox they are seen best before the vesicular stage.

The most important difference is in the distribution so ably described by Ricketts (1908). The smallpox rash is centrifugal (Fig. 133), chickenpox essentially centripetal or casual. Smallpox lesions tend to be less profuse on protected parts in the flexures such as the axillae whereas in chickenpox the rash is indiscriminate on these areas. This peculiarity, the so-called Ricketts'

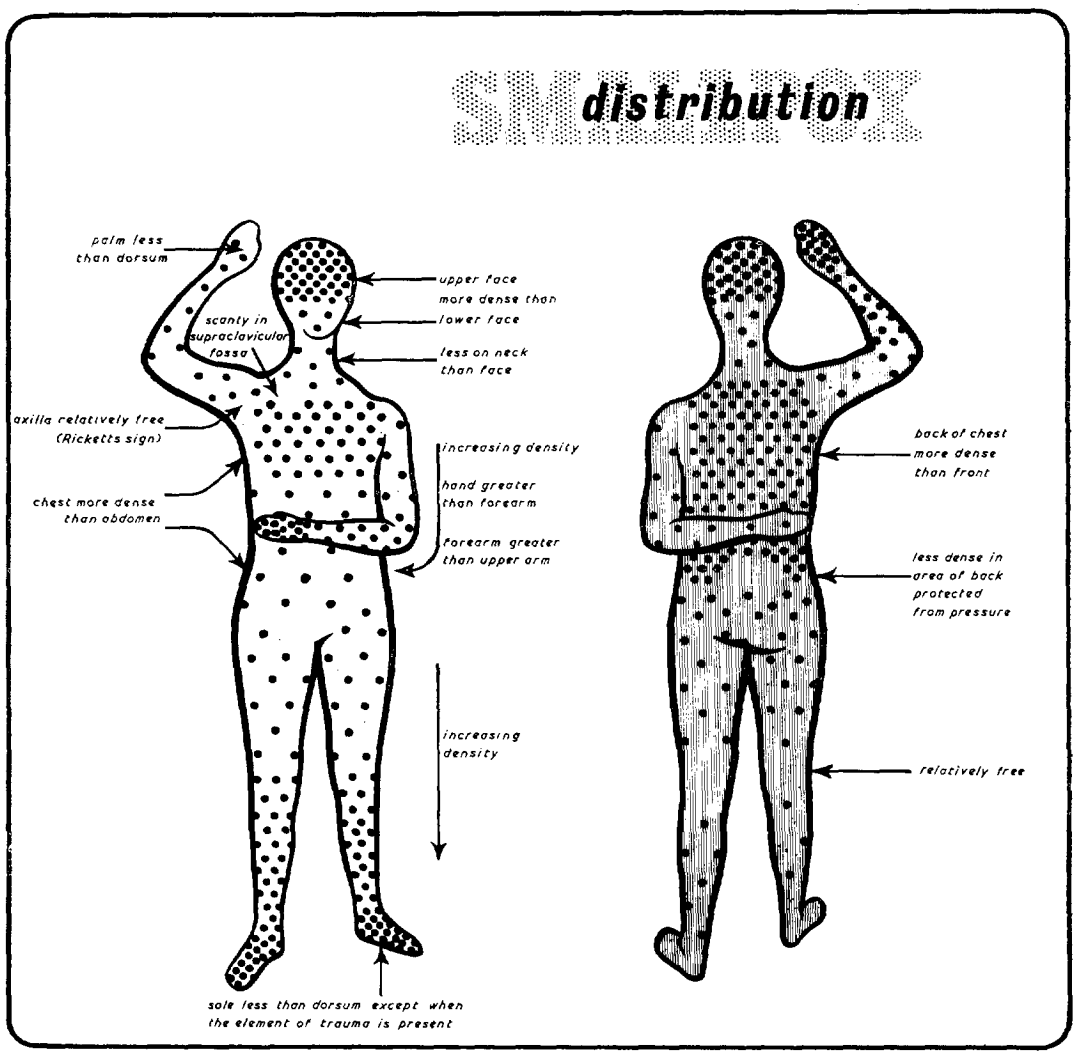

FIG. 133.

sign as Marsden (1936) points out, is often misstated to imply that in smallpox the rash is always absent from the axilla. Ricketts taught that whereas in chickenpox the rash is often present in the axilla, depending largely on the density of rash on the trunk, in smallpox the rash is *proportionately* very much less in the axilla than on nearby areas of skin. It is absent in most discrete cases, but in confluent attacks a few lesions are usually present (Fig. 134). The

evolution in chickenpox is very swift so that within a few hours the lesion becomes a very superficial vesicle followed by crusting and scabbing and successive crops appear over a period of four or five days or more. This is in complete contrast to smallpox where development is slow and orderly. Those cases of vaccino-modified variola major or minor, where the lesions evolve rapidly are unlike chickenpox lesions in the vesicular stage. In chickenpox the palms and soles usually escape, because in many cases the rash is not very profuse. When it is, however, the palms and soles may have extensive lesions and small seeds are produced as in smallpox, although somewhat more superficial. In the vast majority of cases differentiation is fairly

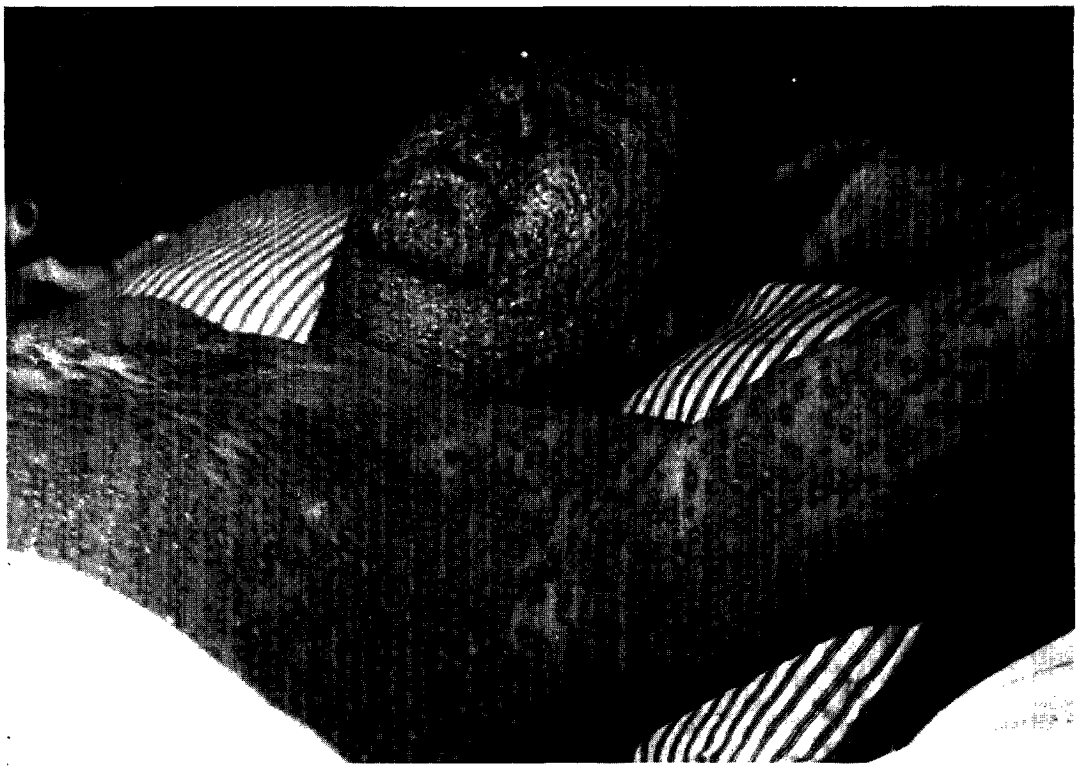

FIG. 134. Variola major, Type 4, seventh day. Note the axilla, Ricketts' sign, the rash here is not absent but less dense than in the surrounding areas.

simple. In the very severe confluent chickenpox the first appearance may be very like smallpox, the patient may be quite ill and the extent of the rash may at first confuse the distribution. The lesions are, however, soft, flat and superficial and therefore can only be those of chickenpox or late malignant smallpox. Haemorrhages may occur into the lesions in this type of chickenpox but a diagnosis of haemorrhagic chickenpox must be accepted with great reserve. However, it is when the lesions assume this appearance that is all important. Malignant smallpox will not show large flat superficial vesicles until at least the ninth or tenth day of the disease, whereas the chickenpox lesions will have developed in three or four days. Figs. 135 and 136 show the backs of a severe chickenpox and of a smallpox patient. The lesser density in the

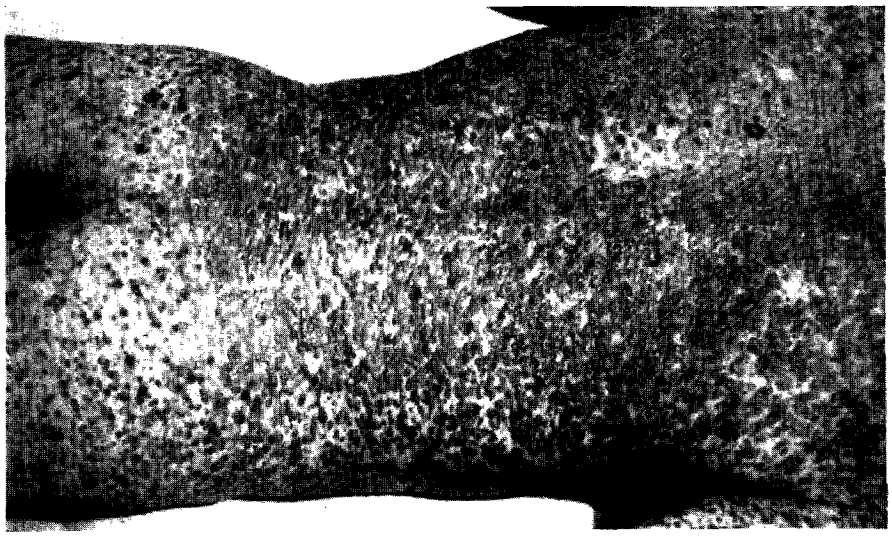

FIG. 135. Haemorrhagic chickenpox, dense rash in protected parts.

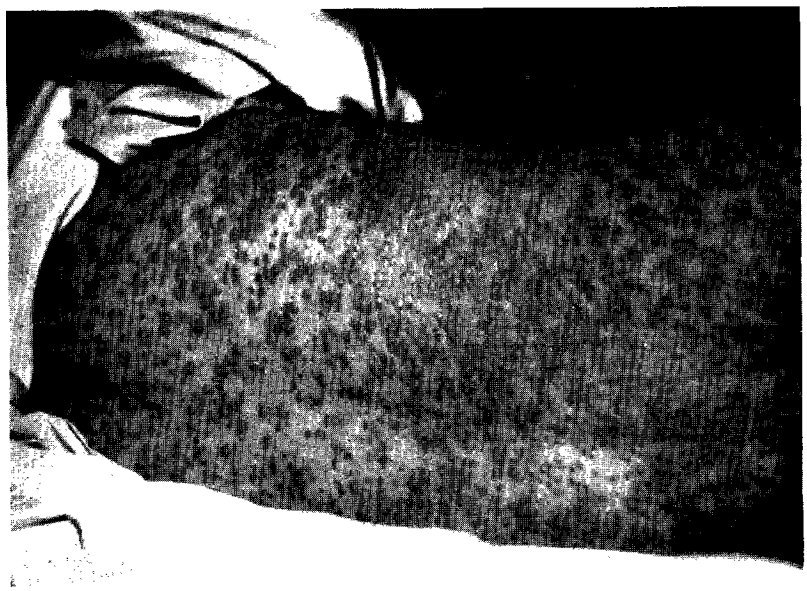

FIG. 136. Smallpox. Note less rash in area protected from pressure.

protected parts of the smallpox patient, in contrast to an increased density in the chickenpox patient, is well shown. The extent of the rash on the abdomen and chest would also be revealing, in chickenpox it being profuse, as much as the back, whereas in smallpox it would be very much less. If seen late in the attack distribution may be masked by separation of the crusts or by materials used in local treatment, especially calomine lotion. When chickenpox occurs in a person who has been sunbathing and becomes slightly burnt during the few days

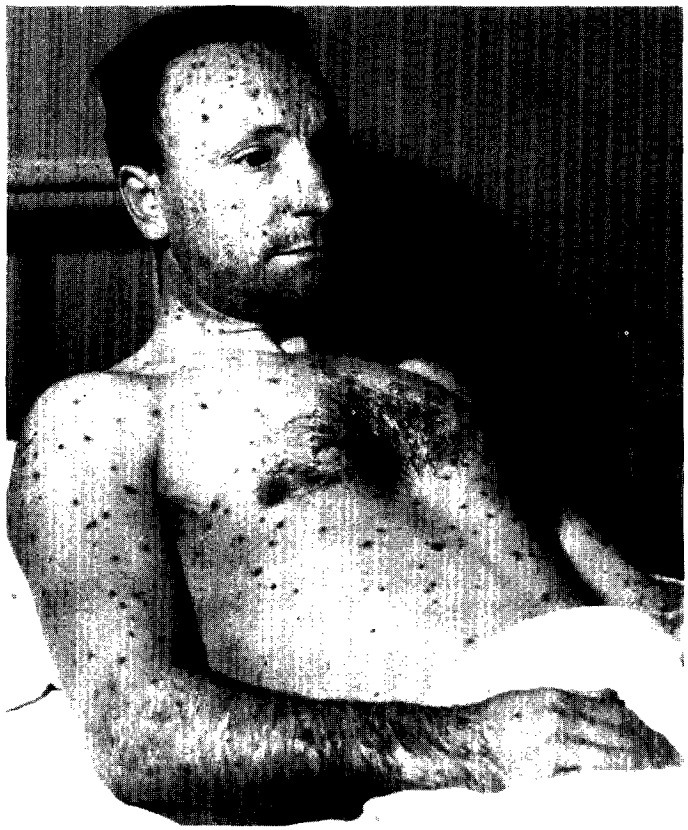

FIG. 137, Variola major, vaccino-modified, Type 7. Patient originally diagnosed as chickenpox. Lesions superficial, at different stages of development. See Fig. 104 for details of face.

preceding the rash, lesions may occur in great profusion on the face, arms, hands, legs and feet, and so present a centrifugal distribution. The rash on the face is like that of an early malignant rash, but the simultaneous appearance on the arms and legs is not consistent with this type of smallpox.

More frequently diagnostic problems occur over very mild attacks of chickenpox and mild, particularly vaccino-modified, attacks of smallpox. In modified smallpox the lesions are superficial, not shotty, dry up quickly with a small scab and leave a scar very little different from

chickenpox. In both, the lesions may be few, cropping of a kind present in both, and when seen late in the scabbing stage distribution may be the only real difference. The history, even allowing for the relatively rapid evolution in modified smallpox, may show that the lesions have developed too quickly to be smallpox.

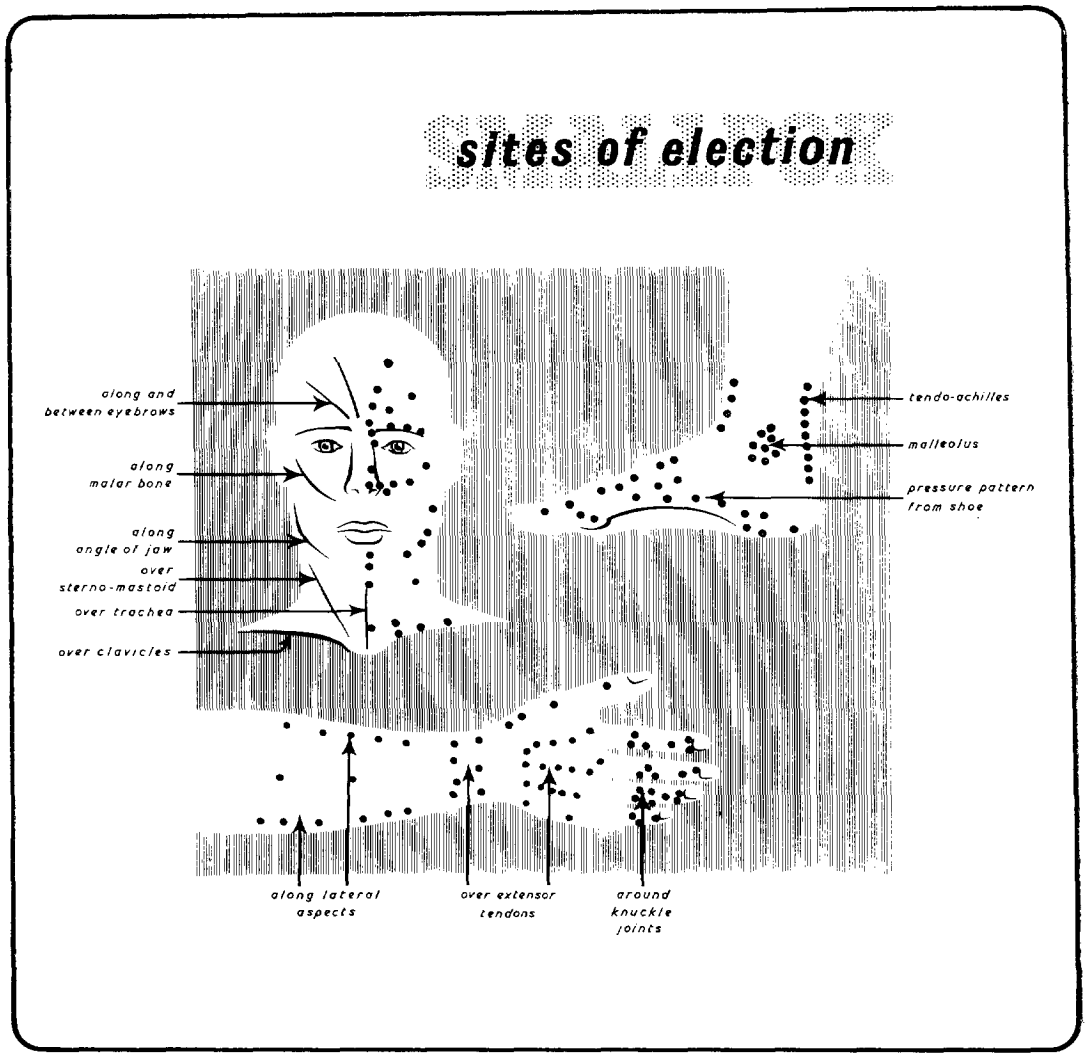

FIG. 138.

Such features as loculation or umbilication of the lesions are of little value as they are unlikely to occur in this type of case whether major or minor. If seen at an early vesicular stage the chickenpox vesicles are more likely to be irregular or crenated, whereas the modified smallpox vesicle is more circular. Although the smallpox lesions when scanty occur in greater profusion on slightly traumatized areas this can also occur in chickenpox and may alter the appearance

of the distribution. In chickenpox with very scanty lesions they tend to be of normal chickenpox size, in smallpox when the lesions are extremely few they are nearly always much reduced in size, particularly when there is residual vaccinial immunity. Irritation of the skin is a frequent symptom in chickenpox, but it is usually absent in the more profuse smallpox rashes until the scabbing stage. With some very modified superficial smallpox lesions irritation may occur in the early stages as in chickenpox.

It should be made quite clear that there is no part of the skin wholly exempt from either smallpox or chickenpox lesions and absence or presence on any part is not diagnostic of either disease as is so often stated. It is the relative density and the predilection for certain sites (the "sites of election", Fig. 138) in smallpox that is the diagnostic feature of real value. Trouble is caused because many observers think severe chickenpox is smallpox because it is severe, and very mild smallpox must be chickenpox because it is mild.

A disease which is causing increasing confusion in diagnosis is erythema multiforme and the Stevens-Johnson syndrome. In both the patient may be quite ill and have a profuse vesicular eruption particularly affecting the extremities so giving at first sight a centrifugal distribution. The history is quite unlike that of smallpox; onset of symptoms and rash tend to coincide and the rash evolves very rapidly to the vesicular stage. The vesicles are soft, superficial and flat. Individually they closely resemble the lesions in malignant smallpox. They may coalesce and produce large bullae also seen in malignant smallpox. Intervening skin is dissimilar and the degree of malaise is not like that seen in malignant smallpox where the patient at this stage has only about forty-eight hours to live. The most important difference is in the speed of evolution. In smallpox with this skin picture the patient will have been ill and getting progressively worse for at least ten days and the vesicular eruption will have only just fully emerged. The distribution is unlike smallpox in that, particularly on the limbs, there are abrupt changes in density of lesions from confluence to almost complete freedom from eruption. The profuse lesions on the mouth and on the conjunctiva with few on the face is also very much against the diagnosis of smallpox. Erythema multiforme, as its name implies, is very variable in its clinical picture. Only cases with a papulo-vesicular eruption are likely to cause any confusion.

Generalized vaccinia causes some difficulty. This complication of vaccination is considered very rare by most competent observers, and yet in smallpox outbreaks reports suggest that these cases are far from uncommon. Doubtless many are not generalized vaccinia at all, but merely a few secondary vaccinial lesions usually limited to the vaccinated limb or occurring as auto-inoculations. None of these cases should cause any difficulty as the lesions are local and in no way fit in with the general distribution of smallpox. Some individuals, however, have a general dissemination of virus with lesions in the skin and the diagnosis calls for much care as many of these patients are smallpox contacts vaccinated during the incubation period. At first sight the case resembles a mild, or type 7, smallpox. The individual lesions will not be different from those occurring in smallpox, particularly vaccino-modified or variola minor. They are much smaller than normal vaccinial lesions and mature much more rapidly. The distribution is the only valuable clinical sign. In generalized vaccinia of this type the lesions occur less commonly on the face and are proportionately less dense than on the limbs or trunk. Lesions are less common on the palms and soles and the distribution lacks the orderly gradation of density and follows no set pattern. Although in some cases, as in Fig. 139, the face and hands are heavily affected, there may be abrupt change of density even on a small area. One has, of course, to bear in mind peculiarities of distribution which occur in smallpox as a result of irritation.

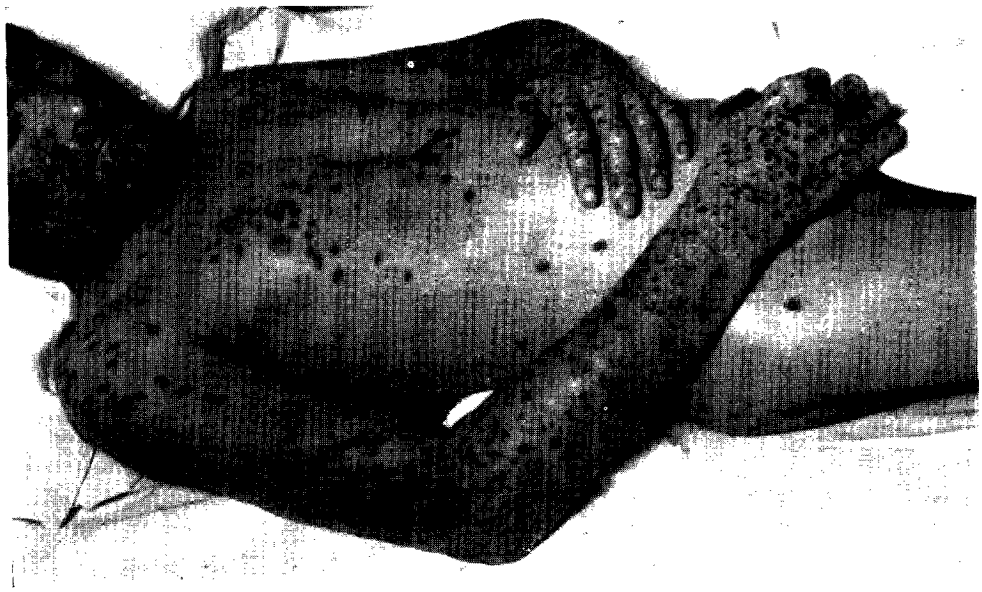

FIG. 139. Generalised vaccinia, irregular distribution, although extensive on the face the tip of the nose is unaffected.

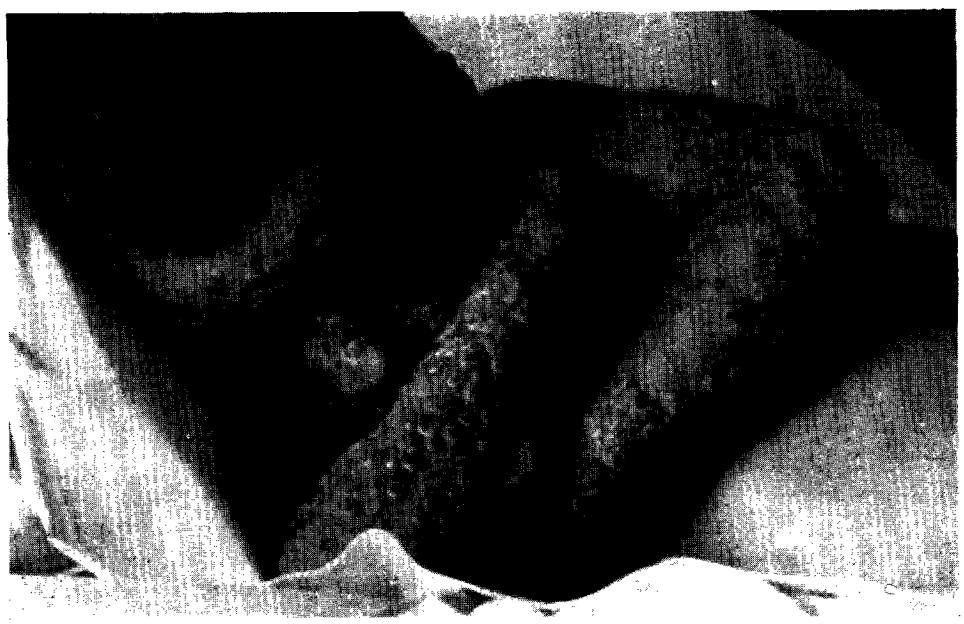

FIG. 140. Generalised vaccinia, soft, flat vesicles, irregular distribution, fatal outcome.

A second type of generalized vaccinia occurs in individuals suffering from infantile eczema. This condition may arise from vaccination of the patient or as a result of infection from some other individual recently vaccinated. Here the infection with virus may be quite severe, producing the picture shown in Fig. 140. The lesions are flat, and of the superficial type seen in malignant smallpox. This type of case is likely to be fatal. Although the individual lesions are similar to those that may occur in smallpox, once again the distribution is not. Although lesions may occur on any part of the body, including the face, there are sudden changes in density quite unlike smallpox. They show no tendency to avoid the flexures as it affects the eczematous areas, and on the face a dense eruption may be present in the orbital fossae with little on the nose. The widespread dissemination is probably due to some constitutional inability of the individual to produce an immunity response. Some of these cases are called Kaposi's varicelliform eruption, but this clinical picture may be due to the virus of herpes simplex or of vaccinia, necessitating laboratory investigation to give the correct diagnosis. Although described as varicelliform the individual lesions are remarkably like variola (see Chapter 19).

In cases of generalized vaccinia, particularly of the mild type, the laboratory can be of great assistance. With plenty of lesions it is simple to collect sufficient material for egg inoculation so that a definite distinction can be made between vaccinia and variola, but sometimes, virus may only be isolated on subculture, which may give a delay of up to six days. If there is any possibility of the case being smallpox the appropriate administrative action should be taken pending confirmation of the diagnosis.

Although one must repeat Wanklyn's (1913*a*) warning that vaccinial history may produce sufficient bias to trap the unwary, it is always desirable to obtain a history from the patient or relatives as to whether the patient has been vaccinated and when, but this must be substantiated by finding the scar. Although in some parts of the world subcutaneous vaccination is practised, most would agree that in the absence of a definite scar little value should be attached to a history of vaccination. The reading of revaccinations is much more complicated, and in the absence of a reliable record by a competent observer the clinician must keep an open mind, as many successful revaccinations leave such a superficial scar that it may not be visible with certainty after three months. Even a history of many repeated unsuccessful vaccinations should not be regarded as evidence of immunity.

From the diagnostic point of view it is important to appreciate that there is great individual variation in the extent to which vaccinial immunity persists. The person presenting symptoms suggestive of malignant smallpox who has had a successful primary vaccination within five years, is unlikely to be suffering from this type of smallpox and the probability of another diagnosis should be seriously considered. The presence of signs or symptoms suggestive of a very mild attack of smallpox should not lead one to discount the diagnosis even in the face of an apparently successful vaccination within a year, particularly with vaccine in current use. On the other hand, it is equally important to remember that exceedingly mild, even *sine eruptione* infections can occur in persons who have no evidence of successful vaccination at any time. In a person who has been vaccinated at the time of, or just after, possible contact, the diagnosis of generalized vaccinia should be made with caution, as recent experience has shown that vaccination performed even on the day of contact may not have produced sufficient immunity to prevent a mild attack of smallpox at first sight very like generalized vaccinia. In general, too much reliance has been placed on the vaccinial state of the patient in arriving at a

diagnosis. It is too readily assumed that there is residual immunity sufficient to prevent an attack, and therefore the present disease could not be smallpox.

A number of writers under different circumstances have recorded the proportion and types of disease mistaken for smallpox. Conybeare (1950) discusses this problem, and the following table has been made from his results:

Alternative diagnosis made in 112 suspected but unconfirmed smallpox cases, 1946–48 (England and Wales)

Final diagnosis	Number of cases	Final diagnosis	Number of cases
Chickenpox	41	Impetigo	3
Acne	10	Syphilis	3
Erythema multiforme	7	Herpes	2
Urticaria	7	Eczema	2
		Measles	2
Sensitization to drugs	6		
		Rubella	1
Vaccinia	5	Scabies	1
Septicaemia	4	Cheiropompholyx	1
		Dermatitis herpetiformis	1
		Psoriasis	1
		No diagnosis made	15

FIG. 141.

It should be noted that these cases were seen by a smallpox consultant after the patient had been seen by a general practitioner or hospital medical officer and by the Medical Officer of Health. During this period a number of cases of variola major occurred in England and Wales.

Marsden (1936) reported that of 994 cases seen at the receiving station during an epidemic of variola minor and ultimately considered not to be suffering from that disease, 307 (31 per cent) were cases of chickenpox and about 10 per cent were only suffering from the effects of vaccination. The remainder were a heterogeneous group, including the conditions mentioned by Conybeare. In the figures given by earlier writers, syphilitic rashes figured much more prominently. It can be seen that in England and Wales in the period 1930–50, chickenpox was by far the most important disease accounting for between 30 and 40 per cent of those cases which have been confused with smallpox.

LABORATORY DIAGNOSIS OF SMALLPOX

The earliest attempts to provide laboratory support for the clinical diagnosis were based on observations of the blood picture. The changes, however, are not characteristic in the more common cases, which tend to be of the benign semi-confluent or discrete types. Today with the use of virus culture and serology, examination of the blood cells is likely to be of little value except in fulminating (type 1) where it is a useful procedure and has the great merit of speed. Death may be extremely rapid without any external signs, or there may be extensive haemorrhages in the skin and other organs, but no focal rash. The main effect of

the toxaemia appears to be on the bone marrow, producing a blood picture which may help to differentiate this condition from some other form of acute infectious catastrophe, the problem facing the forensic pathologist. As described by Ikeda (1925) and more recently by Haviland (1952), there is thrombocytopenia and lymphocytosis with a marked granulopenia. Fragments of the nuclear bodies of polymorphonuclear leucocytes are seen, indicating recent infection. Although this blood picture is not pathognomonic of smallpox its presence in a patient dying suddenly, within seventy-two hours, from some obscure febrile condition with vague or no clinical signs or with purpura should warrant the sending of heart blood and skin to the smallpox virologist, and the public health officer should quietly attend to his aspects of the case. A normal blood picture would be against smallpox of this type.

It is well known that malignant cases show this type of blood picture in the early stages of the clinical attack, and this shows little change as the case develops, whereas in the benign case the initial leucopenia, by no means severe, is replaced by a leucocytosis with increasing number of polymorphs. Some writers have thought the difference of value in assessing prognosis, but the experienced clinician can judge very easily directly from the patient's appearance.

Councilman (1904) believed that a biopsy of the skin could provide evidence of smallpox infection, but the method does not appear to have received any general support until revived by de Jong (1955) for variola minor. He believes that frozen section biopsy can assist the clinical diagnosis within about thirty minutes, and an ordinary preparation should not take more than twenty-four hours. There are no histological differences between variola major, variola minor and vaccinia, and its chief value is the differentiation between variola-vaccinia and varicella. The method is only really of value in the very early eruption, when in variola the cell degeneration is reticular, there are sporadic polynuclear giant cells, thickened epidermis in the border area and heavy lymphocytic infiltration, in contrast to varicella, where ballooning degeneration predominates, there are numerous polynuclear giant cells, no thickening of the epidermis, and little lymphocytic infiltration of the corium.

The virus is present in considerable amounts in petechiae, macules, papules and early vesicles and scrapings made from these may be examined under the oil immersion lens after staining with Paschen's, Gutstein's, the Feulson reaction or similar techniques. Although particles were recognized by Buist (1886) and Paschen (1906) and this method has been known and used on and off for a number of years, "it was revived and considered favourably" by van Rooyen and Illingworth (1944), by Illingworth and Oliver (1944) and de Jong (1956). In my experience those cases where the test is clearly positive can be diagnosed by any moderately proficient clinician. The disadvantages of the method are the need for considerable experience in the observer and for specimens free from cellular debris. It is therefore of no value in the late vesicular, pustular or scabbing stages and of limited value, for these reasons, in lesions which mature rapidly, such as abortive lesions. Vaccinia cannot be differentiated from smallpox, and chickenpox has to be differentiated principally on the numbers of stained granules present and not on any characteristic differences in size or structure. For this reason it is also necessary to have controls of typical smallpox and typical chickenpox slides for comparison. The clinical "problem case" with abortive lesions will, however, give just those few granules which are so unconvincing. The advantage, however, of an opinion within half an hour should not be overlooked, but the clinician must take the responsibility and the virologist must resist the temptation of being too dogmatic either way. Even a smear showing large numbers of granules

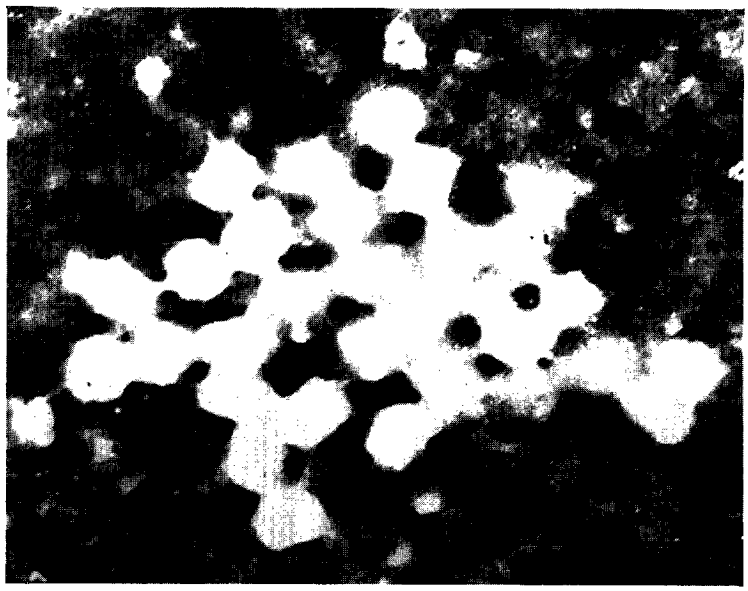

FIG. 142.

Smears from vesicles made under field conditions.
The virus particles are recognizable for diagnostic purposes.

FIG. 143

thought to be elementary bodies does not confirm the diagnosis. In those countries where the pathologist is very experienced in reading this type of slide, his clinical colleague will also be experienced.

The development of electron microscopy has opened up the possibility of identifying the structure of the virus more exactly, and in the hands of some workers (van Rooyen and Scott, 1948; Lepine, 1954) the results are regarded as diagnostic (Figs. 142 and 143). The latter is confident that with fifty particles he can differentiate on particle size between variola and vaccinia, but other virologists do not accept this. Results should be interpreted in a similar manner to those obtained from stained specimens. Should our experience and techniques advance so that exact and certain identification is always possible, then the method will be of great value because of the speed with which it can be done. It is, however, slower than the direct smears and requires between four and twenty-four hours for the preparation of the material, depending on the technique and the amount of contamination.

The most certain method in the laboratory diagnosis of smallpox is culture of the virus on the chorioallantoic membrane of the hen's egg. Smallpox lesions, when in sufficient number, are of characteristic size and density to allow a differentiation between smallpox and vaccinia and smallpox and herpes. The chickenpox virus does not grow on egg culture. Positive blood culture may be obtained during the initial stage, and although the chance of this being obtained is quite high in fulminating and malignant cases, in the milder forms of benign smallpox the stage of viraemia is very short, a matter of a few hours, and may be missed. Virus has been grown from throat washings (Verlinde and van Tongeren, 1952), but a great deal more experience is required to see if this will have any practical bearing on the detection of early infection in contacts. Downie was unable to isolate virus from contacts in the Cheshire outbreak in 1958 (Pierce *et al.*, 1958).

Virus can be readily grown from the skin and, particularly in the fulminating and malignant types, from the "normal" skin as well as from petechiae, ecchymoses, macules, papules, vesicles, pustules and scabs.

Although laboratory tests can be applied to variola major and variola minor, it is in variola minor that so many cases can occur with less than five lesions, and it is in these, as MacCallum (1953) has stressed, that the test may be negative because insufficient material is sent to the laboratory.

Another difficulty which may arise is that although variola major and variola minor normally give the same type of lesion on the chorioallantoic membrane, there is more variation in size with variola minor and in some cases the colonies may be very small, closely resembling those of herpes simplex. In this case it will be necessary to carry out the additional procedure of histological examination of the egg membrane, when the lesion caused by the two viruses can be readily distinguished.

One disadvantage of egg culture is the necessity of having to keep incubated fertile eggs at ten to twelve days incubation always available and the need to inoculate a sufficient number of eggs. Apart from the desirability of this specialized work being in the hands of an experienced virologist, the economics of egg culture necessitates that this examination be done at relatively few laboratories. Unfortunately this means that, in many countries, at least one extra day will elapse before the specimen can reach the laboratory from the clinician. Growth should occur in three days from the time of receipt in the laboratory. Sometimes only one pock colony occurs and this necessitates subculture which brings the time up to six to seven days. Virus

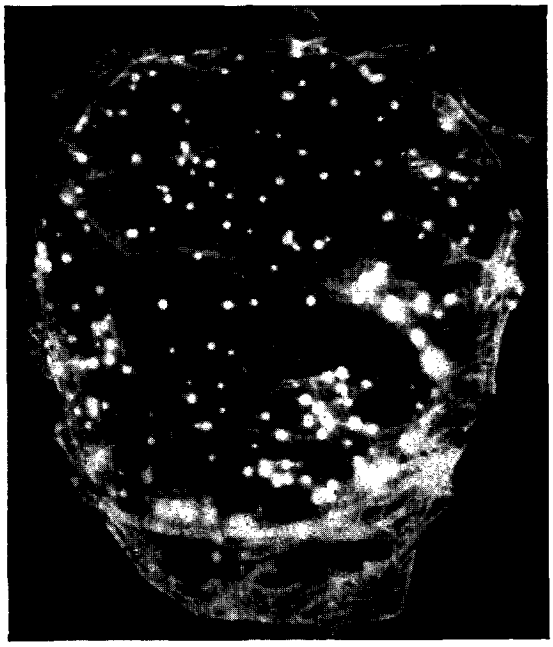

FIG. 144. Chorioallantoic membrane, smallpox.

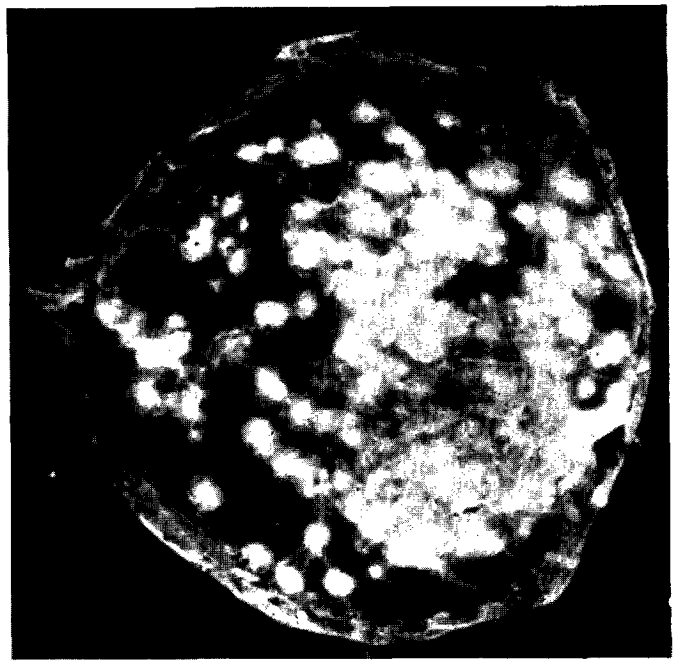

FIG. 145. Chorioallantoic membrane, vaccinia.

culture is of greatest value where it can be used for examination of the blood in the initial stage, examination of the earliest lesions in the malignant, and examination of abortive lesions in the exceedingly mild. Downie *et al.* (1953) point out that infective virus may disappear if kept in the refrigerator and that blood should be examined as soon as possible. It is also important for the clinician to send the virologist sufficient material.

In 1950 MacCallum *et al.* suggested soluble antigen might be tested for in early smallpox, and Downie *et al.* (1953) have reported its presence in the patient's blood. This is done using a complement fixation technique and antivaccinial rabbit serum. Antigen can be demonstrated simply using the Ouchterlony precipitation technique (Dumbell and Nizamuddin, 1959). One advantage with this test is that the result should be available within twenty-four hours of material being received in the laboratory. Soluble antigen is, however, only present in fulminating and malignant cases and has not been observed in any benign forms of smallpox. Although the test has not yet been given any extensive trial, it would appear to be a definite improvement in our technique for the early diagnosis of fulminating and malignant cases. It is not known what effect, if any, will be produced by concurrent vaccination, which in this type of case is frequently negative.

The next most widely used test is the complement fixation test using material from the patient likely to contain virus as antigen and put up against immune rabbit serum. A fair quantity of material is needed, at least six "crusts" or one capillary tube from vesicles or pustules. It may be difficult to obtain this amount in some very early cases except *post mortem*, when a piece of skin is likely to give a positive result. Sufficient material can be obtained from scabs, pustules and vesicles when there is any degree of eruption, but in abortive cases the collection of sufficient antigen may be extremely difficult if not impossible. A result may be available later the same day or early the day following receipt of material (MacCallum, 1953), while most other writers prefer to say within twenty-four hours. In the view of Tulloch (quoted by van Rooyen and Rhodes, 1940), the procedure of holding at 4° C. for at least eighteen hours is extremely important in maintaining the sensitivity of the test and should not be reduced. A positive result will indicate that antigen of smallpox, vaccinia, or cowpox has been identified. A negative result is significant if sufficient material has been tested, but if the quantity is small should be regarded with caution. This test will not differentiate between smallpox and vaccinia and should not be used where there is concurrent vaccinia without appreciating its limitations in such a case.

After the seventh day of illness antibodies may appear in the serum of the patient and should normally be present by the tenth day. In variola minor the complement fixation test may not be positive until the tenth day, although virus-neutralizing antibodies may be present in the serum as early as the fifth day. The earlier flocculation test of Craigie and Tulloch (1931) has given way to the more general use of the complement fixation test using variola or vaccinia antigen. Complement-fixing antibody remains for at least nine months after vaccination (MacCallum, 1953), but its final duration is not really known. Downie and Macdonald (1953) suggest up to a year and van Rooyen and Rhodes (1940) over a year. Clarification is required if this test is to be of value in the diagnosis of *sine eruptione* infections in fairly recently vaccinated persons. In a smallpox contact whom I saw the clinical signs were quite unlike smallpox, and he was ultimately proved to have a bacterial infection, but it seemed possible that a C.F.T. titre suggestive of infection might have been due to residence in an endemic area and repeated vaccination, although the last had been done some four years previously.

It is not known whether in highly vaccinated persons an anamnestic reaction can occur due to some other stimulus. Further information is required on this point, but obviously strong clinical evidence against smallpox would have to be present to disregard high titres more than one year after vaccination. In the technique used by McCarthy and Downie (1953) a titre of 1 in 10 is regarded as indicating infection. Convalescents, however, show much higher titres, 1 in 80 being not uncommon.

In some infections with vaccinia the complement fixation test remains negative whereas the anti-haemaglutinin antibody shows a considerable rise (MacCallum, 1953). In one paper by Collier, Smit and von Heerde (1950) and abstracted by Bauer in the *Bulletin of Hygiene* (1951), titres of anti-haemaglutinins were investigated in 800 patients with smallpox and in 3,000 individuals who had been vaccinated or revaccinated. Although an average value of 1/149 in those revaccinated less than one month previously was obtained, the titre fell to an average of 1/40 after an interval of seven to twelve months. In a person suspected to have smallpox these writers are of the opinion that a titre of 1/100 in an unvaccinated person, of 1/800 or higher in a person vaccinated three or more years previously, or of 1/3200 or higher in any circumstances, all establish a diagnosis of smallpox. These figures were obtained with variola major. McCarthy's and Downie's (1953) figures for variola minor were between 1/40 and 1/320. (A difference in technique accounts for their values being one-third of Collier *et al.*'s.) Although more complicated to do than the complement fixation test, Collier *et al.* (1950) think that the test is of considerable value. The level of anti-haemaglutinins does not run parallel to the level of virus neutralizing antibody and there is no proof that even this measures the level of the patient's real immunity to disease. Downie (1951) quotes a case of Bradley's where a nurse vaccinated two years previously and possessing a considerable titre of neutralizing antibody immediately before exposure, contracted a very mild attack of smallpox. The detection of virus neutralizing antibody is more complicated in that titration must be done on the chorio-allantois and it is therefore not the type of test that can be easily used as a routine. On the other hand, antibodies can be detected as early as the fifth day, and it may therefore be of advantage in the diagnosis of certain cases of sine eruptione infections. McCarthy and Downie (1953) consider the order of reliability of these techniques for antibody estimation is first neutralization, second anti-haemaglutinin, and third complement fixation.

Time-honoured tests like Paul's test (1919) should no longer be required. At no time did this test give 100 per cent positive results, and if it has to be used because other facilities are not available, this fact should be borne in mind. Other animal inoculation techniques are now displaced by the superior procedure of egg inoculation.

The Tièche (1918) test has recently been revived by Kaiser (1950). In this a volunteer, by a process of repeated vaccination of the skin several hundred times, achieves a state of hypersensitivity. Material from the skin of a suspected case of smallpox is ground with 70 per cent glycerine in a mortar and the material placed in a capillary tube and immersed in boiling water for five minutes. A control is made in a similar manner using vaccinia. The test and control material are applied to the scarified skin in a similar manner to vaccination. If the material contains smallpox antigen an allergic response should be present in the skin within five hours of inoculation. Little information seems to be available on sensitivity, but it seems of doubtful value in variola minor and its use seems likely to be limited to the smallpox enthusiast!

Below are set out the practical procedures necessary in collecting and despatching specimens. The procedure is that advocated by MacCallum (1952) and recommended by the Ministry of Health, England (Circular Port Med. 21 1953), and in a memorandum on the Diagnosis of

Smallpox, 1957. Information has been added on the removal of specimens from infected surroundings.

APPARATUS REQUIRED

(1) A dry, sterile 10-c.c. syringe and needle for venipuncture. A dry, sterile rubber corked test-tube for specimen of blood.

No citrate or other material must be added. Haemolysis must not occur.

Virus culture, detection of soluble antigen and other serological tests can be done on such a specimen.

(2) Hagedorn or similar needle in a sterile test-tube.

Needle is used to scrape petechiae or papules, open vesicles and pustules, or lift crusts. After use the needle should be replaced in the sterile tube and sent with the specimens.

(3) Capillary tubes similar to vaccination lymph tubes to remove fluid from vesicles by capillary action. Both ends of the tubes should be broken to allow fluid to enter.

Tubes are to be replaced in a small screw-capped bottle.

(4) Six clean glass slides should be provided in a small box or with interlaced pieces of card and rubber bands so that they can be packed without damage to the surface.

Smear surface of the slide on to the exposed base of the lesion from which debris, vesicle roof, crust or other material has been removed. At least two areas of each slide should be smeared and allowed to dry in the air without heat. Use all the slides on as many lesions as possible.

(5) Small bijou screw bottle to hold scab material. About twelve scabs should be collected if possible.

All these could be placed in a metal container such as an ordinary commodity tin with removable lid and in this form can be removed from the smallpox ward. The metal container, the outside of which as well as the inside will potentially be infectious, can then be placed into a strong lined cardboard or metal box to suit the local postal regulations, held by another person at the clean side of the infected/clean boundary and sealed by the latter so as to minimize the chance of spread of infection. The sealed container can be further wrapped in impervious material such as polythene and then travel by the speediest means available and will only be opened when it arrives at a laboratory *prepared* to handle smallpox material.

An increasing use is made of laboratory examinations and care must be exercised to see that infection is not conveyed by the methods of transit. There appear to have been one or two instances of infection conveyed by letters. It is possible, however, that as much of the material sent to the laboratory is, from the beginning, thought to be negative a somewhat casual handling of the specimen may occur. Unfortunately, sooner or later a specimen will be transmitted which will be a positive one. Most countries have regulations regarding the transmission of infective material and there is no doubt that smallpox virus is one for which we should maintain a healthy respect.

A further very practical, but sometimes neglected, point about the laboratory diagnosis of smallpox is that the laboratory which handles this material must have completely protected personnel. Smallpox in a diagnostic laboratory worker, which fortunately only spread to his brother, occurred in England and Wales in 1949. Laboratory staff, doctors, technicians, clerical workers and cleaners must be vaccinated and revaccinated at appropriate intervals, so as to maintain a complete barrier of immunes. It is particularly important that cleaners, either of premises or of laboratory equipment, should be adequately protected *before* they undertake any work of this kind, even if this means paying them for a fortnight and excluding from work

until their vaccination reactions have been properly inspected and approved, a policy found necessary in hospital personnel by Ricketts as long ago as 1893.

POST-MORTEM APPEARANCES

In the past, most writers, including Councilman (1904), Ricketts (1908) and even quite recently Burnet (1945), assumed that many of the deaths from smallpox were due to secondary streptococcal infection. As discussed previously, deaths not directly due to the virus but to septicaemia and pyaemia do occur depending on local environmental conditions. Although haemolytic streptococci have been isolated from a wide range of tissues at post-mortem, as I pointed out before (1948), virtually all the fulminating and malignant cases die from the effects of the virus alone. The benign confluent die from a combination of smallpox and some complication such as broncho-pneumonia. In other types death is directly due to some complication or intercurrent infection, the smallpox attack being a contributory factor or precipitating cause. Encephalomyelitis is a direct result of the smallpox attack and is not a secondary effect.

Although it is usually assumed that most patients die from toxic myocarditis, pathological changes supporting this are rarely seen (Bras 1952*b*). I think one must recognize that the virus acts on a wide range of cells in many organs, interfering with function without necessarily producing effects demonstrable by our current examination techniques. In our present ignorance of the cell changes, one can only say that the patient dies from general toxaemia.

Secondary causes of death are: (*a*) broncho-pneumonia, (*b*) streptococcal septicaemia, (*c*) staphylococcal septicaemia, (*d*) pyaemia, (*e*) multiple staphylococcal abscesses, (*f*) osteomyelitis, (*g*) empyaema.

The following information on post-mortem appearances is given to assist those who may be called upon to identify smallpox after death. Cutaneous appearances may change rapidly and profoundly after death. Marsden (personal communication) quotes Pereira: "Never make a diagnosis on the external appearance of a corpse." This is sound advice, particularly when laboratory facilities such as virus culture are available, but for administrative reasons a diagnosis must frequently have to be made without waiting for laboratory confirmation of smallpox. Deaths usually occur in fulminating cases between the first and fifth day of the disease, in the malignant between the tenth and fourteenth day, and in other types principally due to complications arising between the fourteenth and twenty-first day. Infants and the aged and infirm may die at other periods of the disease, but more often this is not directly due to smallpox but to complications or some other disease.

	Fulminating 1–5 days	*Malignant 10–14 days*	*Benign 14–21 days*
Skin	Few petechiae, often on face to *purpura variolosa* with very extensive haemorrhages particularly dense in the groins	Exfoliative eruption. Gross haemorrhages in the skin	Pustular rash to scabbing stage, there may be boils, pyaemic abscesses, etc.
Mucous membranes			
Mouth	Occasional haemorrhagic blebs on the soft palate or more general petechiae	Extensive ulceration of mucous membrane, some sloughing with a diphtheritic appearance	No specific lesions
Tongue	Occasional early erosions, often no change	Ulceration, particularly posterior part	No lesions

Mucous membranes—continued	*Fulminating 1–5 days*	*Malignant 10–14 days*	*Benign 14–21 days*
Trachea	Sub-mucous haemorrhages, small erosions in the mucous membrane	Ulcerative lesions in trachea and larynx covered with evil smelling glairy fluid	Depending on secondary complication as in broncho-pneumonia
Oesophagus	Occasional petechiae or nil	A few ulcerative lesions at upper end. May be no change	Nil
Alimentary Canal	Sub-mucous haemorrhages. May be free blood in the stomach	Nil—occasionally blood in the stomach	Nil
Serous membranes:			
Pleura and Peritoneum	Occasional petechiae	Nil	Nil. Peritoneum normal, sometimes empyaema
Heart	Normal or occasional subserous or sub-endocardial haemorrhages	Normal	Normal (apart from the effects of complications)
Lungs	Slight hyperaemia in bronchi, oedema	Little abnormal, occasional blood and mucus from lesions in trachea	Signs of broncho-pneumonia when this is the cause of death
Liver	Normal or slightly enlarged, pale	Slightly enlarged or normal	Slightly enlarged
Spleen	Normal, firm, or slightly enlarged, white or yellow follicles	Normal	Normal or septic spleen depending on complications
Ovaries	Occasional haemorrhages	Occasional haemorrhages	Nil
Testes	Occasional haemorrhages. Small microscopic foci	Small microscopic foci	Microscopic foci present or absent depending on stage of disease
Kidney	Haemorrhages in substance and renal pelvis and retroperitoneal haemorrhages	Haemorrhages in substance and renal pelvis	Nil
Uterus	May be haemorrhages in uterine cavity	May be haemorrhages in uterine cavity	Normal
Brain and Cord	Occasionally slight oedema	Nil	Nil except in death from encephalomyelitis
Blood	Leukaemic blood picture	Leucopenia and lymphocytosis	Normal or leucocytosis, depending on complications
Bone marrow	Dark red, liquid	Dark red	Nil
Laboratory investigation	Blood, skin, liver, etc., should yield virus on culture. Soluble antigen should also be present	Skin yields virus on culture. Scrapings should show virus on electron microscopy and give positive C.F.T. Soluble antigen may be and C.F. antibody should be present in serum	Skin lesions will yield virus on culture and may show virus on electron-microscopy. Scrapings will give positive C.F.T. for variolavaccinia. Blood will show antibodies in high titre.

It should be stressed that in the fulminating case death may occur within forty-eight hours. Extremely little abnormal will be seen *post mortem* and laboratory investigations are essential if one is to avoid missing the diagnosis in this type of case.

CHAPTER 5

Complications Treatment and Nursing Sequelae

COMPLICATIONS

THE SKIN

Although the process of pustulation is a normal stage of certain types of smallpox, as mentioned previously "pustulation" is a descriptive term applied to the appearance of the rash and it does not necessarily follow that the lesions contain frank pus. In many cases these pustules

FIG. 146. Septic type of pustulation, particularly on the arms, and face, common in the neglected and undernourished.

dry up quickly and without any marked septic reaction of the skin, particularly in the well-cared-for and nourished patient. However, fifty years ago, Ricketts (1908) and others regarded frank sepsis in the lesions—"thousands of boils"—as normal, and this also tends to occur today in tropical and subtropical countries, particularly where the hygiene is poor.

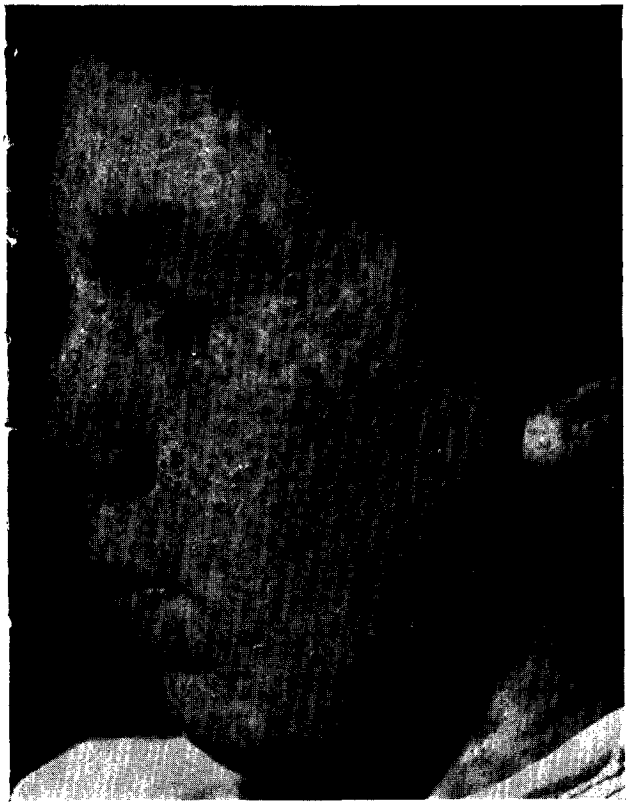

FIG. 147. Variola major, terminal stage of facial scabbing. Secondary eczematization of scar area. This scaling is not infectious.

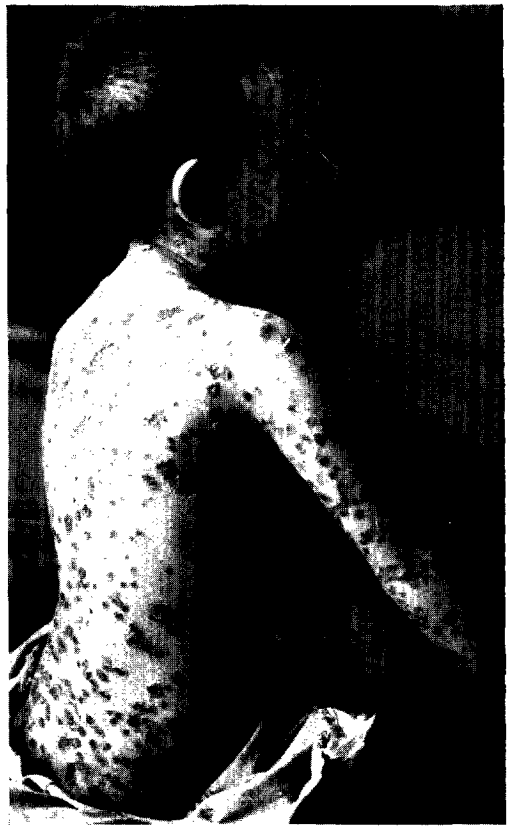

FIG. 148. Secondary sepsis.

FIG. 149. Variola major, discrete. Bullous lesions on the face due to secondary infection.

The division, therefore, between sepsis as an inherent part of the disease and as a complication will depend much on the experience of the observer. It is, however, of importance as sepsis can be controlled by the use of suitable drugs, but in many areas of the world supplies of these may be inadequate and only those patients who really need them should be so treated.

Many English writers during the last hundred years have commented on the apparent decrease in "septic" complications in their experience compared with the experience of their

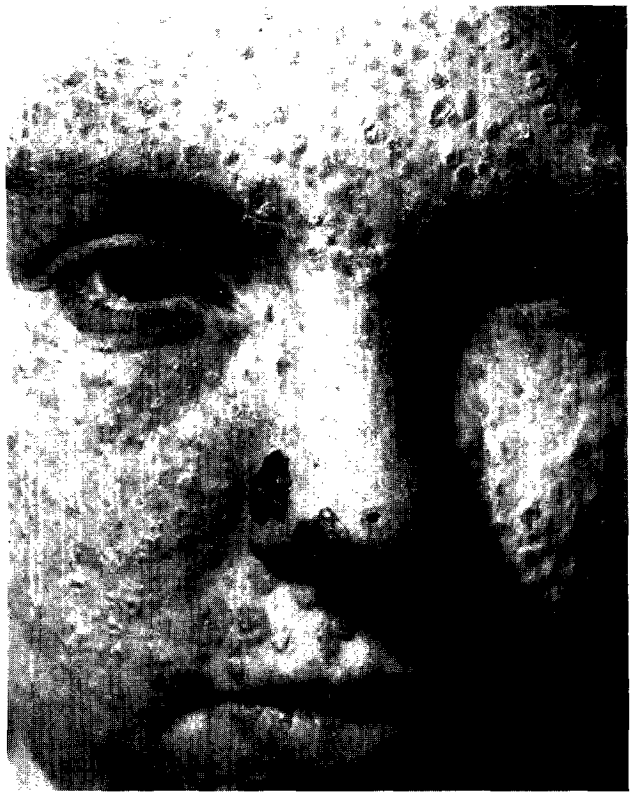

FIG. 150. Variola major, secondary eczematization, face.

immediate predecessors. Even without modern control by chemotherapy, one cannot but feel that the incidence is partly dependent on personal and environmental hygiene and is possibly also affected by the nutritional state of the patient. Because of this, it is very difficult to give general figures for the frequency of such complications.

In some of the outbreaks in the nineteenth century, 30 per cent or more of patients suffered from boils and abscesses. In Tripolitania about 8 per cent of cases of types 4–6 (variola major) were affected. Millard (1892) remarks on the frequency of this complication without giving any figures and comments on a man who had fifty-two boils, twenty of them appearing within three days. He drew attention to the fact that although described as a boil many

of these lesions appear very rapidly and without the central core usually associated with a boil, and are more in the nature of a localized suppuration in the subcutaneous tissues. Prior to the use of chemotherapy, treatment of these was difficult and led to a very protracted convalescence.

Marson (1866) relates how previous injury may cause localization of deep-seated inflammation such as an abscess between the large muscles.

Although in variola minor the patient usually feels well once the rash appears, septic complications are by no means as rare as one might expect. Robertson (1913) found boils and superficial abscesses frequent, even in the mildest cases, and impetigo often affected the lesions on the forearms, wrists, backs of hands and feet. Marsden (1936), in his very large series, had 3·6 per cent with boils, 2·3 per cent with secondary septic dermatitis, and 0·95 per cent with whitlows on fingers and toes. There were a few deep abscesses and four cases of fatal pyaemia.

In many cases the skin on the face and arms may be the seat of secondary eczematization soon after the scabs have separated and dry eczematous crusts appear (Figs. 149 and 150), which, however, should not be regarded as infective material. If the condition is not treated chronic eczema may occur in those individuals susceptible to this condition.

The pockmarks or scars on the skin following certain types of smallpox is normal, but in some cases a keloidal hypertrophic scar occurs and this would appear to be commoner in those with pigmented skins. Scarring on the face may cause blocking of the sebaceous glands and lead to an intractable acne-like condition.

Alopecia, partial or complete, may follow severe smallpox affecting the scalp. The effect is partly due to direct destruction of hair follicles, but the complete form is really "secondary", as smallpox lesions never destroy all the hair follicles. In some cases, after much of the hair is lost, luxurious regrowth occurs. The age and sex of the patient also influence the final outcome.

RESPIRATORY

Respiratory complications are rarer in smallpox than in most other acute exanthemata. Broncho-pneumonia does occur, particularly in infants and the aged and infirm, but the incidence seems largely dependent on nursing conditions, overcrowding in home or hospital, climatic conditions and the virulence of prevailing secondary organisms, such as streptococci, or the presence of concurrent community infections such as influenza. The complications are more serious in a debilitated smallpox patient than in a normal individual. The physique and history of previous respiratory disease will also affect the possibility of this complication. The treatment and prognosis appears to be no different from that of secondary broncho-pneumonia as a complication of other diseases. In the early nineteenth century, according to Gregory (1838), pleurisy was a frequent complication between the twelfth and twentieth day characterized by sudden onset progressing to empyaema, usually fatal. This condition does not appear to be associated with smallpox today. Bras (1952*b*) in his large series of autopsies makes no special note of this condition. The presence of respiratory symptoms in the "pulmonary allergy" type of "illness of contact" syndrome in some individuals has been mentioned before.

Tracheitis and laryngitis and a certain amount of bronchitis are not complications, but a normal feature of types 2 and 3 and to some extent in types 4. Laryngeal oedema and

obstruction may occur occasionally and can be a cause of death. If patients are nursed in large wards there is always a risk of tonsillitis or intercurrent infections of the throat.

ALIMENTARY

Alimentary symptoms and complications are conspicuous by their absence if one excludes the tongue, mouth and oesophagus. Although Sydenham (1685) and others wrote of *variola dysenterica*, implying smallpox lesions in the gut, I do not think it really exists. In any large series of cases, particularly in hospitals, diarrhoea is quite likely to occur, but this will almost certainly be due to infection with dysentery or salmonella organisms, or it may be due to some pre-existing functional condition of the bowel.

EYE

Frequently there is an eruption on the eyelids, particularly along the lid margins. Much swelling may occur, particularly in benign smallpox, making it difficult for the patient to open the eyes for the physician to examine them (see Figs. 63 and 86). It is for this reason and not because of keratitis or corneal ulceration that there are many references in the old non-technical literature that a person was "blind with smallpox". Dr. Dover (1732) wrote of his own attack of smallpox treated by Sydenham: "I went abroad by his direction, till I was blind, and then took to my bed." In the malignant types there may be many lesions, but there is no oedema, rather dehydration and sinking of the eye (Figs. 24 and 41). Often there is much lachrymation and discharge which may appear mucopurulent. Frequently there is a mild conjunctivitis, but this is a normal accompaniment of smallpox, occurring from the fifth day onwards, and it is of no special significance.

Pocks occur on the palpebral conjunctiva but much more rarely on the ocular. I formed the opinion from experience in Tripolitania that previous eye disease such as trachoma greatly increases the liability to localization of lesions on both the palpebral and ocular conjunctivae, and also appeared to increase the likelihood of other eye complications. Lesions themselves, even on the ocular conjunctiva, do not appear to do any harm and heal without complications. When they do occur on this site they are usually between the inner canthus of the eye and the corneal margin, or more rarely between the outer canthus and the corneal margin. In both these sites the conjunctiva is thicker than elsewhere (Fig. 78). Occasionally secondary infection of the palpebral lesions with severe scarring may lead to ectropion.

Pocks do not occur on the cornea. The only exceptions to this absolute rule are in extremely rare cases where there is previous disease with vascularization of the cornea. The lesions causing blindness do not arise from "pocks", but from corneal ulceration which commences at about the fourteenth day of the disease. The ulcer starts at the corneal margin and rapidly spreads across. In some cases healing occurs immediately behind the advancing lesion and the resultant opacity is very slight or may disappear. In other cases ulceration is deeper and perforation may occur with a resultant staphyloma or panophthalmitis. Keratitis may also occur, commencing with redness and some pain. The rapidity of the development and degree of involvement seems only partly related to the severity of the original attack. It is more usual for one eye to be involved.

Another form of keratitis occurs in malignant smallpox usually commencing on about the tenth day of the disease. The cornea loses its lustre rapidly and becomes opaque within a very short time and looks dead. There appears to be no tissue reaction and the patient experiences no

pain. The patient, however, is suffering from a type of disease from which he usually dies within two to three days, but the whole cornea may slough allowing discharge of aqueous humor followed by a complete anterior staphyloma. Panophthalmitis is likely to follow.

It is curious that the serious lesions in the eye producing permanent blindness occur late in the disease and do not appear to be due to direct viral growth in the tissue concerned.

Robertson (1913) had six cases of iritis and six of corneal ulcer in 545 cases of variola minor. Mild conjunctivitis is of course quite common, occurring in about 5 per cent. The most important ocular complication, beginning in early convalescence, is corneal ulceration, and this was seen in 0·91 per cent (Marsden, 1936). In only one fatal case did perforation occur. Keratitis profunda occurred in nine, and iridocyclitis in eight of the 13,000 patients.

It is commonly assumed that smallpox is a frequent cause of blindness, particularly in tropical countries, but it seems that smallpox *alone* causes relatively little blindness as those

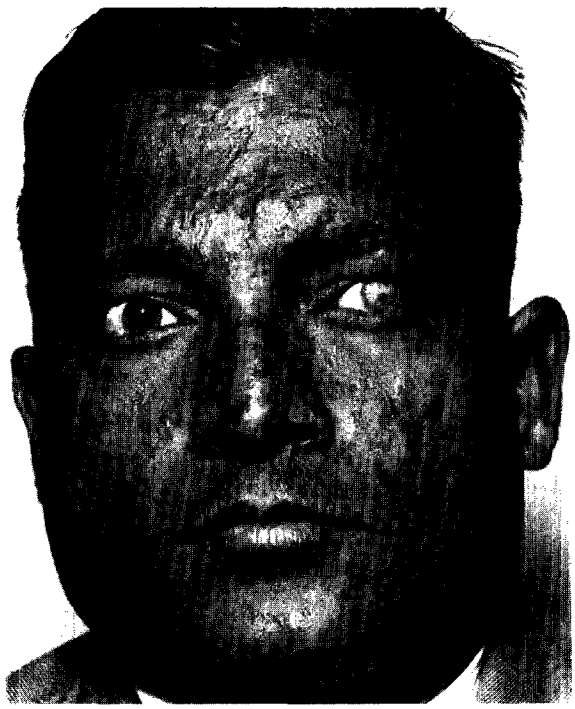

FIG. 151. Corneal scarring, facial scars suggest much super-added sepsis.

patients with mild attacks have no eye lesions and those with severe eye lesions have malignant attacks from which only a small proportion recover. In those patients in which corneal lesions occur with relatively mild non-fatal attacks there are gross nutritional deficiencies which almost certainly account for part of the damage. For this reason eye lesions seem to be very much less frequent in European countries today. There has, I feel, been some confusion between the common statement of a patient being "blind with smallpox" due to palpebral oedema and disease of the cornea or other structures giving rise to real blindness.

There is a tendency, of course, for individuals and even their medical advisers to assume that blindness in someone who has once had smallpox must be due to that disease and not to some less exotic cause.

CENTRAL NERVOUS SYSTEM

Specific complications of the central nervous system are encephalomyelitis and acute psychoses. In the series of 486 variola major cases in Tripolitania, two cases of encephalitis occurred, both of which were fatal. In Kramer's (1951) series in Indonesia the incidence was thought to be one in 1,000. In Marsden's (1936) series of 13,000 cases of variola minor nine cases occurred with three deaths, and twelve other patients exhibited symptoms suggestive of mild attacks. In Kramer's series and the Tripolitanian cases, the attacks were benign semi-confluent or discrete, whereas in Marsden's series of variola minor they were quite mild discrete attacks. The incidence would appear to be slightly higher in variola major than in variola minor, but in the former adds little to the mortality. Because the overall case mortality

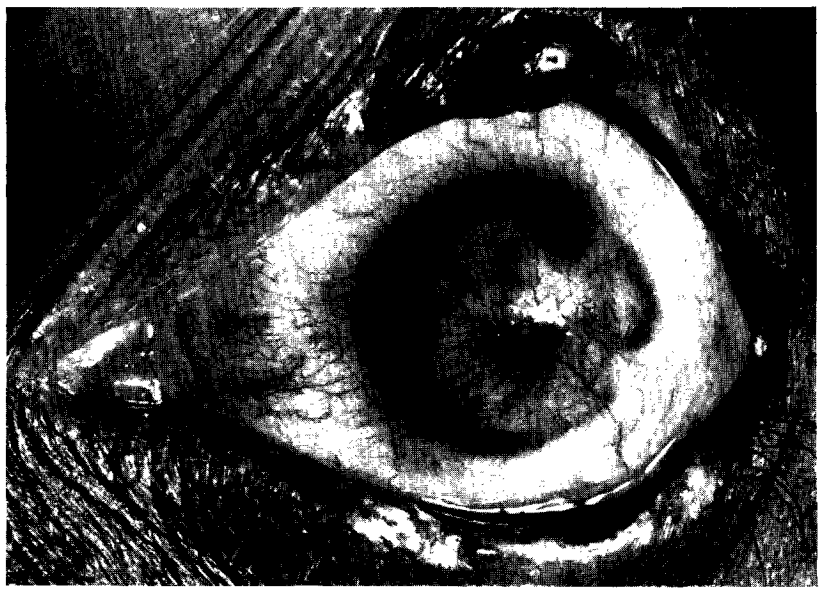

FIG. 152. Corneal scarring.

in variola minor is so low, in spite of its rarity, encephalomyelitis is one of the principal causes of death really attributable to the disease.

The complication occurs relatively late, about the tenth day of the disease, a similar timing to post-vaccinial encephalitis. The attack commences with increasing drowsiness which may go on to stupor. Localizing signs may be very varied but trismus may be extreme. There may be profuse sweating of the head and salivation. Sometimes the first sign that anything is wrong, apart from slight drowsiness, is some disorder of speech. The period of drowsiness or stupor may last days or weeks and recovery may occur quite suddenly from an almost moribund state, but it is usually more gradual. Whether this stage is passed depends on avoidance of bed-

sores, trophic ulceration and broncho-pneumonia. In the spinal type drowsiness is less marked and disappears sooner, but incontinence of urine and faeces is usual. Urinary infection is likely to occur, flaccid paralysis may be present and, on recovering, spasticity may develop which may take a very long time to disappear completely. Sensory loss and hyperaesthesia may also occur.

Of very great importance are the mental changes. Loss of speech is a common phenomenon and probably the most constant symptom noticed. Personality changes, delusions, abnormal behaviour are also quite common and particularly well described by Kramer (1951). This syndrome is discussed very fully by Marsden and Hurst (1932), whose cases all appear to have been mentally normal after the attack. In Kramer's series abnormalities were still present some months after attack, but he was not able to follow the cases further. It is stated repeatedly in the literature that permanent sequelae do not occur, but there seems to be no series in which cases have been followed up for a number of years. From the severity of some of the attacks one would doubt very much whether some form of mental scarring was completely absent. Increasing recognition and possibly increasing incidence of encephalitis as a complication of

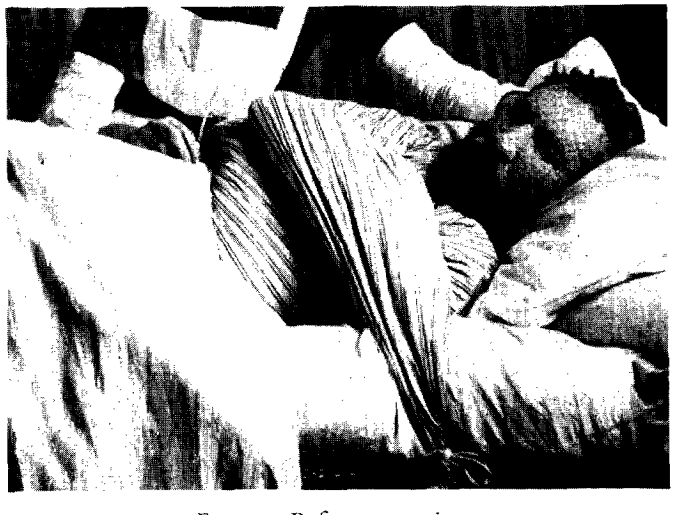

FIG. 153. Refractory patient.

other infectious diseases and of the occurrence of sequelae, particularly personality changes, suggest that mild attacks of encephalitis, of great social significance, may be commoner than usually thought. The condition is similar to post-vaccinial encephalitis in which it has, in the past, often been erroneously stated, that mental sequelae do not occur. This is discussed in Chapters 7 and 14.

There is no real difficulty about diagnosis as it occurs when the general effects of the attack of smallpox have passed. The patient will frequently be afebrile and the onset of this complication will once again cause the development of fever. Changes in the C.S.F. are not of much diagnostic significance. There is early increase in cells, but this soon becomes normal and there is only a slight increase in protein. Details of both clinical diagnosis and pathological changes are given in the papers by Marsden and Hurst (1932) and in that by Kramer (1951).

Acute toxic psychoses are common in the first ten days of the disease, particularly in chronic alcoholics, and in the past have led to patients running out of hospital and even being accidentally drowned.

JOINT

Effusion into the joints may be serous or purulent but the frequency of either appears to vary considerably in different outbreaks. Simple serous effusion is not uncommon in variola major, and would appear to resolve without any disabling effects. It seems commonest in the wrist or elbow, and Marson (1866) thought that it might be connected with leaning on the elbow whilst feeding. Pickford Marsden (1936) does not record this complication in his large series of variola minor cases, and he commented (1950) concerning Chatterjee's (1950) series of cases of this condition, all affecting the elbow, and suggested that this might be due to some effect of modern treatment. Presumably this was meant to imply that the use of antibiotics would suppress but possibly not wholly prevent low-grade sepsis. These cases and those of Wiersema (1950) appear different from the serous effusion described by earlier writers, in that they show some feeble growth of staphylococci, and some permanent disability may result. Cases occurred in children under the age of sixteen, the focus of infection appearing to originate at the epiphysial line. Cockshott and Macgregor (1958) saw fifteen cases. In every patient at least one elbow was involved, and occasionally other joints. They state that these cases do not usually follow confluent smallpox, as this is relatively rare in childhood. The state of nutrition of the infected children varied from appalling to excellent and they felt that neither good nutrition nor mild smallpox would necessarily confer protection. On the other hand, five of their cases were grossly anaemic. Elbows were usually involved first. The joints were moderately swollen and not tender. Cases were afebrile or had a slight fever. Limitation of movement is the major disability.

An interval of ten days to four weeks occurs before the complication appears, and Wiersema (1950) and Cockshott and Macgregor (1958) think the osteitis commences at the stage of primary viraemia and is clinically silent until exudation occurs round the joint, by which time considerable bone changes have occurred. The term *osteomyelitis variolosa* was first used in this sense as a specific viral infection by Brown and Brown (1923).

Suppurative arthritis and osteomyelitis as part of a general pyaemia undoubtedly do occur, but are much rarer than generally supposed. As long ago as 1875 Curschmann remarked that the frequency with which these conditions were mentioned in textbooks as complications of smallpox was not in accordance with the facts. This type of condition is most likely to arise after benign confluent or semi-confluent cases, particularly in the very young and where there is malnutrition and neglect.

OTHER COMPLICATIONS

Very rare complications have been recorded by the older writers, but many appear more in the nature of intercurrent secondary infections, determined largely by the prevalence of such organisms as haemolytic streptococci. Although haematuria is frequently present in malignant cases, acute nephritis when it occurs is not due to the smallpox virus. At post-mortem characteristic lesions are seen in the testes microscopically, but although orchitis has been noted on rare occasions, the development of symptoms does not seem correlated with the post-mortem findings to render it certain that this is really a variolous condition.

TREATMENT AND NURSING

"It is a melancholy reflection but too true that for many hundreds of years the efforts of physicians were rather exerted to thwart nature and to add to the malignancy of the disease than to aid her in her efforts." Gregory wrote this in 1838, but it is unfortunately only too true today.

There is no specific treatment for smallpox. So far no drug has been produced which appears to have any effect on the virus in the human body. Attempts to influence the course of the disease by increasing immunity passively by the use of convalescent serum or anti-vaccinial serum have been made on many occasions, but unfortunately never on a scale and with satisfactory controls that its effects could be evaluated. Earlier workers in this field (Ledingham *et al.*, 1931; Fairbrother, 1932) had to use a large volume of serum, which is not necessary today, due to our ability to refine, but even where modern gamma-globulin has been used there is no conclusive evidence that there is any appreciable effect (Murphy, 1954). It seems probable that, as in measles, even large doses of antibodies given relatively late in the disease, when the diagnosis is usually first made, will have no appreciable effect on mortality. Once again one has to emphasize that the rash, although an important indicator, is not the most important part of the disease. By the time the rash has appeared irreparable damage has frequently been done to other tissues and it is this damage which normally causes the patient's death.

If smallpox is diagnosed in the initial stage then the treatment is on general symptomatic lines. The patient may be extremely restless with severe headache and backache, and various drugs may be used to relieve pain, but morphia appears to be valuable in this respect. If salivation and laryngeal and bronchial secretions are very profuse care must be taken in the use of sedatives. Fluids should be given freely throughout the disease as smallpox has no specific effect on kidney function. In the malignant case swallowing may be extremely difficult and painful towards the later stages of the disease, but the condition of the skin makes subcutaneous or intravenous replacement of fluids far from easy. Plasma, blood and synthetic preparations of various kinds have all been tried (Boeck, 1946), but it is very doubtful whether they affect mortality.

The patient should be encouraged to eat as well as his general condition and the condition of his mouth and lips will allow. Benign cases, even the confluent where the appearance may be so unpleasant, usually have quite a good appetite from the sixth or seventh day onwards and can eat as well as their facial masks will allow them. They undoubtedly should be encouraged to eat as much as and whatever they like. When the mouth is sore, ice-cream seems to be a popular article of diet, but in malignant cases patients seem unable to tolerate even a small amount of fat and will only suck ice.

In the malignant types, by the twelfth or thirteenth day it is obvious that the patient is for all practical purposes being starved and that life is maintained at the expense of reserves in the tissues. In spite of attempts that have been made to replace protein, etc., in a similar way to the treatment of burns, results to date do not suggest that it has any appreciable effect. On the other hand, there can be no doubt that starvation must be very harmful and possibly impedes the already feeble antibody response. It is here, of course, that skilled and sympathetic nursing plays an important part in coaxing the patient to take some nourishment.

In my opinion chemotherapy is of no value during the pre-eruptive stage, and if a drug of

this group is given which has even a slight toxic effect on the bone marrow it can do nothing except add to the damage that the virus can do to these tissues. I have seen drugs such as chloromycetin used from the very earliest stage in malignant confluent and semi-confluent cases and am of the opinion that in the latter, where there is a greater chance of recovery, the chance may well be lessened. The drug also increases the patient's misery by inducing nausea and increasing the likelihood of severe vomiting.

Of the drugs that have been used I gave penicillin a fairly considerable and controlled trial (1948), and streptomycin, chloromycetin, aureomycin, have all been tried within the last few years on very small numbers of cases without controls, but the results would appear to be the same (Anderson *et al.*, 1951; Breen, 1951; Marsden and Coughlan, 1951; Murphy, 1954). Stolte and Sas (1951) used ACTH in three cases and it appeared to them to influence the rash. Whether it was of benefit was so doubtful that they concluded that the administration of ACTH is "fraught with danger". Pierce *et al.* (1958) reported treating a case with cortisone on the twelfth day of attack, but the favourable outcome could hardly be described as entirely unexpected. Unfortunately the treatment was not tried on a subsequent case of fulminating smallpox, seen sufficiently early to have provided a good test. I think the only type of case in which systemic cortisone or ACTH is worth risking is the fulminating, and probably the malignant confluent, where the mortality in any case is extremely high.

It is only when a fair-sized sample of cases is available, classified according to type, and treated by a clinician experienced in smallpox, that one can have any hope of assessing the value of any particular form of treatment.

As far as the eruption is concerned, a vast number of treatments have been suggested, from hanging red curtains round the bed, red light, covering the face with a mask, to opening the lesions with a golden needle. None of these treatments has any effect on the development or the final effect, the amount of scarring. It is unfortunate that accounts are repeatedly published affirming that a particular treatment or drug will prevent scarring. Only too frequently the author is oblivious of two facts: (1) malignant confluent and semi-confluent cases that recover may have no "classical" pocks, but thin superficial scars, and that many mild and discrete cases, particularly vaccino-modified, have no permanent scars; (2) many patients who on discharge from hospital have only level pigmented scars, which the clinician hopes will resolve without a blemish, show classical pocks when seen six months to a year later at a time when most clinicians unfortunately do not see their patients.

Sulphonamides (Vengsarkar *et al.*, 1942), penicillin (Foulis, 1945; Dixon, 1948), chloromycetin (Breen, 1951; Marsden and Coughlan, 1951), and other antibiotics having an action on streptococci and staphylococci do have an effect in preventing secondary infection occurring in the skin, particularly in the large non-modified smallpox lesions. Although the "pure" smallpox vesicle is sterile (Sweitzer and Ikeda, 1927; Mair and Parker, 1953) and many remain so, staphylococcal infection occurs (Leishman, 1944), and, in spite of the doubt expressed by Wilson and Miles (1955), it does appear that chemotherapy instituted at the vesicular stage will suppress the occurrence of frank sepsis in the lesions, and appears to accelerate the drying up and scabbing process; it certainly makes the patient feel much more comfortable and boosts morale. Although it prevents the aggravating effect sepsis can undoubtedly have on the formation, depth and size of scars, it does not prevent them. Chemotherapy should be commenced on about the sixth to seventh day of the disease in the benign types when the vesicular lesions are nearly fully developed on the face and should be continued up to about

the thirteenth or fourteenth day. Treatment is of undoubted value in benign confluent type 4, benign semi-confluent, type 5, and discrete, type 6, and should be given in the normal maximum dosage of the particular drug concerned. It is doubtful whether it is required or has any material effect on the mild, type 7, and abortive, type 8, as the lesions will dry up and secondary sepsis is unlikely, even with no treatment at all. Malignant cases are entirely unaffected and, because of the possible damage to the bone marrow, chemotherapy should not be given even in the vesicular stage unless definite indication of some secondary infection is present. This, however, is rare. Drugs of this kind do not produce any visible change in the cutaneous lesions as these normally dry up without the formation of a "pustule" and the scabbing is light and superficial. Doubtless clinicians will find it difficult to resist giving chemotherapy, but I would like to emphasize that in my opinion, unless there are definite complications which would benefit, this form of treatment may do more harm than good.

In my experience irritation is not a serious problem, except when the eruption is drying up and there is much scaling and scabbing. It is more common in vaccino-modified smallpox and with the more abortive lesions but is best treated on general lines, with dusting powder, lotions and frequent bathing.

Lesions under the nails may be painful and some clinicians soften the nail or cut it over the lesion. Rings on the fingers may have to be cut off due to swelling and danger of gangrene. There seems to be no advantage in painting the skin with any antiseptic, although this undoubtedly may have some psychological effect on both patients and staff. A wide range of substances have been used, from dilute tincture of iodine to potassium permanganate. It is very beneficial to get the patient out of bed as soon as possible, and this may be practicable while the rash is still in the late vesicular or early pustular stage. The benign confluent may not be able to get up for fourteen days or more, but many discrete cases can get up on the tenth day and mild and abortive as early as the fifth day. There is a great tendency to keep the patients in bed far too long; such patients are more liable to develop complications, lose muscle tone and stay in hospital longer than is necessary. The factor which keeps most patients in hospital is the presence of seeds in the palms of the hands and soles of the feet. If the patient walks about from the earliest possible moment the shedding of keratin will be accelerated and the seeds extruded more quickly. When the general condition of the patient is sufficiently improved, and this occurs much earlier than is usually supposed, the patient should be bathed, and if a bath is not available a hot-shower should be used. Unless the hospital is well equipped and staffed to ensure that bath hygiene is satisfactory, showers are probably preferable in avoiding cross-infections, and they use less water. These have a very beneficial effect on the patient's general condition and washing assists in loosening the scab material, particularly from the feet. Reluctance of some of the older clinicians to bath the patients may have been due to the risk of making the skin sodden and so incurring the risk of infection. Some treated the patient by continuous immersion in hot water, but this seems quite unnecessary, time-consuming and inconvenient.

As the scabs come away, the skin, particularly on the face and arms, may be very tender, a dry secondary eczema may occur, and this should be treated by rubbing the skin with lanoline or olive oil. It is usually thought that attempts to remove facial scabs will result in increased scarring. On flat surfaces and where the lesions are few it probably makes no difference whether the scabs are removed or allowed to shed naturally. On the nose, however, and where confluent areas exist, a large scab mass may be so dense as to exert pressure on the epithelium and increase

tissue destruction. To avoid this it is advisable to inspect the scab mass carefully and see whether some can be freed after soaking in olive oil or after warm compresses. Although many older writers believed it was beneficial to open the vesicle with a needle before pustulation, the only successful cases appear to be the mild and abortive, where scarring is likely to be very slight in any case. I do not think a properly controlled trial of this method has ever been done. Where there are many lesions it is not very practical.

Plastic-surgery techniques such as sandpapering of the scarred area is often advocated some six months after the attack, but it does not appear to be very satisfactory in discrete cases with deep-pitted scars. In the benign confluent, the profusion of scars may naturally leave the surface irregular in colour but not in contour.

The scalp may have become one large scab mass entangled with hair. The hair must be cut short if the rash is very profuse, but in women should not be cut in the early stages, even in quite severe cases. The prospect of smallpox scars on the face is quite enough for a young woman to contend with without cutting her hair. In the case of men it is different and where the hair is completely matted something should be done. The best way is to soften the scab mass with olive oil and gradually let it loosen. The patient should be asked to refrain from the temptation of pulling away large masses and nursing staff should carefully attend to the hair toilet.

If the seeds in the soles of the feet are slow in progressing they may be opened up with a sharp scalpel or needle or fine curved scissors, the contents removed, and after further bathing the patient can be regarded as free from infection. This can accelerate discharge from hospital by as much as a week.

Treatment of complications must follow the orthodox practice of the time. The use of chemotherapy from the sixth to the fourteenth day may serve to assist in preventing respiratory infections. Unfortunately these are most common in the very young and the very old. The eye complications are amongst the most serious and are difficult to treat. An eye specialist should advise. In the cases in Tripolitania penicillin appeared to have no effect on the incidence or course of eye complications. Although no evidence appears to be available, no response is likely to come from other chemotherapeutic agents. Whether cortisone may have any effect on smallpox keratitis is not known.

The cases for which we are completely powerless to do anything are the fulminating and the malignant. In the fulminating the sledge-hammer blow is so rapid and so devastating that it seems difficult to visualize any treatment having any effect, even assuming the diagnosis is made. With the malignant we have twelve to thirteen days from onset to death, but so far nothing has been of any value. Heroic measures such as intravenous injection of proteins other food substances, vitamins, plasma and blood have all been taken. Innumerable other drugs have been administered without result and may well make the patient's life more miserable. The acute consciousness of this type of patient should not be forgotten.

As far as the actual nursing is concerned there are two distinct problems. In the malignant cases there is progressive deterioration in the patient's condition and increasing difficulty in maintaining fluids—let alone food. Due to the damage to the skin the development of bed sores is very difficult to avoid. Extreme care and patience is required. From the sixth or seventh day individual nursing is required day and night. The patients are particularly restless at night, and the possibility of maniacal phases must not be forgotten. A male nurse is frequently a great asset. In countries where smallpox is rare the relentless deterioration in the patient's condition,

with almost certain death, coupled with the acute consciousness of the patient, makes this type of nursing a real test of skill. The staff may become depressed, and this is enhanced if long quarantine is enforced.

The other problem in nursing is that the very mild cases although feeling perfectly well will be incarcerated in hospital for some weeks and it is necessary to keep the patients amused

FIG. 154. Variola major, scarring of pigmented skin. Compare depigmentation of hands with the scar on the face.

and happy. The provision of books, newspapers, radio, television, rug-making etc., or anything to relieve monotony, is an important part of the treatment. Telephone facilities for ambulant patients and a long lead extension for the less seriously ill will do a lot to overcome the isolation imposed by a ban on visiting.

As Marsden (1936) points out, mirrors should not be allowed in a smallpox ward.

SEQUELAE

Sequelae can be physical or psychological, but the two are closely linked. As already mentioned, permanent eye defects leading to blindness may occur, although the effect of smallpox alone is much less than is generally thought. Every writer on smallpox over the last 150 years

FIG. 155. Variola major, depigmentation of arms and trunk, hypertrophic red scars on the face.

has pointed out that in his experience the amount of blindness due to smallpox was much less than that quoted by previous authors.

Some loss of hair may be permanent, although even in benign confluent cases a fairly normal head of hair may return; other factors, particularly the age and sex of the patient, have a big effect on the result (Fig. 156).

Much of the scarring on the trunk and arms will disappear entirely, the scars only being visible when the skin is cold or if there is depigmentation as commonly occurs with those with

pigmented skins. Even if the effect is noticeable soon after the attack a return to normal gradually occurs over the years. Some of the scars, particularly on the forearms and hands, may still be visible, but they are very much less noticeable than immediately after the attack.

It is on the face, particularly the nose and forehead, that the scarring is permanent and may be very severe (Figs. 86, 150 and 157) and produce the characteristic "pitting". On these areas

FIG. 156. Variola major, Type 4, residual scarring two and a half years after attack. Note the hair has regrown well. See Figs. 62 and 64.

secondary dry eczema is common but some increased sensitivity of the skin may trouble the patient for some years. Some patients complain of irritation of the skin on other parts of the body where no scars are visible. It is important to appreciate that while the scarring on the remainder of the body diminishes with the passage of time, scarring on the face is more noticeable at the end of a year than it is when the patient is first discharged from hospital. This is due to progressive fibrosis around sebaceous glands which have been destroyed (Bras, 1952*a*). In some patients cheloidal scarring occurs with warty outgrowths which may require removal. In the days when multiple subcutaneous abscesses occurred, considerable scarring would result from efforts to treat these.

Of great importance, however, are the psychological sequelae. In a community where smallpox is common, as in Europe in the past and in Asia today, scarring on the face causes little or no comment. At one stage in history, it was even considered inadvisable to marry an unpockmarked woman for fear she might contract smallpox and have a severe attack. The lightly scarred face was recognized as safe and almost beautiful. Today in those countries where

FIG. 157. Scarring six months after attack. Variola major, Type 6. Cases of severe variola minor also look like this.

smallpox is a rarity, the sight of a scarred face causes comment and a varying degree of ostracization. In the large cities these things may pass unnoticed, but in the small town or village where an outbreak of smallpox has been a major catastrophe in its history and will be remembered for many years, any pockmarked person is for ever identified and regarded as an object of curiosity. The public in their ignorance may regard the visitation as partly due to some peculiarity of the individual and years afterwards he may still be regarded as being slightly unclean. The town's tradespeople and others still regard the unfortunate person who has had smallpox as being in some way the cause of the disorganization and loss of trade that occurred during the outbreak.

On one occasion a convalescent patient, quite non-infectious, and with very slight, almost invisible scarring was, on the advice of their medical adviser, refused admission to a convalescent home run by the man's trade union.

The following extract from the letter written to such a patient emphasizes the peculiar ideas of the public even supported by the medical profession.

Rochdale (Lancs.) dated 28th April 1953: "The Medical Officer of the Home" (a general practitioner) "who whilst admitting that your condition is not contagious he is very much concerned as to the effect on the minds of the people who are at present in residence in the home." How far have we progressed from the Middle Ages!

FIG. 158. Variola major, vaccino-modified, Type 7. Facial scars two and a half years after attack. Those on the nose are the only ones easily seen.

It is not uncommon, of course, where personal appearance counts in a job, for the persons to be discharged, and obviously it is difficult for them to obtain similar employment if they have considerable facial disfigurement. Eventually they shun society, and if there is any degree of mental instability they have been known to commit suicide.

This intolerance and ignorance is widespread through all walks of society, but it leads to tremendous harm being done to those individuals unfortunate enough to be badly marked. In 1954 a television programme was put on to show the course of a smallpox outbreak and

the methods used to control it. A very laudable object, but the story was so closely based on the occurrences in a recent outbreak that the unfortunate victims were again made fun of by their neighbours and workmates.

In those countries where smallpox is rare, it should be recognized that the convalescent patient requires special after-care largely directed to the education of the public around him, and this should be the responsibility of the Medical Officer of Health.

Although the majority of cases of variola minor will not have permanent scars, about 5 per cent of those admitted to hospital will be affected, some quite severely—a fact sometimes forgotten by those who claim it is of no more importance than chickenpox.

CHAPTER 6

Variola Inoculata
Congenital Infections

It is only rarely that a person naturally contracts smallpox by the cutaneous and not the respiratory route. In the past it was a recognized hazard of the wet nurse and the nursing mother, although due to partial immunity there was often only a local lesion or a modified attack in these cases. Boobbyer (1894) reported a number of cutaneous infections in an outbreak amongst lace-workers handling infected material. It could also occur in unprotected laboratory workers handling smallpox virus, and has occurred in those engaged in post-mortem work (Lyons and Dixon, 1953) (Fig. 101).

Cases of smallpox have always been recognized in which a very early lesion, sometimes

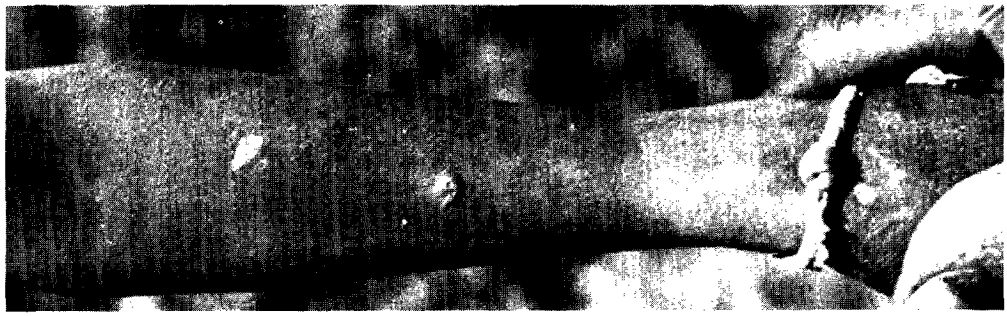

FIG. 159. Variolation, primary lesion.

called a proto-vesicle, appears on the skin, usually of the hand or face, before the general eruption. It seems probable, although it cannot be proved, that some at least of these cases are primary cutaneous infections. Most are accelerated lesions at the site of some trauma in an otherwise normal type of infection. The most common type of cutaneous infection was intentional smallpox by inoculation—variolation—practised extensively in the eighteenth century, the history of which is dealt with at length in Chapter 11. The practice is probably still performed in some parts of the world today, when vaccination facilities are not available and a smallpox epidemic is in progress. It was reported in Tanganyika by Rosenwald (1951), although in most countries it is an illegal practice.

In accidental inoculation the virus can enter the skin through invisible abrasions. The original Graeco-Turkish technique was to lightly scarify the skin, but this was soon modified by the early Western inoculators to a rather deep incision through the true skin. The virus can also grow in the superficial layers of the epidermis on the floor of a blister, and this technique was sometimes used, particularly by French inoculators.

Whether the subsequent course of the disease, the severity, is modified by the technique, we shall doubtless never be able to prove. The available evidence suggests that with deep incisions accompanied by gross secondary infection induced by foreign material such as linen thread and treated by primitive dressings such as cabbage leaves, there is sometimes poor local response and subsequent severe general infection. A viraemia might be produced by direct introduction of the virus into the circulation and multiplication in some internal organ, rather than initial multiplication in the skin. In this way fulminating and malignant types of smallpox might occur in individuals who had been inoculated. However, most of these cases would appear to have occurred during epidemics of smallpox when they could well have been infected by the natural or respiratory route. It is of interest that the early inoculators were most frightened for the welfare of their patients when the fever occurred earlier than the seventh or eighth day, which would occur under these circumstances. All the old accounts of the clinical conditions leading to death were coloured by the feelings of the inoculators and their desire to be excused any possible blame. Often they described how the secondary rash was of the distinct kind, but by the time the patient died it was often described as "the pock not filling she sank under it", whether as an accurate description or as an excuse for dying, we shall never know. In my opinion fulminating and malignant cases will not occur unless the virus gains direct access to the circulation and multiplies in an internal organ, when the primary lesion may not show the normal development. This has been noted in some of the fatal cases. When the virus is localized in the skin, primary growth first occurs there and types 4–9 can then occur. When this is so, case mortality will be quite low, particularly when children under two years are not done and the aged and infirm and the pregnant are also excluded—a common policy in the eighteenth century.

In the majority of cases, however, the process of inoculation of virus into the skin was followed by fairly constant and orderly changes ably described by Dimsdale (1767) and others.

If smallpox virus is applied to a small clean abrasion of the skin as in a modern vaccination, nothing is seen for about forty-eight hours when a small papule forms surrounded by a small area of erythema. During the third and fourth day the papule grows, becomes rather hard to the touch, the part may irritate slightly, and by the fifth day a very small vesicle can be seen. By the sixth day the vesicle will be growing and there may be some pain in the axilla. The local lesion continues to grow and by the seventh day, but more often the eighth, general symptoms appear with fever, and slight pain in the head and back. Dimsdale stated that it is usual for the patient to complain of an unpleasant bitter taste in the mouth and the observer noticed a peculiar smell of the breath characteristic of smallpox. By the eighth or ninth day the lesion on the arm has considerably increased in size, depending partly on the size of the original inoculation site, but there may be much oedema and erythema, sometimes extending half round the arm. There also may be a number of secondary pustules at the edge of the original lesion. The pyrexial attack does not normally last for more than forty-eight hours unless the patient is getting a severe attack. It may only last a few hours or may be completely absent, particularly when no general rash appears. On about the ninth day further lesions appear in the skin, commencing as macules, rapidly becoming papules and within forty-eight hours vesicles. These lesions, similar to modified smallpox, first appear on the face and then on other parts of the body. When the lesions are very few it is not uncommon for them to appear over the next three or four days similar to the cropping of natural vaccino-modified smallpox, but when there are a large number, between 300 and 1,000, they appear more consistently like a

normal attack of discrete smallpox, so that these cases at the eleventh or twelfth day are almost identical in appearance with a natural attack. Even in those cases that have a large number of lesions the latter mature more rapidly than in natural smallpox so that scabbing occurs three to four days earlier and the lesion, being more superficial, gives rise to less scarring. The more superficial nature of the lesions even in the severe attacks, and the more rapid maturation, gives very much less chance for serious secondary suppuration to occur, a point in favour of even moderately severe inoculated smallpox compared with the natural disease and much stressed in the eighteenth century. By the eighteenth or nineteenth day most of the scabs will have been shed except the seeds on the hands and feet.

FIG. 160. Variolation—primary lesion on the arm—secondary satellite lesions and a few more general.

When the rash was of type 7 the process of maturation was so accelerated that it was exceptional for many of the lesions to leave permanent scars. The frequency of this type of case gave rise to the claim that inoculated smallpox never caused scars. This, of course, is no more true than the popular opinion that natural smallpox always gives rise to scars. The development of the primary lesion followed by a mild fever but no rash surprised the early inoculators and probably accounted for the more energetic techniques to ensure evidence of "genuine" smallpox. The later workers recognized by the experiment of repeating the inoculation and finding it fail or exposing their patients to smallpox without harm, that the individual had indeed had smallpox, but without a general rash. Some then remembered the observations of de Haen (1775) and others that natural smallpox could also occur without a rash. Although the majority of primary lesions were larger, it seems clear that, in some individuals at least, it is possible to produce a local smallpox primary lesion indistinguishable from a vaccination lesion and without any more serious effects. What degree of immunity this lesion produces compared with that of a similar vaccination lesion is not known. It probably gives a much greater degree of immunity, but, as Jenner tried to prove variolated individuals may subsequently suffer from attacks of smallpox.

Although it would seem that all grades of severity can occur from type 4 to type 9, it is impossible to assess what proportion of these different types occurred, largely due to the professional jealousy and secrecy surrounding the results and the controversial nature of the practice. From the old accounts it would appear that with a good technique the large majority of the cases were types 6, 7, 8 and 9. It is difficult to know what the real mortality of this procedure was and what it would be if practised under good conditions today. If one eliminates those who died from being inoculated during the incubation period of natural smallpox, those who died from sepsis, pyaemia, etc., largely due to faulty local treatment of

the individuals, those who died from other diseases not connected with inoculation; to these add the hazard of nutritional diseases of various kinds and the physicians who starved, purged, bled, and treated their patients with huge doses of mercurials and other drugs, the number of persons who really died of inoculated smallpox alone was probably very few. This is borne out by Rosenwald's (1951) observations of variolation in Tanganyika.

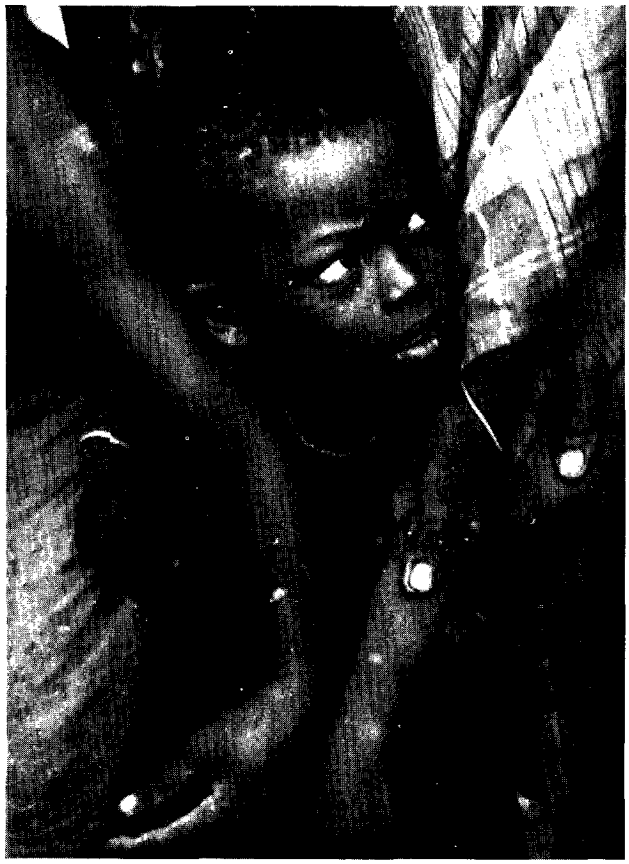

FIG. 161. Variolation—scars on the arms of three individuals. Any general dissemination, if it occurred, was very slight, as no secondary scars are visible.

RE-INOCULATION (RE-VARIOLATION)

If smallpox inoculation is done on a person previously inoculated, or in those who have had natural smallpox and occasionally in others with no history of either, after a few hours there is some redness of the skin—there may be slight oedema and irritation suggesting an allergic response like an insect bite. In general there is no vesicle, but if contaminated material is used a non-variolous pustule may result. It would, however, appear probable that if the interval between inoculation re-inoculation was sufficiently long a vesicular response and a secondary rash might occur.

CONGENITAL INFECTIONS—SMALLPOX AND VACCINIA

Smallpox, particularly variola major, is a serious complication of pregnancy. Most authors have noted the frequent occurrence of severe, fulminating and malignant cases in pregnant women. I (1948) reported that of the fulminating cases in the 500 cases in Tripolitania, three out of the four in women were pregnant at the time. Welch (1877) had forty-six cases in pregnancy. Fourteen of these died. In variola major the foetus is likely to suffer profoundly, but this will to some extent be affected by the vaccination state of the mother. In variola minor the effects on the mother and on the foetus are very much less.

Infection within the first three months of pregnancy is likely to give rise to some uterine haemorrhage, and miscarriage will commonly occur. Although Jelliffe (1952) reported a case of possibly congenital cataract, due to maternal smallpox in the first three months of pregnancy in a vaccinated woman, congenital malformations of the kind recorded with rubella are not seen. Death of the foetus is much more likely, and depends on the pyrexia and maternal toxaemia. Cases recorded in the literature are of smallpox infection in late pregnancy, when the infant is likely to be viable. Whether it suffers from smallpox seems to be largely a matter of chance, and on a number of occasions, as in the case of twins, one twin has been infected and the other has escaped (Fumé, 1759; Davis, 1838; Warner, 1903; Marsden, 1930). A review of the literature by Lynch (1932) shows how incomplete the records are. In forty-six cases where the infant's condition is recorded, twenty-six were stillborn, and of the twenty born alive, eleven died later. Although, in variola major, 80 per cent would therefore appear to die, many of these cases occurred in the nineteenth century, and it seems possible that more might survive under modern conditions of handling and treatment.

The incubation period is of interest. In a series of cases reported by Marsden and Greenfield (1934) the incubation period was between nine and twelve days. In the cases I reported in 1948, it appeared to be between ten and twelve days, to the appearance of the rash. As pointed out by Marsden and Greenfield, this corresponds very closely with that of variola inoculata, and is in keeping with the foetus being infected by the bloodstream. Although the foetus might be expected to share in the maternal immunity, if present, this doesn't appear to be so. In one case in Tripolitania, the mother suffered a type 2 attack and died, but the infant, although infected *in utero*, had a type 7 (mild) and recovered, but in another instance the mother, who had been vaccinated successfully ten years previously, and had a type 6 attack, the infant had a type 2 attack and died.

In variola minor, the condition is somewhat different. Marsden had seven cases in which premature labour was not induced, and normal infants were born at least a week after the focal rash had appeared. Out of thirty-four mothers who had smallpox in late pregnancy, in seventeen cases the infant was infected, whereas in the remainder it escaped.

Robertson (1913) recorded how, in an outbreak of variola minor, twenty-seven pregnant women developed the eruption. Premature labour or abortion took place in ten, and one woman died after giving birth to a healthy full-term male child. The death was due to smallpox rather than childbirth. Premature labour occurred near term in four, two gave birth to healthy eight-month children the day after the appearance of the eruption which was mild discrete in both cases. The third was confined with 6½-month twins nineteen days after a mild eruption. The twins were both slightly macerated, and showed traces of a mild eruption in the desiccation stage. The fourth was delivered of six-month twins, a few weeks after the

eruption which was mild. One twin was stillborn without trace of eruption, the other was alive and was covered with a smallpox rash, but lived for a few days. Abortion occurred in six cases: five were mild attacks, the abortions occurring 19, 21, 24, 29 and 30 days after the eruption (at $3\frac{1}{2}$, 3, 5, 4 and 4 months respectively). In four there was no evidence of disease in the foetus or placenta. In the fifth the foetus had a profuse smallpox eruption in the pustular stage. The sixth case was a woman four months pregnant, with a severe attack of variola minor. Abortion took place on the twentieth day of eruption. The foetus and the placenta were not diseased but a section of the placenta in one case was of interest. It showed polymorphonuclear infiltration in parts, also areas in which the chorionic villi had undergone cell necrosis. It was suggested that, nutrients to the villi being cut off, they had undergone degeneration and subsequent invasion by polymorphonuclear leucocytes. Sixteen pregnant women were not affected, four had severe attacks and they were all seven months pregnant. They eventually gave birth to full-time, healthy children. The remaining twelve all had mild attacks, and were from two months to full term. Six babies were born whilst the mothers were in an infective state, four developed the eruption 5, 9, 11, and 15 days after birth respectively; of the other two, one was successfully vaccinated when two days old and the other was unsuccessfully vaccinated, neither acquiring the disease.

Although Marsden and Greenfield (1934) classify inherited smallpox into four types, there appear to be two principal divisions:

(i) True congenital smallpox, where the infant is born with a rash at any possible phase of development, although usually in the vesicular or pustular stage. The maternal attack of smallpox is mild, and the infant remains *in utero* for more than ten days from the onset of the mother's illness.

(ii) Infection occurs *in utero*, or possibly at the time of separation from the parent. In some, the interval between the onset of the mother's pyrexia and the appearance of the child's rash is from nine to twelve days, indicating a blood-borne infection, but in others it may be fourteen days, suggesting that it has been infected by the respiratory tract at the moment of birth, presumably from virus on the skin of the mother, or on clothing or bedding and derived from her respiratory tract. Successful vaccination, performed at birth, may modify the attack, and save the infant's life. It is important to remember here that at least three insertions should be done, using a fairly "horrific" technique, cross-hatching and large insertions. Hyper-immune gamma-globulin might be of value in this type of case but vaccination is essential. Siegenbeck van Heukelom (1949) quotes a case where the mother suffering from smallpox breast-fed the baby and had it in bed with her, but it did not contract smallpox and when vaccinated some time later had a typical primary reaction.

It seems that, in variola minor, infants who are born during the late convalescent stage of the mother, and who are immune to vaccination after birth, may possibly have had an intrauterine attack of smallpox, and completely recovered without leaving any scar (Marsden and Greenfield, 1934). This, however, would appear to be unlikely in any but the mildest cases of variola major. In the majority apparently immune to vaccination, immunity is more likely to be due to passive transfer of antibodies from the mother. It would be unwise, however, to assume that failure to obtain successful vaccination was due to this cause, and if the infant is to remain in a smallpox-infected environment, attempts at vaccination should be persisted in. In many infants born of variolous mothers vaccination performed at birth is successful and should obviously be attempted in all cases.

Much less is really known about intrauterine infection with vaccinia. It would appear that vaccination within the first three months of pregnancy may cause the death of the foetus more frequently than was previously supposed (MacArthur, 1952) (see Chapter 7). Of infants born at or near normal term, the problem is much more complicated, owing to difficulties of diagnosis between variola and vaccinia. Jenner reported a case of a woman vaccinated in the eighth month of pregnancy, in which foetal movement was noticed to cease twenty-three days later, and at five weeks a stillborn foetus was delivered. About thirty pustules were present, and yet he regarded this as "smallpox infection communicated to the foetus *in utero* under peculiar circumstances". It could also have been a vaccinial infection. Unfortunately many of these cases occur during outbreaks of smallpox, when vaccination has also been done, although the reports rarely give any indication as to whether the individual has really been exposed to smallpox. It should be noted that on a number of occasions where vaccinia can be ruled out the foetus has had evidence of smallpox infection, although the mother has only had an attack of variola sine eruptione. If, therefore, vaccination has also been done, the blame is likely to be laid to this instead of to smallpox.

It would seem that some cases that have been labelled smallpox are really due to vaccinia, although Ballantyne (1902) and other writers have been convinced that cutaneous manifestations of vaccinial infection do not occur in the foetus. Lynch (1932) surveyed the literature and presented a case that he described as generalized vaccinia in the foetus, and a second case was recorded in considerable detail by Macdonald and MacArthur (1953). In this case, shown in Fig. 162, the infant, who died some fifteen hours after birth, was premature and about six months' gestation. The mother had been given a primary vaccination when she was about three months pregnant. She developed a fairly severe reaction, with induration, and was off work two or three days. Eleven weeks later, she was spontaneously delivered of the premature infant. She had given birth to a normal healthy child eighteen months before, and her blood Wassermann and that of the child were both negative. The lesions on the skin were large, circular umbilicated, greyish-white sodden lesions, with no surrounding erythema. Underneath was some caseous material, on a basis of granulation tissue. A number of lesions had coalesced to form a large confluent area. All the lesions had obviously been present for some considerable time, and clinically were somewhat similar to those present in vaccinia gangrenosa, bearing in mind that they would be protected in an aqueous medium. There was no abnormality of any other organs, except in the substance of the right lung, a firm area one centimetre in diameter was found in the posterior lower lobe, and next to it, beside a small bronchus, was a smaller red focus. The details are given fully in the paper by Macdonald and MacArthur (1953) and they put forward some interesting theories as to the possible mechanism in this rare type of infection. First, infection could be blood-borne direct to the foetus, traversing the placental barrier. It has been claimed that infants who are born insusceptible to vaccinia may have developed active immunity *in utero* by being invaded by virus at the time of the maternal viraemia, although it is more likely to occur by the transfer of antibodies. In view of the frequent, almost universal viraemia accompanying primary vaccination, it is surprising that the foetus would not be infected more often, or that a much larger proportion of infants would in fact be born insusceptible to vaccinia. Earlier observers (Ballantyne, 1902) have suggested that it is only vaccination within the last three months of pregnancy which will give rise to sufficient degree of immunity to prevent vaccination at birth and then only in about one-third of cases.

The second theory is that maternal viraemia may lead to a lesion in the placenta, and subsequent blood-borne invasion of the foetus from this lesion. The foetal lesion would then occur later than that in the mother, and is likely to be influenced by immunity she has developed.

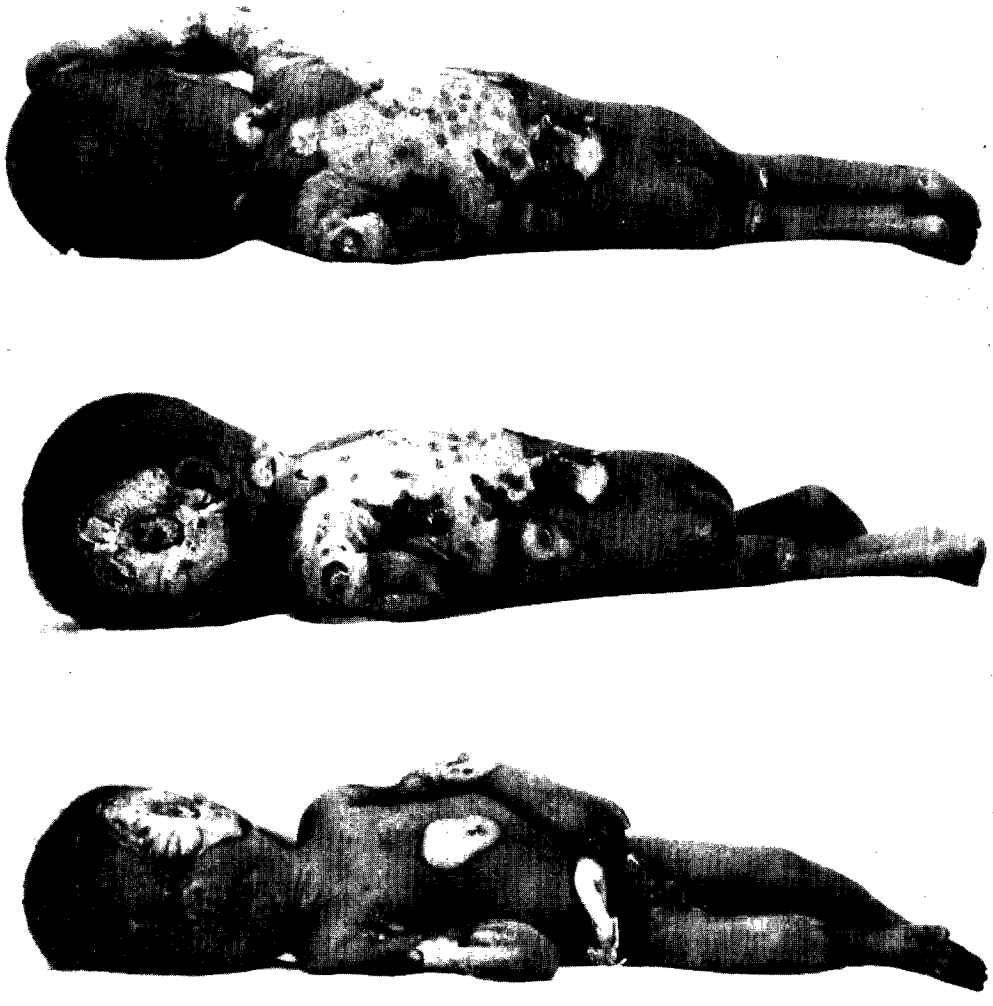

Fig. 162. Congenital generalised vaccinia.

The third suggestion is that the placental membranes might have had a general infection, and the foetal skin would be bathed in infected amniotic fluid. Unfortunately the placenta and membranes were not kept in this case, so that neither of these possibilities could be proved, but the writers feel that the peculiar distribution, largely on the extensor surfaces of the foetus subjected to pressure, suggests that infection was through the amniotic fluid, rather than

through the blood-stream, and that the lesion in the lung was not blood-borne, but due to contact with infected amniotic fluid during respiratory movements. Although it is suggested that the pressure might have induced lesions on the extensor sites in the manner similar to pressure points in smallpox, it seems much more likely that the infection was a mechanical one, particularly via the hair follicles, due to the pressure on the skin, the infant being bathed in infected amniotic fluid.

The fourth hypothesis, which the authors admit is purely conjectural, but which is of some interest in view of the rarity of this condition, is that this woman, who was three months pregnant, was unmarried and had already had one illegitimate child, was ill and unfit for work during the period of viraemia from vaccination, and possibly may have attempted abortion at this time, and in this way opened up the vessels, allowing the transmission of virus direct from her blood-stream to the amniotic cavity.

Possibly the condition may not be as rare as the two recorded cases would imply, but much further investigation is required to test these interesting theories. The clinical similarity with vaccinia gangrenosa would suggest that some defect of immunity mechanism or serum proteins might also occur, and perhaps determines the rarity of skin lesions in foetal infection with vaccinia virus.

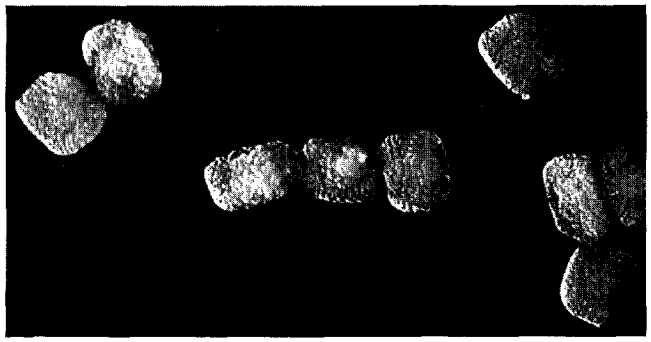

FIG. 163. Vaccinia virus (×64,000).

CHAPTER 7 | *Clinical Vaccination*

ORIGIN OF LYMPH

The original material for vaccination was obtained from cowpox lesions on the udder of the cow, or from human cases.

The nearly clear exudate, called "lymph", was taken from the vesicle and inoculated into the skin of the arm, and a supply was maintained by removing lymph from the vesicle at about the eighth day, sometimes earlier, and using this for further human vaccination. The material was also dried on threads and pieces of ivory, but generally had a short life. Jenner's original strains were soon lost.

The material first used in London by Woodville and Pearson was obtained from a cowpox lesion on the arm of Sarah Price, milkmaid in a dairy in Gray's Inn Road. Supplies were also obtained from Clarke's farm in Kentish Town, and Jenner was sent some from this source. As related in the chapter on the history of vaccination, Woodville's lymph probably became contaminated with smallpox virus, as it was used within the smallpox hospital, but he continued to use it and distribute it widely, Jenner receiving a supply derived from a case named Bumpus. Although Woodville's lymph, used in the smallpox hospital, gave rise in two-thirds of the cases to a secondary rash, almost certainly smallpox, the same material when used in the country or on his own private patients, very rarely gave any general eruption. Much, if not most, of this smallpox was due to simultaneous infection by the normal respiratory route, but it would appear that if a mixed variola-vaccinia lymph is used, it will yield vaccinia on human propagation rather than variola. Apart from vaccinia virus being more dermatrophic, the operator will tend to reject for further use material from a case having a generalized eruption, so that a selective effect occurs.

Sacco in Italy obtained an independent supply from a case of cowpox in the cow, and sent some to Austria (de Carro, 1804) and elsewhere, but much of the lymph used in early vaccination in Europe came from Woodville in London. This material, through the hands of Lettsom, Jenner, Haygarth and others, was also sent from England to America. Although

some claim to use a direct descendent of Jenner's "lymph", and some strains undoubtedly passed through Jenner's hands, none are derived from his original experiments.

Jenner regarded arm-to-arm vaccination as the normal method of propagation, but others wished to simulate cowpox more closely by inoculating a cow with material from a human case, the process being termed retrovaccination. There appeared to be no difficulty or uncertainty in the process, so long as the animals were sufficiently young, and it enabled a considerable amount of vaccine material to be produced. It was used in 1805 by Troja, shortly after the introduction of vaccination into Italy, and was continued until 1842, when Negri gave up retrovaccination, and began to propagate the virus by inoculation from one cow to another. Subsequently he came across natural cowpox in Calabria, and continued with this source of virus, but in 1858, for reasons unknown, he renewed his supply, but this time it was obtained from London, and therefore there can be no certainty as to its source. This strain was obtained by Lanoix in 1864, and taken to Paris, where with Monsieur Chambon he set up what was ultimately to become the Institut de Vaccin in the Rue Ballu. Shortly afterwards, a natural source of cowpox was discovered at Beaugency, and the Neapolitan strain was abandoned. In 1866, another source of cowpox, at Saint-Mandé, provided a new source of virus, and the two strains were mixed, and have been used ever since. Bovine vaccine was increasingly used. It was introduced into Boston in 1870 by Martin, using the Beaugency strain, into Japan in 1874, but not into England, largely due to the efficient collection and distribution of human lymph, until 1881.

Arm-to-arm vaccination, over long periods, undoubtedly weakens the virulence of some strains, giving rise to poor reactions. Gins (1949) states that by 1860 vaccination in Germany bore only faint resemblance to Jennerian vaccination. As new sources of cowpox could not be easily found, its possible derivation from smallpox was tried early, although never attempted by Jenner. In 1801, Dr. Gassner of Günzberg in Bavaria is reputed to have successfully inoculated smallpox virus onto the cow once in eleven attempts. In 1828, Dr. Sonderland claimed to have infected cows from blankets which had been in contact with smallpox patients. Thiele in 1839 and Ceely (1840) both produced artificial cowpox, which was used in large-scale vaccination. Haccius (1892) gives a list of some twenty investigators, eight of whom made successful inoculations of smallpox virus in the calf, which after two or three passages in the calf, and five or six in humans, produced entirely normal vaccinations in children. Success came to most of the investigators only after many attempts. Badcock is reputed to have made five hundred attempts, over a period of twenty-five years, thirty-seven having been successful (Copeman, 1898). Jenner himself suggested that some special traumatic factor was necessary, even for the transfer of cowpox from cow to cow. Copeman (1921) stated that smallpox virus derived from inoculated smallpox in man was necessary, and that virus derived from natural cases of smallpox failed. He appears to have assumed this following his successful experiments using variolation of the monkey as the source of his material for the calf, but he gives no proof.

Crookshank (1889), supporting the work of the Commission of Lyons, believed that vaccine derived from the inoculation of cows with smallpox was still smallpox virus. The experiment was not continued long enough, and contamination of the site, or of the instruments, did give rise to the persistence of smallpox virus, so that direct inoculation of the scrapings gave rise to this disease and not to cowpox. This also happened to Martin in 1860. Badcock's 1840 strain was used for over 14,000 vaccinations which never gave rise to an infectious disease capable of spread from individual to individual, such as had occurred with

every other strain of genuine smallpox virus used in variolation. The problem is further confused in that cowpox lymph derived from the earliest passage, when inoculated into man, gives rise to a considerable amount of reaction, and occasionally some generalization. Nobody today seriously suggests that modern vaccinia strains are variola virus.

The relationship between the viruses of variola major, variola minor, vaccinia and cowpox has been studied by laboratory workers for a long time, from Blaxall (1923) and Gordon (1925) to the more recent studies of Downie and his colleagues (Downie and Macdonald, 1950; Downie and McCarthy, 1950; Downie, 1951*b*) and by Fenner (1958). Although variola major and variola minor are so distinct epidemiologically, there was until recently no method of detecting any difference between these viruses, whose antigenic structure appears to be almost identical, but the work of Dinger (1956) and Helbert (1957) suggests that growth in the chorioallantoic membrance may show a quantitive difference. Nizamuddin and Dumbell (1961) describe a simple test which appears to differentiate clearly between a number of epidemiologically distinct strains. Ten variola major strains produced lesions on the chorioallantois at 38–38·5° C. after 2 to 3 days' incubation. Four strains of variola minor virus did not.

Cowpox virus recovered from accidentally infected man or from cows in "spontaneous" outbreaks can be clearly differentiated from current strains of vaccinia (Downie, 1939*a*, *b*; Fenner, 1948) on the characteristics of growth on the chorioallantois. It would seem possible that even the so-called "spontaneous" strains of cowpox which are recovered in England, Holland and some other countries today are derived from strains of vaccinia rather than from smallpox, which was probably the origin of the cowpox seen in the time of Jenner. Perhaps a clue to this lies in the white variants of cowpox grown on the chorioallantois described by Downie and Haddock (1952) and van Tongeren (1952) and found again in the strains examined extensively by Fenner (1958), as these closely resemble strains of vaccinia in some but not all characteristics. Although some of the outbreaks of clinical cowpox in both animals and man have been shown to be due to direct vaccinial inoculation of the animals, the source of spontaneous cowpox often cannot be discovered, and must be derived either from previous clinical cases which have been missed, or from symptomless carriers of virus in bovines or some other animal. (See Chapter 8.)

Fenner (1958) states: "The variability in the characters of vaccinia strains, all of which are undoubtedly vaccinia, is great, and there is no reason to believe that we have traversed the whole gambit of differences. Perhaps the only characteristics that are relatively constant are the antigenic structure, as determined by neutralization and complement-fixation tests, the morphology of the elementary body and the fact that all strains of vaccinia produce relatively large pocks on the chorioallantoic membrane. Even in such properties as heat resistance and the production of haemagglutinin, strains were found which differed profoundly from most of the others." This evidence supports the view of many epidemiologists, clinicians and others intimately concerned with smallpox over the last 100 years, that considerable variation exists in the power of vaccinial strains to produce lasting immunity in man. Figures from India, quoted by Thanawala (1956, 1959), showing high fatality rates in children under ten years of age, with evidence of having been successfully vaccinated, suggest that the immunity produced must be of a very short duration. The virulence, or power to infect, so important in revaccination, was shown by Rivers *et al.* (1939) to vary widely in three different strains, two of them commercial vaccines used for public vaccination in the U.S.A. The information from vaccine institutes is sometimes obscured by the pride which each takes in its own product.

The pedigrees of vaccinia strains in use today are very mixed. Most are claimed to be derived from natural cowpox, or from smallpox, both variola major and variola minor. That used by the Lister Institute is derived from a smallpox strain from Cologne, in the late nineteenth century (McClean, 1949). Almost all strains have been in use since the end of the last century, but some are older. One at least, in use in Korea, is a recent strain, having been evolved from smallpox virus by the Japanese about 1942. It is not uncommon for a vaccine institute to import a strain of vaccinia and to use it as seed virus mixed with the local strain. Fenner and Comben's work (1958) would suggest that new strains might be evolved in this way.

Repeated passage of the virus through the calf or other producing animal is usually considered to lead to loss of virulence, and many laboratories, either as a routine, or from time to time, passage the virus in the rabbit, monkey or in human beings, to rejuvenate the seed virus. McClean (1955) considers human passage is unnecessary and possibly dangerous. There is considerable lack of uniformity in policy in different institutions. In Bandoeng in Indonesia, buffalo lymph has been used for many years without passaging the material in any other animal. Field results obtained with this lymph, admittedly in a dried form, suggest that its potency is not as great as some others (Dixon, 1954). The Buddingh strain of virus used in Texas for nine years through 240 transfers in the chorioallantoic membrane showed loss of potency, and was ultimately replaced by a new strain derived from calf lymph (Cook *et al.*, 1953), although other writers have claimed long use of chick virus without loss of potency.

Commercial techniques in vaccine production vary in detail, but are similar in general principle. The animal is kept in quarantine, usually for a fortnight, and after an examination to ensure that it is healthy, the skin is prepared by being shaved and washed with ether soap and rinsed with sterile distilled water. This reduces the bacterial contamination. The cleansed area is lightly scarified with a sterile, eight-bladed scarifier, and about 8 ml. of seed vaccine are applied to the scarified area (in the sheep). Each animal is then returned to a special pen, and after a four-day incubation period, or when the operator considers he will get the maximum yield, the animal is killed, washed again, and the vaccinated area is curetted with a special Volkmann's spoon. A post-mortem examination is done, to ensure as far as possible that the animal was healthy. The pulp, which is pale pink, because of slight blood contamination, can be stored at $-10°$ C. for long periods, until required for further purification. At the Lister Institute, McClean (1949) grinds the crude vaccine pulp with twice its weight of 1 per cent solution of phenol in sterile distilled water, and allows this to stand at 22° C. for forty-eight hours. Phenol greatly reduces the number of contaminating organisms. Glycerine, equal in volume to the amount of phenol solution, is then added, so that the final concentration of phenol is about 0·4 per cent. The lymph is then sieved and stored at below $-10°$ C. In recent years, laboratories have also used penicillin, streptomycin and other antibiotics to reduce the bacterial content below the minimum required by the therapeutic substances regulations of different countries. The vaccine should not contain human pathogens, and haemolytic streptococci, *Bacillus coli*, tetanus and anthrax organisms are specifically tested for. On the other hand, absolute freedom from harmless contaminants is not essential; indeed, they may have some synergistic effect on vaccinial growth. Although the virologists attending the seminar on smallpox vaccination under the auspices of WHO at Lima in 1956 resolved unanimously that vaccine lymph should be obtained with as low a bacterial count as possible, I wonder whether the quest for absolutely pure virus suspensions is as valuable a contribution to the prevention of smallpox as may appear at first sight.

It should be noted that vaccine may contain other virus material derived from the animal, such as that of foot-and-mouth disease (Magnusson, 1930). To overcome these difficulties, purified vaccinia suspensions have been prepared by Yaoi (1934) and others, and more recently by L. H. Collier (1952). Some involve the preparation of virus in the chorioallantoic membrane of hen's eggs (Rivers 1935), when a bacteria-free suspension can be obtained, or a technique is used depending on fractional centrifugalization (Collier, 1952), or using bactericidal substances. The sheep, used by Green at the Lister Institute during the 1914–18 war, appears in many ways to be more satisfactory than the calf, and is cheaper (Topa, 1951), and most of the world's vaccine is still produced by animal inoculation. There seems to be

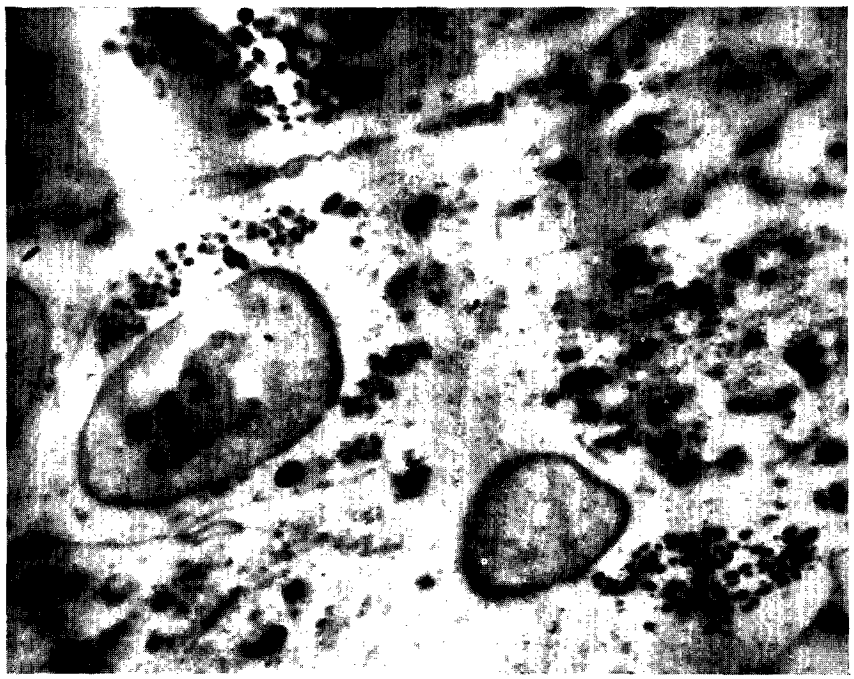

FIG. 164. Vaccinia virus in the cells of the Chorioallantois.

some reluctance to substitute egg vaccine, although, in the opinion of some, the yield appears to make it an economic proposition. Technically, it requires more skilled personnel and supervision than animal inoculation, and there would appear to be a greater risk of contamination with viruses pathogenic for man, although bacterial freedom can be readily achieved.

The difficulties in maintaining glycerinated lymph, particularly in tropical climates, led to many experiments with other forms. Lanolated lymph was introduced at the end of the nineteenth century, with varying degrees of success, but today is usually regarded as unsatisfactory, although it has been used in parts of Africa quite recently (Blair, 1955).

Dried vaccine has been used since the time of Jenner to allow a carry-over between successive series of arm-to-arm vaccinations. According to W.A. Collier (1952), dried vaccine was officially

recognized in Austria in 1836, and was commented on favourably by Seaton in 1868. Prior to 1881, all methods had used natural drying, and protection from light, but Reissner (1881) dried the lymph in a desiccator. It appeared to be satisfactory not only in Europe, but was also tried in the tropics. From then on, a number of workers (Blaxall, 1902; Carini, 1906; Achalme and Phisalix, 1909) all claim to have produced dried vaccine which would remain viable at tropical temperatures for a month and sometimes as long as three months. Although claims were often made of a high take rate, up to 85 per cent in primary vaccinations, these were often done on a very small number of cases, and success in revaccination was taken for granted, any sort of reaction being regarded as positive. Many of the experimenters were satisfied with take rates in primary vaccination of only 60 per cent, and it was rare to find any with a take rate of much above 80 per cent. Variation between different batches of lymph, dried by the same process, seems to have been one of the main troubles, and although live virus might be present for as long as nine years as in Otten's technique (W. A. Collier, 1952), the normal primary take rate was not above 85 per cent, and local doctors could produce a better response with glycerinated lymph from the same source.

In 1952, L. H. Collier dried a purified virus suspension in a peptone medium, and following the WHO trials in 1952 of dried vaccines produced in different countries (Cockburn *et al.*, 1957), it was shown that this one, produced by the Lister Institute, gave a product which satisfied all the requirements. Tested by Cross, Kaplan and McClean (1957) it is a considerable advance, on anything previously used, and a description of the method of production is given in full in Appendix 1 page 450. It is taken from the WHO report of the tenth World Health Assembly. The vaccine remains potent at 37° C. for at least three months. In the original trials carried out by Cockburn *et al.* (1957) it was claimed that 100 per cent successful primary vaccination was obtained in adults, with vaccine containing 10^8 infective units (I.U.) per ml. The series tested was relatively small, and primary vaccination in infants, although not reported upon, would probably give a take rate of 96 to 98 per cent. Partly deteriorated vaccine of 10^6 I.U per ml. produced smaller lesions and a 50 per cent take rate, but Cross (1959) has shown that these lesions, small when seen at the eighth day, are really delayed normal vaccination, and the level of immunity, as judged by serological tests, appears to be satisfactory.

The importance of the time of vesiculation, rather than the time of vaccination, has been repeatedly stressed in the past by Ricketts (1908), Marsden (1948) and others. The delay in obtaining immunity from partly deteriorated lymph would be no serious disadvantage in routine primary vaccination, although it would be in attempting to control smallpox outbreaks by expanding ring vaccination. No evidence has been presented to date of the power of this vaccine to effect revaccination, compared with glycerinated lymph. This is a far more critical test, the importance of which I have stressed before.

Potency of vaccine is normally tested by comparison with a standard vaccine, in the production of lesions on the scarified skin of the rabbit. More recently, pock-counting techniques have been used, growing the virus on the chorioallantois. These methods are discussed by McClean (1955), Westwood, Phipps and Boulter (1957) and Dumbell, Downie and Valentine (1957). The WHO study (Cockburn *et al.*, 1957) suggested that satisfactory smallpox vaccine, from whatever source, should have a pock count of 10^8 I.U. per ml. Although the take rate will be affected by the vaccination technique, in particular size and number of lesions, approved vaccine should produce at least 95 per cent (plus or minus 3) insertion take rate of genuine

Jennerian vesicles in infants over three months of age, and at least 98 per cent (plus or minus 2) take rate in known susceptible adults. For significant results, a suitable sample size for infants is about 210, and a suitable sample size for adults is about 190.

It seems unfortunate, as I have pointed out before (Dixon, 1954), that some laboratories have little idea of the success or failure of their vaccine in practice. In some, small quantities from each batch are used in the routine vaccination of infants, but often little attention is paid to this, and practically never is a comparative trial in revaccination performed, such as that done by Rivers *et al.* (1939). It is of interest that McClean (1950), commenting in the *Bulletin of Hygiene* on the dried vaccine produced by Fasquelle complained that the only result recorded was the take rate in human beings, and not the virus counts. Unfortunately we have no laboratory tests which effectively measure the immunity level produced by vaccination against smallpox, but it would seem there is room for more combined field and laboratory tests, similar to that of Cockburn *et al.* (1957) but on a larger scale, to try and determine which vaccinial strains give a high level of immunity, and which have the property of overcoming skin insusceptibility in giving effective revaccination. Even allowing for the over-optimism of the early vaccinators, the literature of the last 150 years records many observations of experienced vaccinators that the vaccine and duration of immunity obtained in their day appeared to be less satisfactory than in earlier times. We have consistently followed the path of producing a more elegant vaccine, but one which need not necessarily produce such a satisfactory level or duration of immunity.

Vaccine pulp of different kinds and concentrated virus suspensions, can be stored for long periods at low temperatures. The life of glycerinated vaccine under different conditions of storage is given by Sachs (1951) as follows:

Storage temperature	Life
(*a*) Minus 10–20° C.	(*a*) Twelve months from date of manufacture
(*b*) Refrigerator temperature, 2–10° C.	(*b*) Fourteen days from date of issue
(*c*) Cool, dark place	(*c*) Not more than seven days from date of issue

It is important to remember that the manufacturers of lymph err considerably on the side of safety, as they have their reputation to maintain. Vaccine should not be removed from cold storage and allowed to remain at room temperature and then returned to store. This appears to hasten deterioration. Exposure to light is also harmful. Batches of lymph will sometimes remain potent for a surprisingly long time, even at room temperature, and hence the dangerous opinion of some practitioners that lymph need not be stored under the conditions laid down in the supplier's instructions. It must be pointed out that some batches of lymph deteriorate quite rapidly, and therefore the instructions are aimed at securing a margin of safety for all batches. Successful vaccination has been obtained, even in tropical countries on a few individuals, with lymph that had been kept at room temperature for over a year, and the most extreme example is a strain reported by Kaiser (1951), reputed to be able to withstand boiling. A small number of virus particles appear able to remain alive under conditions adverse to the majority. The great virtue of dried lymph is its ability to withstand storage at ordinary temperatures, and in the more modern ones at extremely high temperatures, 45° C. for over

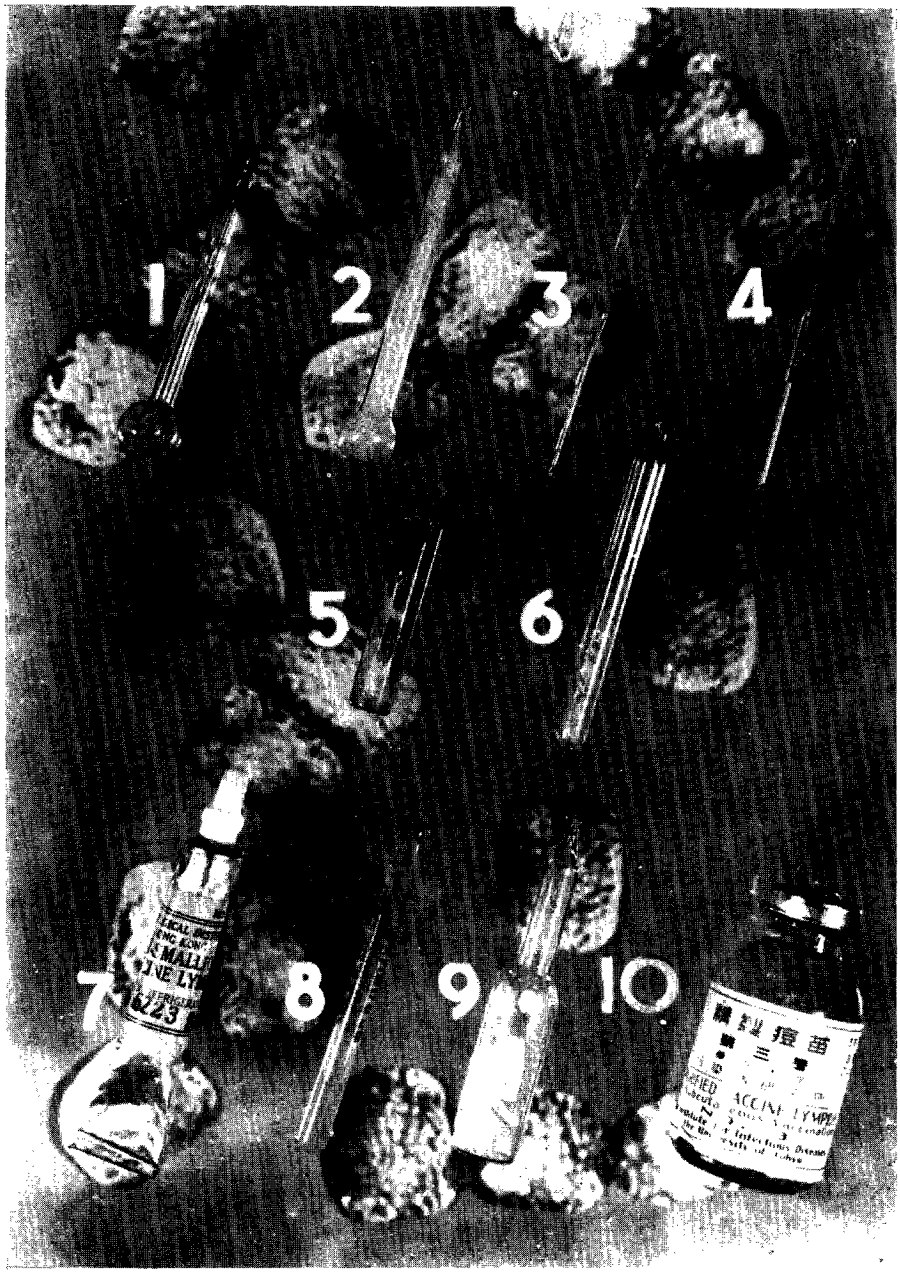

FIG. 165. Varieties of smallpox vaccine.

1. Dried vaccine, Bandoeng
2. Dried vaccine, Saigon.
3. Glycerinated lymph, Canton.
4. Glycerinated lymph (egg), Wellington
5. Dried vaccine, Manila.
6. Dried vaccine, London.
7. Glycerinated lymph, Hong Kong, 8 c.c.
8. Glycerinated lymph, Saigon, 100 doses.
9. Dried vaccine, London, 100 doses,
10. Virus suspension, Tokyo.

eight weeks, 37° C. for at least three months. Even this type of lymph should be stored at as low a temperature as is practicable, and should not be exposed to light. It is very important to appreciate that once dried vaccine is reconstituted, usually with glycerine saline, its life at full potency is very short (as with ordinary glycerinated lymph); under tropical conditions it may not be more than a few days. Due to the dangers in reconstitution of adding infection, particularly under field conditions, it is desirable to regard reconstituted lymphs as having a shorter life under the same conditions as ordinary glycerinated lymph, and limiting its use to the day of preparation.

Amongst clinicians, it is an almost universal opinion that during a smallpox outbreak, when the lymph is being issued fairly rapidly from the producing centre, the later batches produce a much greater take rate, particularly in adult revaccinations. The possibility of this is denied by most laboratories. One must admit that during an outbreak the clinicians may do their vaccinations more conscientiously, perhaps with larger inoculations, but it seems possible that there are other factors affecting the avidity of lymph which are not revealed by the ordinary tests carried out to satisfy the legal requirements in each country. I feel there is room for further investigation on the possible effects of long storage, even under conditions which to the virologist appear quite satisfactory.

In most countries, vaccinia virus is supplied to practitioners in glass capillary tubes. These are nominally sufficient for one vaccination, but even those issued in England, which are very fine, can be used to vaccinate quite a large number, over twenty persons, if an economical technique is used. In some countries the capillary tubes are much larger, and may contain five or ten "doses". Metal tubes similar to those used for toothpaste, and ampoules and larger bottles of various sizes, contain quantities recommended for 25, 50 or 100 vaccinations, but in general many more vaccinations can be done than the number quoted. The vaccine deteriorates at room temperature, and therefore the size of the container should depend on the number of vaccinations to be done. In general, the issue of lymph in very small containers, capillary tubes, is probably the best, as this allows a small number to be taken from the refrigerator, and after vaccinations are done, any unused can be thrown away, and not returned to the refrigerator. If larger containers are used, these may be satisfactory for the vaccination of large groups at a time, but there is a real danger of the vaccinator, particularly if a medical auxiliary, keeping a partly used ampoule from one day to the next with, under tropical conditions, a serious decline in activity. My survey of vaccination practice in some fourteen countries in the Western Pacific and South-East Asian regions for WHO in 1954 showed that much of the failure of vaccination was due to the lack of appreciation by vaccinators of the rapid deterioration of lymph. In some instances, this was aggravated by the size of the container in which the lymph was issued.

Failure to understand the situation was often due to not appreciating that in the deterioration of vaccinia suspensions some more resistant particles survive longer, and so give some positive takes in primary vaccination, even under adverse conditions. Unfortunately the negative response in the remainder of individuals is taken to imply immunity, although they are often susceptible to fully potent lymph, and so to smallpox.

TECHNIQUE

Although some immunity can be obtained by subcutaneous inoculation, maximum immunity and true Jennerian vaccination is only achieved by growing the virus in the

epidermis. It is essential therefore that virus be applied by a suitable technique to living cells. With live virus, an exact dose is not necessary, although Jenner himself had no clear views on this subject. Pearson, his contemporary, thought that in inoculated smallpox the quantity of virus did not influence the severity of attack. On the other hand, Sutton and Dimsdale only used a scratch an eighth of an inch long. Hime, writing in 1896, felt that the application of much virus overcame any inherent protective mechanism, as is commonly seen in invasion of the body in other ways, and believed that increasing the area of contact between the virus and cells not only increased the chance of virus growth, but the degree and duration of immunity.

There appears to be some evidence that the more virus that is applied per unit area, the greater the chance of success, and that vaccine suspensions with a large concentration of virus particles appear to be more successful than those with few, particularly in revaccination, but positive takes can occur with extremely weak concentrations, diluted to 1 in 500,000, and inoculated on exceedingly small sites.

There is some variation in the susceptibility of different areas of the skin. In revaccination of partial immunes, using multiple sites, it is not uncommon to see one take, with definite viral growth, and the other two or three show an allergic response. Although the dose of virus is very small, increasing the bulk of the material applied, of allergens and possibly of contaminating, non-pathogenic organisms, may act in increasing the chance of take.

The level of immunity obtained appears to be independent of the site, but successful primary Jennerian vaccination always leaves a scar. Site therefore has to be considered from a number of aspects. The primary vaccination techniques described below will leave a minimal size scar about a quarter of an inch in diameter, free from keloid formation, and although not a beauty mark, it need not be very disfiguring. A little artistry can be used in selecting the site, and if a B.C.G. scar is also present, it is my practice to site the vaccination so that the two give a nicely balanced appearance. If vaccination is done in infancy, the scar will grow to roughly double the size of primary vaccination by the same technique in the adult. In old age, the scar tends to become less distinct, particularly if foveation was originally absent. Deeply foveated scars never completely disappear.

In some countries it is increasingly difficult to find sites on the body where scars are not exposed to view on some social occasion. The medical literature abounds with descriptions by enthusiastic medical practitioners of recently discovered "ideal sites". Almost every part of the body appears to have been used at some time or another. At first appearing so advantageous, these "new" sites never seem to gain popularity, and their inventors return to what is almost universally regarded as the best site, that is the outer aspect of the arm, about the level of the deltoid insertion. It is convenient of access, without much laborious undressing, it is unlikely to get knocked, and the secondary lymphatic reaction appears to be minimal. It is, however, a conspicuous place, and some prefer the inner aspect of the upper arm, or the flexor aspect of the forearm. The skin is particularly thin at these sites, and appears to give relatively small reaction, although more likely to injury. Although the forearm has never been particularly popular in England, it is used considerably in some continental countries, and for self-vaccination. In some parts of the world, the anterior abdominal wall is used. It has the advantage that it is usually covered. The leg has also been a popular area, but the upper part of the thigh is particularly unsatisfactory as the skin is thick and the reaction tends to be much greater than on the arm. The lower part of the thigh, particularly the outer aspect, and the lower leg, over

the calf muscles, have also been used, with varying degrees of success, but both are liable to injury. In a young infant, the sole of the foot is a satisfactory site, particularly from the point of view of the scar.

Owing to much personal bias over choice of site, it is not easy to prove the merits of one or other in giving the lowest rate of complications. It is probably fair to say that, when complications arise, they are more inconvenient on some sites than on others. In some parts of the world, due to habits in dress and tight clothing on the upper arm, the lower leg is used. The hand should not be used for primary vaccination, as the reaction tends to be more severe than elsewhere, although it might be used more for the revaccination of smallpox contacts, as it appears particularly receptive to virus growth. Vaccinial lesions sometimes occur on the hands in workers in vaccine institutes, and on the hands of doctors doing large numbers of vaccinations, who are usually assumed to be immune.

If, for no apparent reason, primary vaccination repeatedly fails on one site, it will sometimes succeed on another—for example, the opposite arm, or the forearm instead of the upper arm. Revaccination can be, and often is, done directly on the old scar, with the idea of preventing a second. However, unless the revaccination is a long time after the primary, a permanent visible scar is unlikely to result, and residual insusceptibility of the skin is likely to be higher on and adjacent to the scar than in other areas of the body. In the revaccination of smallpox contacts, it is advisable to use the opposite arm to that on which the primary vaccination has been done.

The procedure of growing vaccinia in the skin is not a surgical operation, and is not even similar to subcutaneous inoculation, and no antiseptics of any kind should be used, particularly persistent ones such as iodine or acriflavine. The sensitivity of vaccinia varies considerably, but it is killed by a feeble antiseptic like potassium permanganate. In many countries it is still the recommended practice to clean the skin with ether, acetone or spirit, assuming that this will volatilize before the virus is applied, but this may not always be so. Some advocate the use of soap and water, but if this is done too vigorously, damage can occur to the skin, and it may encourage secondary vaccinial lesions, and increase the reaction. No cleaning of the skin is required in a person whose skin is normally clean. If the skin is really dirty, the person should be asked to wash before presenting for vaccination.

The quantity of lymph required is very small. If put up in glass capillary tubes, it is my practice to break off both ends of the tube, to tap the lymph to one end, and to apply the end of the tube to the skin. By breaking the area of surface tension, a small quantity of the lymph will pass on to the skin.

It is not necessary to use a rubber bulb or teat to expel the lymph, unless it is particularly glutinous. It is obviously not desirable for the operator to blow the lymph from the tube onto the skin, although this still does occur. Apart from the risk of infection to those vaccinated, the vaccinator may inoculate his or her own lip. A further disadvantage of this method is that much surplus lymph will remain on the skin, requiring removal by a swab, to prevent it contaminating the hands of the patient or some other person, with the risk of accidental vaccinial lesions on the face or other part of the body. If the vaccine is in larger containers, it may be applied direct from the container, such as a lead-foil tube, or from an opened ampoule by means of a glass rod or sterile orange-stick. The virus can then be introduced into the living-cell layer by scratch, puncture or pressure, as described below.

Most vaccinators apply the lymph first to the skin, and make the puncture or scratch through

it. I think this is easier, but some make the scratch or puncture first, then apply and rub in with the applicator. Minor variations in technique are not important so long as the operator is entirely satisfied that he is able to obtain a consistently high successful primary vaccination rate in susceptible individuals.

A great variety of instruments have been described with which to perform the scratch. Much was claimed of them, but few have lasted; special vaccinaters, vaccinostyles, the point of a scalpel or a knife, and a variety of needles. I use a large, straight, triangular surgical cutting needle of the Hagedorn type, No. 1.

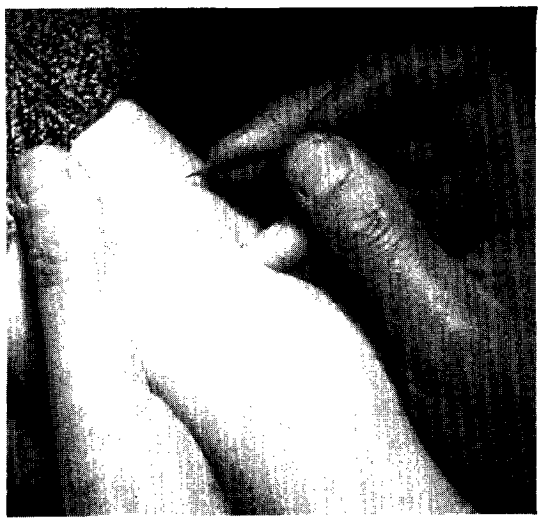

FIG. 166. Vaccination, scratch technique. The third and fourth fingers steady the hand.

The instrument does not want to be too sharp, as it will cut too deeply, but if very blunt, greater pressure will be required. If vaccine is applied to the unbroken skin, no reaction will occur. It is necessary to remove some of the cornified, keratinized layer, to allow access to living cells. I point out to students, particularly to auxiliary vaccinators, the analogy of getting through the skin of the onion to something which is succulent and alive. It does not matter how this is achieved.

The oldest method, and one most frequently used, is the scratch technique, a single scratch being made with the point of the instrument. The length of the scratch is important; the longer it is, the greater will be the ultimate size of the vaccinial lesion. On the other hand, the smaller the scratch, the greater the possibility that virus will not be introduced to a living-cell area which will allow its growth. In routine primary vaccination, the scratch should not be more than one-eighth of an inch long. This will give rise to a nearly circular, primary lesion, about one-quarter to three-eighths of an inch in diameter. If more certain attainment of infection is required, it is far better to repeat the procedure on two or more sites of the arm separated from one another by a distance of at least two inches, rather than to increase the size of a single scratch, and so increase the area of a single vaccinial vesicle. Two or three scratches

made parallel to one another and close together will again give rise to larger lesions, and this technique, together with cross-hatching, where the scratches are multiple and done in two directions at right angles to one another, should be reserved for smallpox contacts and those individuals who prove refractory to vaccination or revaccination by simpler methods. Large vaccinial lesions are likely to give rise to much local discomfort, and are more liable to secondary infection, and give rise to painful axillary adenitis (Fig. 166).

Another method much advocated is the multiple-pressure technique (Leake, 1927). The needle is held parallel to the stretched skin. Due to its elasticity, each time pressure is applied

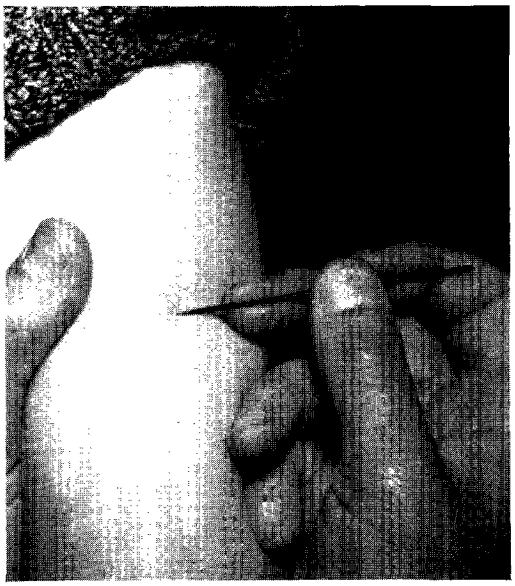

FIG. 167. Multiple-pressure technique. The side of the hand rests on the arm, and the hand is rocked. The needle is pressed on to the stretched skin.

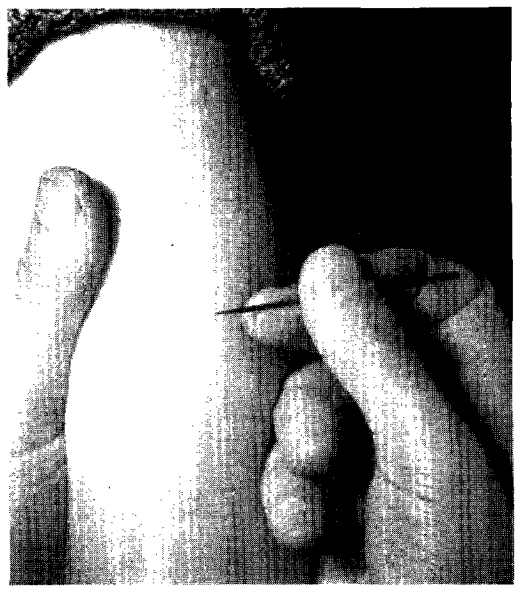

FIG. 168. Multiple-pressure technique. Without moving the position of the hand, the needle is rocked just clear of the skin.

the point enters, and on being raised strips up minute parts of the cornified layer (Figs. 167 and 168). Thirty such pressures have been advocated for a primary vaccination, but Rees (1948) suggests that ten are enough. Mitman (1952) pointed out that in many instances even one pressure will take. The multiple-pressure method is really a multiple-insertion technique, using a very small area for each insertion. It is important, however, that the total area on which the needle is operated should not exceed one-eighth of an inch in diameter, otherwise a large coalescing lesion will result. It is therefore necessary for the operator's hand to be resting on the patient's arm, and the pressures obtained by a rocking movement. The skin must also be stretched, and this is not so easy to obtain in some areas of the body. Even as recently as 1955, one well-known textbook still suggested that application of the needle be made to an area between one-quarter and half an inch in diameter. This would give rise to a very large lesion, similar to the cross-hatching technique of the older vaccinators.

Many other methods of vaccination have been described. In the multiple puncture, the

needle is made to enter the skin, either vertically, on the slant, or nearly parallel with the skin, and a few superficial punctures are made through a drop of lymph. A round-bodied needle is usually used for this purpose. The drill method is done with a single revolution of a "drill", pressure not being sufficient to draw blood. A variant of this is to use the broken end of the capillary tube, but this is unsatisfactory as small pieces of glass are quite likely to be left in the skin. A small quantity of vaccine may be given by very superficial intradermal injection with a fine needle, but a successful result appears to be produced from the virus growing at the skin puncture, rather than from that in deeper tissues. Parish (1958) suggested using a Heaf gun, but this seems unnecessarily complicated and would produce too large a lesion for primary vaccination. Elisberg, McCown and Smadel (1956) have reported on the use of jet inoculation for this purpose. Although vaccinations may be done very rapidly by this method in military establishments, much of the virus injected is subcutaneous, it uses a far greater quantity of material and does not appear to possess any real advantage over a well-organized scratch or multiple-pressure technique.

Simple as it may appear, it is difficult to get unbiased, accurate observations on different techniques carried out under identical conditions. The enthusiast for one particular method frequently does this with considerable care and attention to detail, but other methods more haphazardly, and often producing quite different size areas of inoculation. It can be emphatically stated that a scratch one-eighth of an inch long, and a multiple-pressure vaccination done on an area of one-eighth of an inch in diameter, produce vaccination lesions identical in appearance, with no difference in the local or general effects, or the character and size of the scar. Parish (1958), however, praises and cites the advantages claimed for the multiple-pressure technique as "complete absence of pain and bleeding, less general messiness, and a less risk of septic infection, less severe and less painful reaction and smaller scars, and a larger number of takes when the pressures are properly performed". The severity and the question of painful reactions are related to the area scarified, and personal idiosyncrasy, whatever technique is used. The question of messiness suggests that comparison is being made with small multiple-pressure vaccinations and old-fashioned gross scratch methods. The subject of pain at operation has often been brought up, but from the experience of questioning over five hundred medical students who had tested both the scratch and the multiple-pressure techniques on themselves, it is clear that the scratch, done with a Hagedorn needle, and only one-eighth of an inch long, is less painful than multiple-pressures. In young infants the scratch is practically painless, and extremely rapid. It is unusual for the child to even notice that it is being done. The time that the multiple-pressure takes to perform and the fact that it can be definitely felt does, I think, worry the infant more.

The Ministry of Health (England and Wales) pamphlet on vaccination against smallpox, 1956, confuses the issue by suggesting that when there is no urgency, and it is desired to minimize local and general reaction, the number of pressures in the multiple-pressure technique should be reduced from thirty to ten or less, but does not explain that the pressures should be done more or less on one spot, not greater than one-eighth of an inch in diameter, and the difference between a few or many insertions is largely on the chance of them taking and not on the area of the vesicle or the amount of general reaction resulting therefrom. The larger number of pressures increases the traumatic factor, and the speed of evolution, but when a person is exposed to smallpox, which presumably is the acid test, the Ministry of Health advises that the scratch technique be used. Which method produces the higher percentage

of takes would appear to be determined more by the attitude of the vaccinator than anything else, although enthusiasts for one or other technique have produced figures to convince themselves, if nobody else.

There is no such thing as the right or perfect technique. One would agree with the views of Seaton (1868, quoted by Marsden, 1946); "A careful man, who thoroughly understands his work . . . will succeed best in the way to which he is most accustomed. So much depends on habit, and if I may say so, on trick of hand."

It is almost universally stated in the textbooks that the operation should not draw blood. In theory, blood is virucidal, and if vaccinations are made very deep, there is the possibility of the mechanical removal of the virus by the flow of blood. I have seen many vaccinations done by non-medical vaccinators with very deep incisions in the skin, but they have been quite successful. Goodall (1942) carried out a small investigation which convinced him that the presence of blood appeared to increase the chance of success rather than decrease it, and Seaton (1870) regarded it as essential. Administrative timidity in those countries where post-vaccinial encephalitis has been common has encouraged similar techniques, and failure of vaccination is often due to lack of determination of the operator, and to the virus not being applied deep enough in the skin, rather than the reverse.

Little is gained by laying down very detailed administrative instructions. Far better to educate students to take an intelligent interest in this subject, and for doctors to watch the success rate of the operation, as this is the only measure of the value of their technique. In the case of non-medical vaccinators, it may be necessary to lay down some instructions to follow, but it is most important that supervisors personally check results, and do not rely on statistical returns, as the safeguard of this practice.

If only a small quantity of lymph has been applied, after the scratch or multiple-pressures have been done, no superfluous material will remain needing to be removed by swab. The site is best left uncovered, although in the tropics immediate direct sunlight on the arm may inactivate the virus sufficiently to prevent growth. In some countries, the intentional application of lime-juice may interfere and prevent success. Virus enters the cells quite rapidly and it would seem probable that, fifteen to thirty minutes after a vaccination has been done, it is not possible to eradicate the virus by ordinary washing. Unless there are special circumstances, such as a very dirty occupation, vaccinations should not have any dressing applied at the time they are performed.

Although the development of a vaccinial lesion depends to a small extent on the technique, it is largely determined by the presence or absence of specific immunity to vaccinia in the host. In primary vaccination in a susceptible individual, no change normally occurs in the skin for forty-eight hours. By the third day, a small papule has formed, and this enlarges, accompanied by a small area of erythema, until vesiculation commences about the fifth day. By the seventh day, the normal period for a primary vaccination to be seen, a well-marked vesicle occurs, white in colour with a slightly bluish tinge at the edge, as originally described by Jenner. The centre is slightly depressed, although this will depend to some extent on the size of the lesion. By the eighth or ninth day, the white colour has become yellowish, and a pustule is said to be present, although it may contain no frank pus. The pustule will dry up from the centre outwards, until by the eleventh or twelfth day it has become a brown scab. This remains attached to the skin, being shed about the twenty-first day, leaving a pink, slightly depressed scar, which ultimately assumes the normal skin colour. The base of the scar is frequently covered

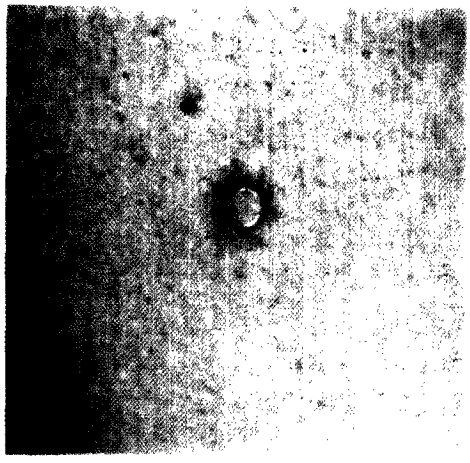

FIG. 169. Minimum technique, primary, at seven days.

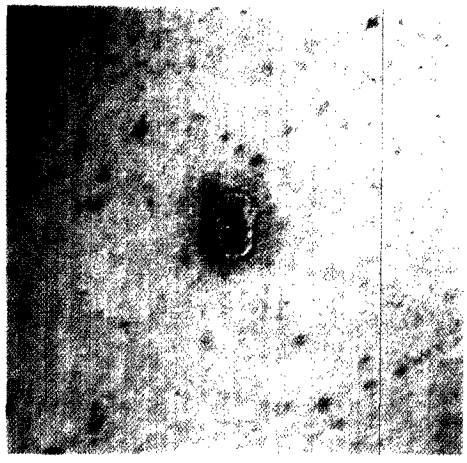

FIG. 170. Average technique, primary, at seven days.

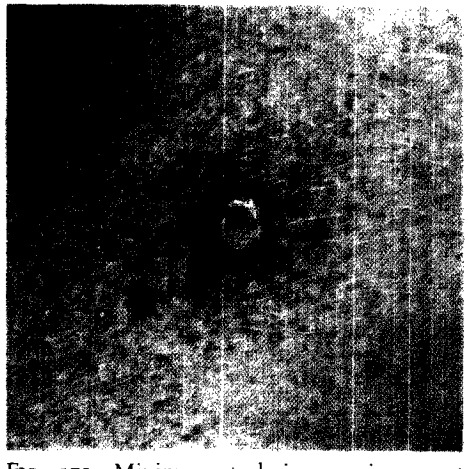

FIG. 171. Minimum technique, primary, at nine days.

FIG. 172. Average technique, primary, at nine days.

FIG. 173. Minimum technique, primary, at twelve days.

FIG. 174. Average technique, primary, at twelve days.

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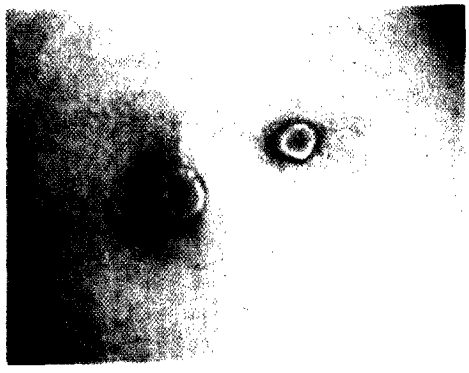


FIG. 175. Scratch and multiple pressure vesicles at seven days.

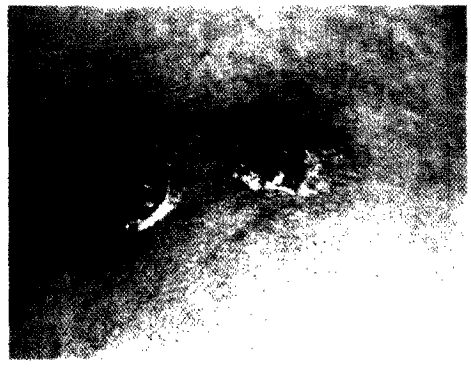


FIG. 176. Scratch and multiple pressure scabs at fourteen days.

There is no material difference in the rate of evolution and the result of these two methods. If the scratch is made slightly shorter, the lesions are identical in size.

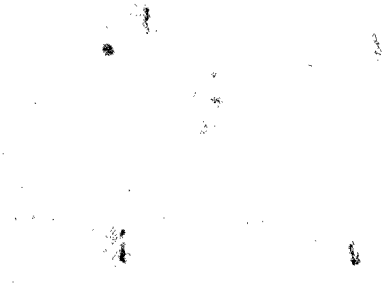


FIG. 177. Allergic reaction at forty-eight hours in an immune person. Upper left, live sheep lymph; lower left, dead sheep lymph. Upper right, live calf lymph; lower right, dead calf lymph. The same kind of reaction occurs whether the lymph is alive or dead.

FIG. 178. Soft papule at five days in a hyper-immune person who had been vaccinated over thirty times.

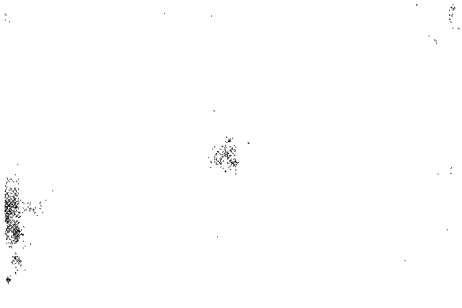


FIG. 179. Early allergic reaction at forty-eight hours.

FIG. 180. Revaccination after nine years. Accelerated vesicle at seven days, the roof has been removed by scratching. The lesion is more superficial and has more erythema than a primary.

with small pits, and is said to be foveated. This was regarded years ago as essential evidence of a good vaccination scar. Secondary sepsis prevents this formation, and small and more superficial vaccination lesions done today frequently leave smooth, non-foveated scars. Although many statistical studies were made in the nineteenth century on the occurrence of smallpox in those with good, foveated and those with "poor", non-foveated scars, it is recognized today that foveation is not a necessary feature of successful vaccination. In persons with pigmented skins, depigmentation first occurs, and may still be present after many years; in some there is an increase of pigment. The erythema surrounding the lesion varies considerably, but is usually present from the late vesicular to the early scab stage, and it may extend for about two inches. Although the public and some inexperienced doctors regard this as evidence of infection, it is probably local allergy to viral growth. Jenner and many of the early vaccinators regarded an area of intense erythema as a very good sign, indicating a good reaction. Later vaccinators (Hime, 1896) had complained of the poor areola as indicating feeble potency of lymph. In some individuals, an area of intracuticular oedema may also occur, particularly in those with fat, brawny arms. With minimal trauma vaccinations, evolution is delayed by as much as two or three days, so that by the seventh day a very small vesicle may be present, not more than one-eighth inch (4 mm.) in diameter, and this may not reach its maximum size until the eleventh or twelfth day.

At about the seventh or eighth day, there is dissemination of virus from the primary lesion in the skin. Accompanying the viraemia there may be a mild pyrexia, malaise and symptoms not unlike those of influenza. It is common for the axillary glands to be slightly enlarged from about the fifth day. The spleen is also enlarged, and may give rise to slight abdominal pain. It is to be noticed that infants under the age of six months appear to show very much less constitutional disturbance than adults, and frequently show no pyrexia between the eighth and tenth days. On the other hand, although many adults are made quite miserable by general malaise accompanying vaccination, others, vaccinated by just the same technique, appear to have no general symptoms at all. Buchanan and Laidlaw (1942), reporting on large-scale vaccination at the Glasgow docks, presumably in those doing quite heavy manual work, noted that vaccination or revaccination resulting in normal vesicular response only gave rise to some constitutional upset in some 16 per cent. It was noticed that less than 3 per cent were off work on this account.

The care of the developing vaccinial lesion is simplicity itself. The basic principle should be to leave it alone. If the site can be left exposed and uncovered, the vaccination will pass through its stages with the minimum of reaction. If the person is engaged in a very dirty occupation, or if he is required to wear tight clothing which might produce friction of the lesion, the site can be covered with a large piece of unmedicated lint or gauze, and this can be fixed to the skin by the application of sticking plaster well away from the site of the lesion, that is, the plaster should be applied practically at the top of the shoulder, and at the elbow, to hold the large piece in place. Otherwise, a piece of lint or gauze can be tacked inside the clothing. Only under very exceptional circumstances should an occlusive type of dressing be applied, as this increases the chance of sepsis and also of tetanus. It should be removed as soon as practicable.

Advice is frequently given that lesions should not be washed until the scab has become detached. This is a quite unnecessary restriction. If the lesion is at the vesicular stage, attempts to wash it will cause it to break. The fluid will escape and this is undesirable, although it will not affect the development of immunity. Later, when the lesion is at the scab stage, it does

not matter whether it is washed or not. Even if allowed to become wet, it will soon dry if exposed to the air, and this can be assisted by the application of sterilized talc or dusting powder. Application of antibiotics to the skin is undesirable. It will not alter the "pustulation" stage of normal vaccination, and will have no effect or alter the appearance of the normal scar. Frankly septic lesions, which may increase the scarring, are very much less common than popularly supposed and can be treated on their own merits.

Vaccination is not a blind immunological procedure. The operator is able to judge to a considerable extent whether an immunity response has been obtained in his patient. For this, as well as for certification purposes, it is necessary to see the patient after primary vaccination at the end of a week. The occurence of a typical Jennerian vesicle at the seventh day will allow the operator to inform his patient that the vaccination has been successful, and that within a further week the individual will have a high degree of immunity against smallpox.

Unfortunately not every primary vaccination turns out in this way. First, and most important, is the absence of any reaction at all. This should be regarded by the vaccinator as failure of technique or failure of lymph, and *not* any failure of the individual to react. The vaccination should be repeated, when, in the vast majority of cases, a normal primary take will occur. If the second vaccination should fail, then a third attempt should be made, this time selecting another site, the other arm or the forearm, increasing the amount of trauma by using a scratch technique, cross-hatching on an area about a quarter of an inch in diameter. If this still fails, it is most important to advise the patient that he appears to be *temporarily* insusceptible to vaccinia, but he must regard himself as being susceptible to smallpox. If there is no urgency, it is advisable to make further attempts on the patient a month or two later, when frequently, and for no apparent reason, these "difficult" primary vaccinations take without further ado. In countries where smallpox, particularly variola minor, is endemic, a number of individuals may be insusceptible to vaccinia as a result of sub-clinical attacks, or even of clinical attacks which have left no scars, but which occurred in infancy and are unknown to the patient.

In the case of adults with no history of a successful vaccination, examination of the body may sometimes reveal unknown scars. Accidental vaccination, particularly on the face in a child, may be the source of unsuspected immunity (Fig. 181).

Although routine primary vaccination of adults gives a very high take rate, the vaccination of smallpox contacts leads to a surprising number of primary vaccinations not taking at the first attempt. Lyons and Dixon (1953) reported failure in 10 per cent. Napier and Insh (1942) found twenty-nine out of ninety-two contacts could be successfully vaccinated after more than one attempt. It has long been recognized that the professional vaccinator, or vaccination enthusiast, may achieve a near-100 per cent successful vaccination rate, whereas the casual vaccinator will only succeed in about 80 per cent (Hime, 1896; Bousfield, 1955), but under the threat of smallpox one would imagine that most doctors would pay great attention to detail. It seems possible that some viral inhibition occurs in the patient, due to the emotional stress of the moment. In a small number of observations, I have found, in routine vaccination, a highly nervous subject appears more likely to get a negative take with a minimal insertion technique, but the matter requires further investigation. Under conditions of mass vaccination of the general public, not smallpox contacts, the failure rate may be quite high, but this is almost certainly due to faulty technique of harassed vaccinators.

Very occasionally, what appears to be a negative response at the seventh day may be a case

of very delayed vaccinial growth, even papule formation not occurring before the eighth day, and a vesicle not forming until the fourteenth or fifteenth. When a repeat vaccination performed on the seventh day is seen a week later, it is found that both the first and the second vaccinations are growing, the second being slightly accelerated by the presence of the late-developing original one.

Occasionally, a primary vaccination is inspected at the seventh day, and there is no vesicle, but the patient states that some twenty-four hours after the operation was performed there was redness of the skin, irritation, and formation of a small papule which had largely disappeared by the third or fourth day. This is an allergic response to the presence of vaccinia

FIG. 181. Scar from accidental vaccination on the chin—no history of vaccination to account for vaccino-modification of smallpox.

virus or its medium, much more commonly seen in revaccination. It is most important to assure the patient that in spite of the irritation and this appearance of activity, it does not mean a successful reaction. It denotes sensitivity and not immunity. Failure is most likely to be due to poor-quality lymph of low titre, or inactivation by heat or faulty storage. This allergic response in a person thought to be unvaccinated may be due to previous unknown contact with smallpox, particularly variola minor, cowpox, or unknown vaccination, on normal or unusual sites. It should be noted, however, that this reaction does occasionally occur in persons who have not had any previous contact with the variola-vaccinia group. In spite of the evidence of the allergic response that some material is coming into contact with the tissues, the operator should persist in repeating the vaccination. Even when fairly satisfied that apparent insusceptibility is not due to failure of technique, or of lymph, he should not give the opinion that the individual is also insusceptible to smallpox, and should advise further attempts at vaccination after an interval of a few months. Here I would strongly disagree with the

practical implication of Ricketts' dictum: "If a person has been shown to be really insusceptible to vaccinia, that fact is proof positive that he is insusceptible to smallpox." Many young nurses have died from smallpox because they were allowed in contact with the disease after repeated failures of primary vaccination. One in the Glasgow outbreak in 1950 had been unsuccessfully vaccinated six times.

Occasionally, a genuine primary shows more rapid evolution of the lesion—a vesicle at the fourth day, smaller and more superficial than normal, and forming a scab by the eighth or ninth day, and leaving a superficial or what the older writers would call a "poor" scar. This would appear to be due to some non-specific immunity reaction, and not related to the vaccination technique. The duration of immunity, however, is probably less than after a normal vaccination, and if there is any smallpox risk, particularly in nursing or medical staff, revaccination should be done within six months.

In primary vaccination, therefore, a normal primary, accelerated primary or retarded primary response, with characteristic vesicle formation, is evidence of vaccinial infection and resultant immunity. A negative or allergic response is not evidence of immunity.

The term "vaccinate" merely means the operation of inoculating virus, and is not synonymous with the attainment of immunity. In the discussion in Chapter 14, on vaccination and smallpox control, the cumbersome phrase "successful vaccination" has to be used. The term "repeat vaccination" should be used for all further attempts, if successful vaccination has not been obtained. The term "revaccinate" should be restricted to the inoculation of virus in *someone who has unequivocal evidence in the form of a scar of primary vaccination.* Some confusion may arise in the future in differentiating these from B.C.G. scars; foveation, regarded as characteristic of Jennerian vaccination scars, is often absent. The term "repeat revaccination" should be used for further immediate attempts, if the first revaccination fails. Successful revaccination can be done many times in life, but one can only be successfully vaccinated once.

I have been at some pains to stress that the production of immunity against smallpox by vaccination is obtained by growing the virus in the skin, and in this way it is different from other immunological techniques, where the antigen is injected subcutaneously or intramuscularly. In most other immunization procedures, immunity is easily boosted by a further antigenic stimulus, sometimes very small. In revaccination, however, we come up against the problem that residual immunity of the individual is also accompanied by residual insusceptibility of the skin to new growth of virus, and without this there is little immunity response. Unfortunately, immunity and residual insusceptibility of the skin do not run completely parallel, and although some individuals become susceptible to vaccinia before they become susceptible to variola, in many the skin insusceptibility may be quite high when immunity to a natural attack of smallpox is low; hence the importance of using vaccinia strains with good invasive power.

Residual immunity may be so low that when revaccination is done, a response almost identical with primary vaccination occurs. This "primary-type response", as it should be called, occurs in individuals who are revaccinated after more than ten to fifteen years, and is very common where the interval is over twenty-five years. There are, however, many exceptions. Some individuals do not give a primary-type response to revaccination, even after an interval of a great many years, whereas in a few it occurs less than a year after primary vaccination.

Revaccination commonly gives rise to what is known as an "accelerated lesion". Although some erythema at the site may occur earlier, Mitman (1952) pointed out that the acceleration is in the evolution of the lesion, papule to scab, and not in the incubation period, which may be prolonged. The maximum growth of the vesicle may be achieved by the fifth or sixth day, when the lesion will commence to dry up, the scab forming by the seventh or eighth day, and this may be shed by the twelfth or thirteenth day. All degrees of acceleration are seen, and although the vesicle can be described as Jennerian in type, it becomes more superficial, smaller, is accompanied by less erythema, and there is a distinctly smaller chance of any secondary infection occurring. The scar is quite superficial, without foveation, and, proportional to the degree of acceleration, may be practically invisible after an interval of six months. Where the skin is pigmented, depigmentation will occur, but to a lesser extent than after primary vaccination.

At seven years of age about half the children revaccinated give a vesicular response of some kind (Ministry of Health, 1928), at three years about 10 per cent, but at two years about 0·5 per cent (Pinto, 1936).

When a greater degree of immunity remains, a true Jennerian vesicle does not occur. An abortive papule may be seen between the fourth and sixth day, but unfortunately in these patients, sensitivity to the material is such that an allergic reaction will have occurred in the first two or three days, making interpretation of the combined reaction difficult without daily observation. If the immunity is still greater, no viral growth occurs, and the patient only experiences an allergic response, with the development of a papule and erythema, reaching its maximum within forty-eight hours, and obviously declining by the fourth day. Irritation is frequently present, regarded by the patient, and also unfortunately sometimes by the doctor, as a sign of "take", but this bears no relation whatsoever to an immunological response.

Marsden (1946) and many others have taught that an unequivocal vesicle must be the minimum reaction for evidence of virus growth. Benenson (1950) showed that revaccination with killed virus might in some instances produce early vesicular response from which virus could never be recovered. This occurred in nearly 50 per cent of immediate reactions to killed vaccine, showing that the appearance of the lesion may be deceptive, although it is far removed from a true Jennerian vesicle. The work of McCarthy *et al.* (1958) on the serological response to revaccination suggests that roughly half of these immediate reactions may stimulate immunity, but they were not able to differentiate on clinical grounds between those that did and those that did not.

It is fairly generally agreed now that any reaction, whatever its appearance, which has reached its maximum and is commencing to regress by the fourth day should be regarded as an allergic and not an immunity-stimulating response. It is, however, rarely practicable to see revaccinations on the second, third and fourth days, to determine whether the lesion is regressing or not. It is certainly inadvisable to rely on the patient's observations. The practical outcome of this has been the omission of the reading of a revaccination for international certificate purposes. This is a realistic alternative to the previous policy of certifying any reaction at all as being positive, but places an important responsibility on the operator to ensure that a revaccination has been done efficiently and with potent lymph. In spite of the certificate requirements, if a person is going to an area of the world where there is a definite smallpox risk, I feel the doctor should revaccinate using three sites, inspect at the fourth day and at the end of the week, and repeat revaccination if he has the slightest doubt. Revaccinations which show

a definite scab at the seventh day have probably had true vesiculation, although some allergic reactions can be severe or be scratched, and produce a very similar appearance. Very occasionally, an individual who has been revaccinated many times develops a rather soft papule, which may still be present at the fifth day, although it is almost certainly allergic (Fig. 178).

Quite a lot can be learnt by repeating the revaccination. If the first response has not stimulated immunity, the second revaccination may give a vesicular response of the normal or accelerated kind, particularly if performed on two or three sites, so proving the allergic nature of the first. If, on the other hand, the second response is similar to the first, it will strengthen the view that the individual possesses sufficient immunity to prevent visible viral growth. It should not be forgotten that some individuals will get a primary- or accelerated-type response at a third or even later attempt at revaccination. Although in a primary-type response in revaccination, general and local reactions are likely to be as severe as a primary vaccination, particularly in adults, the accelerated response is rarely accompanied by general malaise, and the local symptoms are much less marked. A completely negative response should be regarded as failure of technique. Many patients examined at the seventh day will state that they have had no reaction at all, although staining at the site of the scratch suggests that an allergic response has occurred which has not been noticed, or is denied because of the commonly held view of the public that failure to obtain a take is some peculiar virtue.

To avoid an unsightly scar, subcutaneous vaccination has been advocated, but it is not recognized for purposes of the international certificate. Kaiser (1948) carried out experiments with this technique, followed by normal vaccination after an interval of three months, and thought that a high degree of immunity resulted, but no extensive trial of this method ever seems to have been made in an area with a high risk of smallpox. Hoffbauer (1951) describes the reaction, and suggests that fever should occur between the fifth and twelfth days, and be regarded as a confirmatory sign of success. The positive result is also indicated by the development of an area of infiltration, with erythema of the overlying skin. It seldom exceeds two inches (5 cm.) in diameter, but may be more extensive and involve the shoulder and forearm. Occasionally there is a morbilliform or scarlatinaform rash. The results should be inspected on the fourteenth day. In revaccination, many of these effects could occur with killed vaccine, and therefore the operator has no check on the potency of his material. Berger (1954) recorded three cases of metastatic skin infection in 10,000 persons vaccinated by this method.

Attempts to use a killed or inactivated vaccinia suspension have also been made. McClean (1945) carried out trials of an alcoholized vaccinia suspension, but the response in rabbits was very poor. Ramon, Richeau and Thiéry (1948) and Ramon (1951) carried out experiments with formalin-inactivated vaccine, but these have not been satisfactorily tested in human beings, and do not appear likely to be successful. Collier, McClean and Vallet (1955) experimented with ultra-violet-irradiated vaccine, but this has not proved satisfactory in trials in monkeys and rabbits.

I think it is fair to state that at the present time there is no proven alternative to Jennerian vaccination in achieving a high degree of immunity to smallpox.

GENERAL CONSIDERATIONS

In the absence of previous infection with smallpox or cowpox, man appears to be susceptible to vaccinia at any age. It is possible to vaccinate a baby immediately it is born, and this may be necessary if there is a smallpox risk. However, it is generally agreed that the take rate in

new-born babies rarely exceeds 85 per cent (Donally and Nicholson, 1934; Dixon, 1954; Bousfield, 1955). In some instances the take rate is very much lower, in the region of 30 to 45 per cent. Isaac (1934) recorded this sort of figure, but the lymph employed was kept in the delivery room at a temperature of about 80° F. for at least two weeks, and up to forty different persons performed the vaccinations. Small wonder that the take rate was low. Points of interest about this particular investigation were that the vaccination reaction in prematures was rather severe, although this is contrary to other observers, and that the reaction on the arm gave slightly less-positive takes than when it was performed on the leg. The proportion of takes in females was slightly greater than that in males. An interesting feature in new-born vaccination is the absence of temperature reaction. No significant alteration occurs in the weight, and no enlargement of the spleen can be detected, all tending to suggest that the new-born infant is peculiarly resistant to vaccinia, and when infection occurs, it produces a minimum of constitutional disturbance. There is also a reduced skin susceptibility, as vaccine stored under less than perfect conditions, although still producing a near-100 per cent take rate in older children or adults, will show a very significant reduction in vaccination take rate in the new-born. Donally and Nicholson (1934) showed that the greater the traumatic effect of the vaccination technique, the higher the proportion of takes in the new-born. Monro (1764) failed to variolate twelve infants two weeks old.

It is generally assumed that this insusceptibility is due to passive immunity obtained from the mother, but the result of vaccination of new-born infants in places like Malaya soon after a severe smallpox epidemic and large-scale vaccination appears little different from the experience in England, amongst a population unexposed to smallpox, and where many of the adults have not been vaccinated, even in infancy. Kellock (1889) found that insusceptibility to vaccination at birth occurred in primiparae if they were vaccinated after the seventh month of pregnancy, but not if they were vaccinated before. In the multiparae, immunity appeared to be present if the mother was vaccinated after the fifth month. The reason for the failure in about 15 per cent of infants born of unvaccinated or remotely vaccinated mothers would seem to be something quite different. Possibly the ease with which the young infant passes through vaccination may be due to some other factor in its defence mechanism, possibly the properdin system. Doorschodt (1954) showed the presence of a vaccinia-neutralizing substance, thermo-stable at 55° C., in the sera of unvaccinated infants, between three and six months of age. Possibly the traumatic factor, such as the six or eight insertions of three centimetres long commonly done in Germany some eighty years ago, might well break down this kind of resistance. Kempe and Benenson (1953) studied four infants found refractory to repeated vaccination, in which a test vaccination later showed an allergic response. They suggested that at the first vaccination, although apparently negative, an active-passive response really occurred, due to the high level of trans-placentally acquired immunity. However, in one infant the first vaccination had been attempted at four months of age, in two at five months, and in one at nine to ten months. For this phenomenon to have occurred, passive immunity would have had to persist for a long time. Another explanation for these cases might be that the first vaccination is immunologically successful without a primary lesion, an occurrence occasionally seen in variolation, where the presence of a general rash showed that infection had taken place. In some infants, failure of vaccination at birth is followed by an accelerated primary lesion a few months later. This is probably due to declining "natural" insusceptibility rather than the presence of material antibodies, as passive immunity tends to

increase the incubation period of the vaccinial lesion rather than the reverse. Although some may be immune to vaccinia and smallpox at birth and then become susceptible, it would seem most dangerous to assume that all infants who give a negative response to primary vaccination at birth do obtain *any practical immunity*. It would also be wise to regard the accelerated type of reaction obtained at three to four months as giving a shorter immunity than a normal vaccination, and if the infant lives in an area with a smallpox risk, revaccination should be done within a year.

Both Donally and Nicholson (1934) and Jelinek (1933) found a proportion—two out of six, and five out of nineteen, respectively—of infants apparently successfully vaccinated at birth gave a vesicular response to revaccination at periods between one and three months of age. This result is different from adult experience, and would perhaps suggest that as new-born infants do not appear to suffer from a vaccinial viraemia as an inherent part of the vaccination process, the level and duration of immunity may be less. The relatively common experience of severe smallpox in vaccinated children in those countries that carry out new-born vaccination also supports this. Although early reinfection with vaccinia can only be interpreted as evidence of rapidly declining immunity, infants born in smallpox hospitals and successfully vaccinated immediately after birth normally escape smallpox infection. On the other hand, they are usually removed within a few weeks, and have ample opportunity to boost their immunity in the natural way.

Because of these difficulties, the routine vaccination of infants should be postponed until the end of the third month of life, when over 95 per cent primary take rate at the first attempt should be achieved, using a single insertion. On the other hand, if there is any real risk of smallpox, vaccination can be done at an earlier age, using a fairly vigorous technique, and at least two insertions.

In the aged, vaccination may also fail, not because of persistent immunity, but because of poor tissue response. It was also noted by Jenner and others that when a positive occurred, the vesicle was poor, with little areola. It seems probable that in these cases it may take longer for sufficient immunity to develop to prevent smallpox—an important point if they are contacts.

In the older books on vaccination, much attention was given to the desirability of ensuring that the individual to be vaccinated was in a "perfectly healthy state". This was probably partly traditional, because it had been recommended when variolating, but it was highly desirable in arm-to-arm vaccination, to ensure that one's future supply of lymph was from healthy individuals. Although we are far removed from the times when patients were prepared by dieting and mild purgation, it is of interest that experimental studies in virus infection of animals suggest that restriction of the diet may minimize the infection, and vaccinators for many years have recognized that the fat, overfed and alcoholic adult frequently has a very severe reaction from primary vaccination, and sometimes also from revaccination done after an interval of many years.

The Rolleston Committee (1928) reluctantly confirmed that strenuous exercise increases and accelerates general and local effects. Although the situation is stoically accepted, it would seem to be a good policy to allow time off between the eighth and tenth day for nurses and other personnel whom administrators hope will co-operate and undergo voluntary vaccination and revaccination at appropriate intervals.

About sixty years ago, the textbooks still advised the avoidance of vaccination at the commencement of menstruation. This may have been due to the reputation of variola virus in

causing uterine haemorrhage, but no evidence has been produced to suggest that there is any need to take this physiological occurrence into account.

Vaccination lesions tend to develop more rapidly in warm weather, particularly in very hot and damp climates, and are also affected by occlusive dressings and the amount of covering by clothing.

CONTRA-INDICATIONS

It is as well to remember that vaccination has no virtue in itself. In those parts of the world where the risk of smallpox is exceedingly remote, there is no need for vaccination of infants or the general population, particularly in view of the relatively short period of absolute immunity. This is discussed in Chapter 14.

Following the discovery of the effects of rubella on the foetus, there has been a renewed interest in the subject of vaccinia and pregnancy. The opinion of Jenner (1798) that pregnancy was no contra-indication to vaccination was reaffirmed as recently as 1949 (Bellows *et al.*). Recent work (MacArthur, 1952) has shown that although congenital defects of the kind following rubella do not occur, there is a higher stillbirth rate amongst women who have been vaccinated in pregnancy, compared with those who have not. Compared with normal foetal loss of 13 per cent (Randall *et al.*, 1950) MacArthur found the foetal loss was 24 per cent, a significant difference. The foetal loss from vaccinia is in the first three months of pregnancy, and therefore will not affect the official statistics of stillbirths. In view of the fact that the virus appears to disseminate widely in the body, it seems undesirable to expose the foetus to the chance of infection, unless it is absolutely necessary. It would therefore appear prudent not to vaccinate a woman during pregnancy at all, particularly during early pregnancy, and to ask this question of adults when they are presenting for vaccination. In well-controlled smallpox outbreaks, pregnant women should not be vaccinated unless they are close Class 1 contacts (see p. 403). In countries where smallpox is more widespread, these risks have to be taken. Where a woman is known to be pregnant and requires to be vaccinated for travel purposes, it is desirable to postpone the vaccination as far as possible to the later stages of pregnancy. This may be done by vaccinating on board ship, rather than before departure. Shipping and air lines have no right at law to make the issue of tickets dependent on the presentation of valid vaccination certificates. If there is a real smallpox risk, then pregnancy at any state is no contra-indication.

In general, it is inadvisable to vaccinate a person who is suffering from some other disease, as this may add to his miseries. There is no evidence that other diseases interfere with the development of vaccinia, but if any complications, such as generalization or encephalitis, should occur, the operator may be blamed for lack of care. The exceptions are cowpox and smallpox. In cowpox, vaccination will be unsuccessful after the full development of the vesicle, while in smallpox, vaccination can be successful if performed during the incubation period, during the initial syndrome, and for the first day or two of the rash. After this it will fail. Persons with neoplasms, particularly lymphadenoma, may suffer from increased local spread, but these persons also appear likely to suffer fatal attacks of smallpox if infected.

Although such a commonly performed operation as vaccination must coincide with the development of many diseases, Lungström (1956) quoted three cases, including epilepsy, imbecility and acute appendicitis, with an unfavourable outcome, where, although vaccinia was not causative, he felt that as a contributory factor it could not be ruled out. However, if

there is a grave risk of variola major, vaccination must be done, without regard to the presence of other diseases.

Although it is relatively easy to postpone vaccination until an acute disease is over, it is more difficult with chronic conditions. Primary vaccination, or revaccination after a lapse of many years, can upset elderly diabetics. During an outbreak, only Class 1 contacts should be vaccinated. If vaccination is required for diabetic doctors or nurses, the patient should remain off work or be under supervision from the fifth until the twelfth day, after a primary vaccination, or after a revaccination after a long interval. If the revaccination is fairly soon after a previous successful response, no precautions need be taken.

Another group who have to be considered are the asthmatics, those who suffer from hay-fever and other allergic conditions of more doubtful origin. If there is a definite risk of smallpox, vaccination should be done, regardless of their asthmatic history. If they are known to be senstitive to calf, sheep or egg protein, it should be possible to select material to which these patients are not allergic. Although Davidson and Davis (1943) report a number of cases of mild generalized vaccinia which arose in patients with histories of allergic manifestations of this kind, many thousands of people with similar histories have been vaccinated without any harmful effects. Patients with acute asthma should not be vaccinated unless there is a smallpox risk. Primary vaccination may upset some asthmatics, but probably no more so than other minor infections, and there does not seem to be any need to question every person about a history of allergy.

If the individual is suffering from any septic condition of the skin, it is advisable to postpone vaccination, not because sepsis will interfere with vaccinial growth, but because there is a danger of auto-inoculation. In the face of a smallpox risk, vaccination should be performed, and the sepsis treated with some antibiotic to which the organism is sensitive, as this will not interfere with the development of vaccinia and immunity. Vaccination should be avoided in patients with extensive burns, because there is a considerable risk of vaccinial infection of the burned surface.

The active phases of psoriasis, lichen planus or chronic eczema are also contra-indications to vaccination, In adults, such conditions are very chronic, and a period of remission should be chosen, but although there is a greater chance of generalization, it must be admitted that many persons suffering from these diseases have been vaccinated without any harmful effect. In many instances, the chronic skin condition improves dramatically during the vaccinial reaction, only to recur when this has passed.

The skin condition of the very greatest importance, however, is infantile eczema. If infants suffering from this condition are vaccinated, there is a considerable risk of generalized vaccinia of the malignant and fatal kind (Fig. 140). It should be made a rule that infants and young children suffering from this condition should never be vaccinated unless there is an immediate smallpox risk. On the other hand, it must be recorded that, in error or in ignorance, a number of infants with infantile eczema have been vaccinated without any harmful effects occurring. Unfortunately no figures are available to really assess the risk. It seems unreasonable to demand vaccination of such infants for travel purposes to or through countries where the risk of smallpox is practically nil. The alternative "explanatory letter" ought to be accepted. A child with infantile eczema may also be accidentally infected, by contact with another individual who has recently been vaccinated, or by indirect contact, through handling by the same nurse. Multiple cases have occurred in children's wards (Nimfer, 1936; Somerville *et al.*,

1951). The eczematous child must be kept away from other members of the family who may require vaccination, and more ought to be done to tell people who are vaccinated that they can be a source of infection to others.

The revaccination of a person who has already had post-vaccinial encephalitis or the vaccination of a person who has previously had post-infectious or other forms of encephalitis presents a problem. I have revaccinated a person who had suffered from post-vaccinial encephalitis without any abnormal effect, but Parle (1949) had a case in which some headache and backache occurred within twenty-four hours along with an allergic reaction, but it seems doubtful whether this was significant. In my opinion previous encephalitis is no contra-indication to vaccination when the latter is really necessary. It has been suggested that patients undergoing steroid treatment may react unfavourably to vaccination, and although there are no reported accidents, it would appear prudent to consider the need for vaccination while such therapy is in progress.

The Ministry of Health (England and Wales) advises that other inoculations should be avoided within three weeks of vaccination, in the hope of reducing complications, particularly post-vaccinial encephalitis. Presumably it is thought inadvisable to give a number of antigens and a live virus at the same time, although this is given in other inoculation procedures, and in former French territories in Africa immunization against smallpox and yellow fever were given together by a scarification technique, possibly a measure of expediency rather than of choice. It is on administrative rather than on immunological grounds that the recommendations generally advise giving yellow fever inoculation and vaccination separately. It is considered that yellow fever can be given four days before a primary vaccination, but if the latter is done first, then an interval of twenty-one days should occur before yellow fever inoculation is given. In the case of infants under nine months of age, it is suggested that there should be an interval of twenty-one days between yellow fever inoculation and vaccination, no matter which is done first, as cases of encephalitis have followed yellow fever inoculations at this age. However, it is suggested that if the individual has previously been successfully vaccinated against smallpox, and has a scar, then yellow fever immunization and revaccination may be carried out at the same time. This is illogical, as many revaccinations in adults after a long interval have constitutional effects as severe as those from primary vaccination. In the light of our present limited knowledge of the interaction, if any, between the antigens, dead or alive, it is better to avoid adding to the malaise from primary vaccination. When required urgently, there would appear to be no real contra-indication to giving a number of inoculations and vaccination simultaneously.

COMPLICATIONS

The vesicle becomes pustular, a descriptive term, just before the scab forms, and many of the older writers believed that sepsis, in the sense of laudable pus, was present. This is heightened by the appearance of the areola, a somewhat fiery erythema, with a distinct edge, not unlike erysipelas, but it seems probable that many of these lesions, as in smallpox, although looking "septic", are devoid of bacterial contaminants, and only contain vaccinia virus and cells. Due to the delicate nature of the vesicle roof, it is common, particularly in children, for this to be ruptured, usually at the seventh or eighth day, and the lesion may then become frankly septic. It seems probable that much of the secondary infection in the past has been due

to over-treatment, and the use of occlusive dressings. If the vaccinial lesions are large, particularly if multiple insertions coalesce, some secondary infection is almost inevitable, but in the case of modern primary vaccination, done with a minimum of trauma, sepsis is quite rare. In older children, where the vaccination site is frequently knocked, the scab may separate early, and some infection of the unhealed site may result. At times, healing is delayed, particularly if the area is large, and occasionally granulations occur. Bousquet (1848) called it the "red tubercle", and Morrow (1883) described it as the "raspberry sore". These infections tend to

FIG. 182. Four insertions nearly coalescing. Technique used about 1892.

occur more readily when the general hygiene and diet are deficient. Some ugly scars may result from this type of chronic sepsis. Occasionally, true keloids may form on vaccination scars, but this appears to be related to individual idiosyncrasy rather than to chronic sepsis.

Fifty years ago, when streptococcal infections were common and lethal, erysipelas occurred as a complication to vaccination, and quite distinct from the normal erythema. Deaths undoubtedly occurred from this cause. Erysipelas is relatively rare and benign today, and it is very unusual for it to be seen as a complication of vaccination. If the streptococcus regains some of its virulence, it might easily occur more frequently.

Lymphangitis may occur from a vaccinial lesion. This again was much more common in

the past, with large inoculation sites, and is rarely seen today. Enlargement of the lymphatic glands draining the site is a normal part of vaccinial reaction, and tends to appear about the fifth day. Nurses and medical students notice their presence, but members of the general public appear to complain far less frequently, and only then of a slight stiffness of the arm. Only if there is frank sepsis in the lesion is there any possibility of the glands breaking down. This is exceedingly rare today, although it was not uncommon in the nineteenth century. The general nutrition then was often so poor that reaction against infection was very tardy. Although septic complications in vaccination are probably often due to skin organisms being introduced into the vaccinial lesion at about the seventh or eighth day, in the past, both with arm-to-arm vaccination and with crude calf lymph, poor techniques and no sterilization of instruments, it was possible for both streptococcal and staphylococcal infections to have been introduced at the time the vaccination was performed.

Post-vaccinial tetanus may occur from infection of a neglected vaccination lesion with tetanus bacilli. It may, however, follow a perfectly normal vaccination, and appears to occur more frequently in countries where tetanus from other causes is relatively common. Rosen and Jaworski (1949) point out that it may be mistaken for encephalitis. Tetanus has been caused by the application of unsatisfactory dressings, particularly felt bunion pads (McVail, 1925; Armstrong, 1925, 1929) or ordinary occlusive dressings (Savolainen, 1950). Cases did not occur with human lymph, and were first recorded by the early users of calf lymph. Councilman (1907) stated that as many as five samples out of fifty-five showed the presence of tetanus organisms. Under modern conditions, vaccine is adequately tested to exclude the possibility of these organisms being present. Purified vaccine suspensions further increase the margin of safety.

Leprosy is reputed to have, and syphilis certainly has, occurred from arm-to-arm vaccination, but neither can be transmitted by animal lymph, or that produced in the chorioallantoic membrane. It is well known that positive serological tests for syphilis may be obtained following vaccination. Sellek *et al.* (1949) found about 10 per cent of primary vaccinations gave positive results within twenty to thirty days. It rarely persisted for more than two months.

Anaphylactic shock is unknown in vaccination, because the dose of material exposed to the body tissue is so minute. As in other inoculations, persons occasionally faint, if they are particularly nervous or apprehensive. In a person extremely allergic to calf, sheep or egg protein, an immediate urticarial reaction may occur at the site, but the vaccination will proceed normally.

Allergic rashes occur, but appear to have been more frequent at the end of the last century, particularly when calf lymph was first introduced. When mass vaccination was done in Glasgow in 1942, amongst about half a million vaccinations the incidence was one in four thousand, while in Edinburgh in 1944, amongst about a quarter of a million vaccinations, the rate was one in five thousand. Chalke (1931), however, saw fourteen cases in 1,600 vaccinations, but of the fourteen, ten had been definitely exposed to smallpox infection, two had no such history, while the remaining two were doubtful. The rashes were generalized macular-papular morbilliform or urticarial in type, showing preference for the limbs, the face remaining relatively free. The commonest time of appearance was about the eleventh day, and all the subjects had had primary vaccination and were between the ages of two and fourteen years. Although it is easy to suggest that some of these rashes were really missed cases of abortive smallpox, it seems possible that simultaneous contact with variola virus might affect the incidence. The incidence in Glasgow and Edinburgh is probably fairly accurate for non-contacts.

There appears to be no evidence that these rashes are associated with any particular batch or type of smallpox vaccine. Although it is possible for the individual to be sensitive to sheep, calf or egg protein, the fact that allergy can be shown in revaccination, using a killed suspension of washed virus particles (Craigie and Wishart, 1933), suggests that the reaction is a true allergy to vaccinia. Although occurring most commonly about the eleventh day, these rashes have been recorded from the fourth day onwards. Erythematous, morbilliform and urticarial lesions occur, and may be local, around the vaccinial lesion, or distributed more widely on the

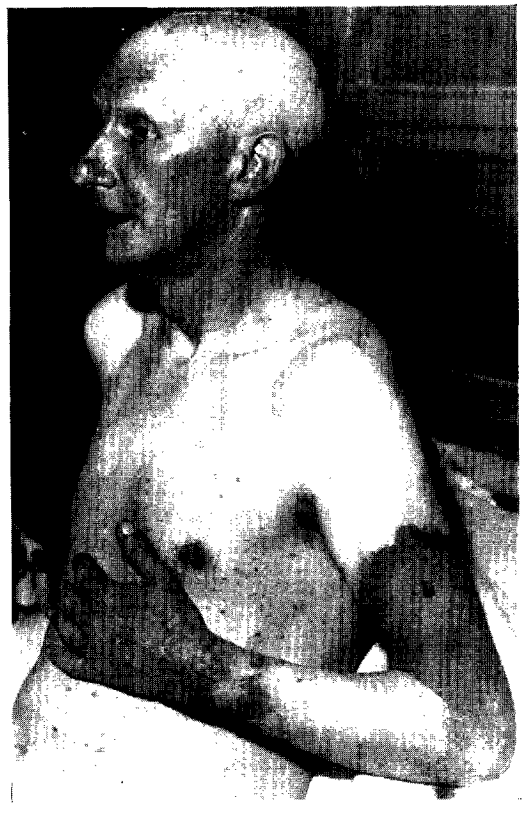


FIG. 183. Vaccinial erythema.

limbs, but more rarely on the face. The rash is often more marked on the vaccinated arm than on the remainder of the body, particularly in the early stages, although by the second or third day this may be much less noticeable. In the case of Fig. 183, the patient, a very doubtful smallpox contact, washed his whole body vigorously in a strong antiseptic, and this probably precipitated the reaction of the skin, possibly determining its localization. It indicates that in some of these cases other factors such as sensitivity to medicated dressings popular years ago may also be implicated. Some of the morbilliform rashes are very fleeting, and bear a close resemblance to similar rashes which occur in some very mild attacks of smallpox in the vaccinated.

AUTOGENOUS VACCINATION

The older vaccinators, using the four-insertion technique, often intentionally auto-inoculated a further site at the seventh day from one of the patient's own successful vesicles, if all had not taken. Today, autogenous vaccination is accidental.

If a vaccinated person immediately scratches the operation site, particularly where, due to a poor technique, a large amount of lymph has been left on the skin, it is possible for the virus to be picked up on the finger-nails and inoculated into other areas, such as the corner of the

FIG. 184. Accidental vaccination on the face and lower eyelid.

mouth and the lid margin. Other parts of the body may be affected, particularly if there is existing skin disease, although, in some, the apparently accidental infection of a very slight chronic eczema may really be blood-borne (de Salles-Gomes *et al.*, 1955). Accidental autogenous vaccination tends to occur in young children rather than in infants, but is not uncommon in primary vaccination of adolescents (Figs. 184 and 185). It is important to avoid it, as simultaneous vaccination will give a primary-type lesion and the formation of a permanent scar, particularly undesirable on the face.

If the developing primary vaccination lesion at the fifth or sixth day is scratched, virus may be inoculated on to other parts of the body, but the resulting lesions will be influenced by the

developing immunity, and will be much smaller, and may abort at the papular or early vesicular stage, and are unlikely to leave a scar. Auto-inoculation will not normally occur after the ninth day (Cory, 1885), but if a minimal vaccination technique is being used, the slow evolution of the lesion may permit auto-inoculation to the tenth or eleventh day, and occasionally even later.

If accidental inoculation occurs in the course of revaccination the secondary site may be small and insignificant, if the revaccination is also small, for it to pass unnoticed. These

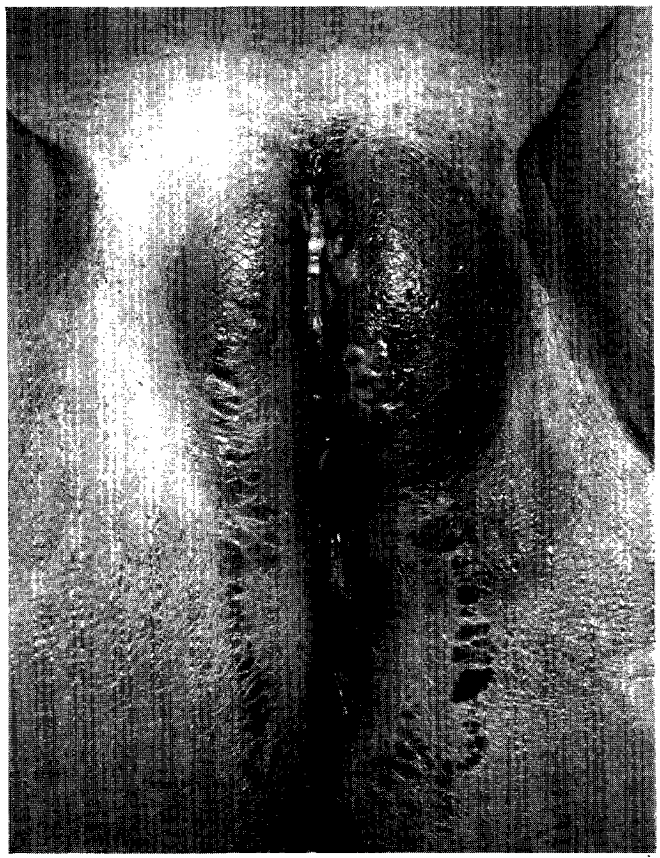


FIG. 185. Accidental vaccination.

probably occur more frequently than is recorded as irritation is more common in revaccination. In this case, the secondary lesions will leave no scar, unless the revaccination has been done after an interval of many years, when quite severe lesions may occur.

LOCAL ACCIDENTAL HETEROGENOUS VACCINATION

Just as a person may inoculate his own skin lesions with vaccinia virus, so this may occur from the hand of a nurse infected with vaccinia from her own vaccination or from another patient. It is not uncommon for the mother to infect a scratch on her finger from attending to

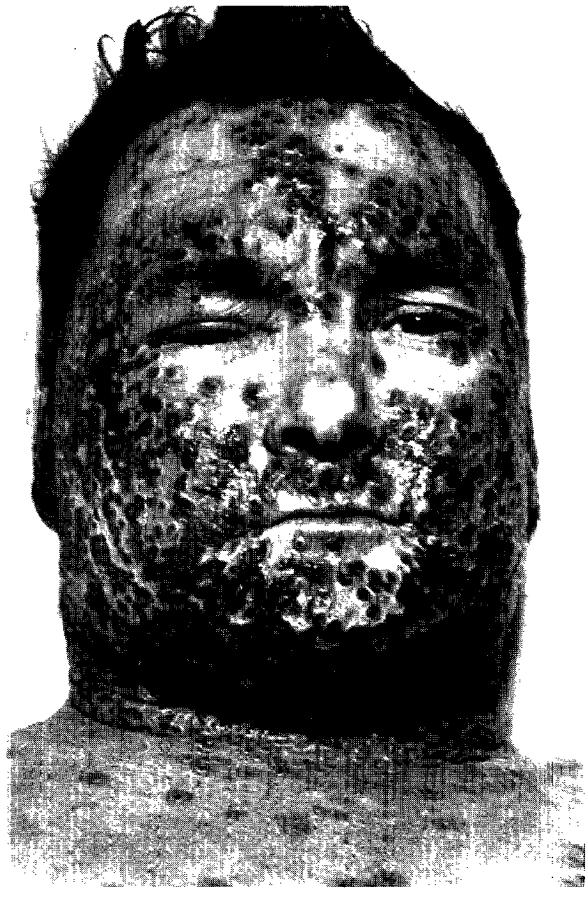
the primary vaccination of her child. Superficial burns, eczema and other atopic skin diseases can be readily infected. Apart from possible serological abnormalities in the eczema cases, and the slightly increased risk of generalization from such large primaries, the immunity response is normal, and should not endanger other than a bad-risk patient. In a laboratory infection in the eye, Pittman *et al.* (1947) stopped the growth of virus by X-ray treatment next day and for the following three days. Taylor (1957) reported an accidental vaccinial blepharitis in a woman aged twenty-five vaccinated in infancy. Severe reaction occurred, with residual increased thickness of the upper lid and loss of lashes, in spite of local and systemic gamma-globulin.

LOCAL SECONDARY VACCINIA

It is not uncommon with large primary lesions to get secondary vaccinial lesions around the primary. These daughter or satellite lesions were quite common in Jenner's time, and would appear to occur with strains which have an enhanced virulence, or are recently derived from cowpox. In some instances these satellite lesions are due to local scratching and auto-inoculation of virus left on the skin. The growth commences a little later than the parent lesion, but matures more rapidly so that, by about the tenth day, both the primary and the daughter lesions appear to be at the same stage of development, although the latter are smaller. In many cases, the lesions are more widely dispersed, three to four inches away from the primary lesion. In these, the daughter lesions do not appear until about the sixth to eighth day and are probably blood-borne, localizing in this area of skin due to the hyperaemia occasioned by the primary lesion, or to dissemination along lymphatics. It seems possible that cleansing techniques such as that recommended by the Rolleston Committee (1928), of cleaning the skin with spirit, which was vigorously rubbed in, might also increase the liability to this. The lesions are much smaller, more superficial and some may not vesiculate at all, corresponding to the abortive lesions in modified smallpox. By the thirteenth or fourteenth day, they will be dry and scab-covered, and will accompany the progress of the primary. Although the primary lesion will leave a well-marked scar, these daughter lesions will leave very superficial pink areas or slight depigmentation, which may be invisible after six months.

BENIGN GENERALIZED VACCINIA

During a perfectly normal primary vaccination, between the sixth to ninth day, a secondary eruption occurs simultaneously on the face, body and limbs which at first sight is very like modified smallpox. Macules appear, turning rapidly into small papules which become vesicular. Although like normal vaccination lesions, they are usually much smaller, only one-eighth to three-sixteenths of an inch in diameter, and more superficial, due to the concurrent development of immunity in the individual from the primary vaccination. The lesions mature very rapidly, so that after two or three days they have dried up, leaving small scabs. In some cases, the lesions are more abortive, and remain small, rather horny papules without true vesiculation. In others the lesions are bigger and more closely resemble those of a mild smallpox. Secondary sepsis does not occur, and when the scabs separate after a few days, there are small, superficial scars, all traces of which will disappear in time. Gammaglobulin may accelerate the natural disappearance of the lesions, but is not really worth giving, unless some continuance of formation suggests an abnormality of serum proteins. As already discussed in the chapter on diagnosis (Chapter 4), this type of generalized eruption does not have a typical smallpox distribution.



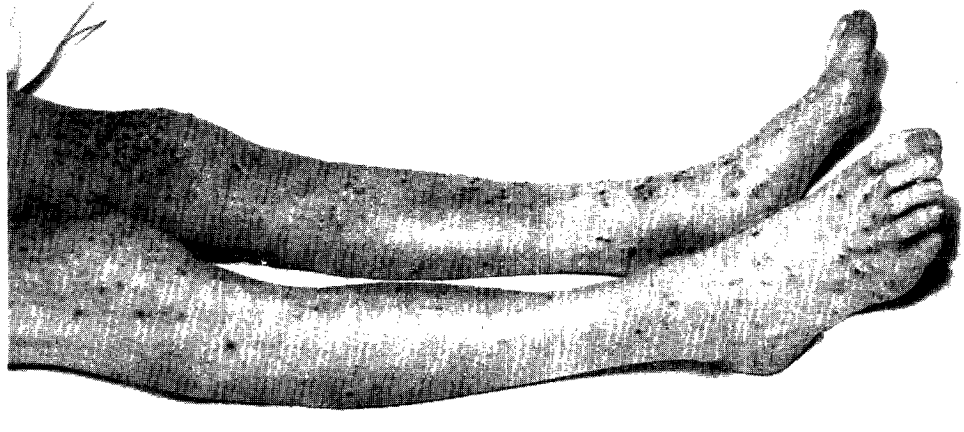


FIG. 186. Generalized vaccinia. Face and legs of the same patient. The absence of rash on the nose is unlike smallpox.

It is indiscriminate, and yet, contrary to chickenpox, the lesions are almost all at the same stage of development. New crops have been known to occur for up to five or six weeks, but in general the type of cropping in modified smallpox or in chickenpox does not occur. There can be no doubt, however, that these are difficult to diagnose, but fortunately the presence of so many skin lesions makes it easy to obtain sufficient material for virus growth.

The reason for this dissemination is not known. If it were due to a delayed immunity mechanism, one would expect a higher incidence in minimal vaccinations, but this does not appear to be so. It does not appear to be related to the use of a more vigorous technique. Whereas in Edinburgh, amongst approximately 270,000 vaccinations, three cases of this kind were seen (Clark, 1944), amongst approximately 500,000 vaccinations in Glasgow (Black, 1942), none of this type occurred. The Ministry of Health (England and Wales) reported thirty-four accepted cases amongst approximately three and a quarter million vaccinations. Marsden (1946) stated that these cases are rare in adults, and also following revaccination. In experimental animals, stepping up the dose of virus, using certain strains such as the neurolapine, or by giving the virus intravenously, generalized vaccinia can be made to occur fairly regularly. On the other hand, in man the strain is constant, the portal of entry is through the skin, the dose is extremely small, and generalized vaccinia exceedingly rare. It appears therefore that there is some failure in the individual, rather than in the dose, site or strain. Generalized vaccinia, or at least metastatic lesions, are more common with subcutaneous vaccination: 3 in 10,000 (Berger, 1954). Concurrence of generalized vaccinia and post-vaccinial encephalitis is exceedingly rare—a case reported in the second report of the Rolleston Committee (1930) one case reported by Weichsel (1931), and one in a Tongan seen in Dunedin in 1957, Caughey (1959).

MALIGNANT GENERALIZED VACCINIA

The second type of generalized vaccinia is that already mentioned as most frequently occurring in individuals with active infantile eczema, and occasionally in adults who have eczema or some other skin disease. More rarely, there is a history of previous eczema or allergy, but no skin lesions are present at the time. The condition is often called eczema vaccinatum, and has sometimes been called Kaposi's varicelliform eruption. This description is not very apt, as the rash more closely resembles variola than varicella, the possible reason for this anomaly being that Kaposi, who first described the condition in 1887, belonged to the school of physicians who regarded both variola and varicella as variants of the one disease. Virological studies have shown that this syndrome may result from infection of the skin, with the viruses of either vaccinia or herpes simplex.

Due to the more widespread knowledge that it is most undesirable and may be dangerous to vaccinate an infant with eczema, most of the cases seen today occur in children who have been accidentally infected with vaccinia. It is important to appreciate this, and not to assume that in the absence of vaccination of the patient the virus involved is likely to be herpes simplex, as this may delay the institution of therapy, with massive doses of gammaglobulin, which holds out a better chance of recovery. Although sometimes there is a primary lesion on the body at the site of entry of the virus, Davidson and Davis (1943), Lynch and Steeves (1947), Fasal (1950), and Grist (1953) described generalized vaccinia in allergic subjects with vesicular manifestations, but without eczema. It seems possible that vaccinia virus may sometimes infect via the respiratory tract, although under the normal circumstances of infection it is usually

impossible to eliminate the greater likelihood of entry through the skin. It has been suggested that the incubation period of the condition is five to nineteen days, but it is often difficult to assess this accurately. There is general enlargement of lymphatic glands, and the lesions normally commence in the abnormal areas of skin, but in this malignant form always involve normal skin as well. Usually, large areas of the skin are infected simultaneously, with a uniform development of the rash, not at all unlike that of malignant smallpox (see Fig. 140). Although in some areas the rash may be confluent, in closely adjoining areas of skin there may be no

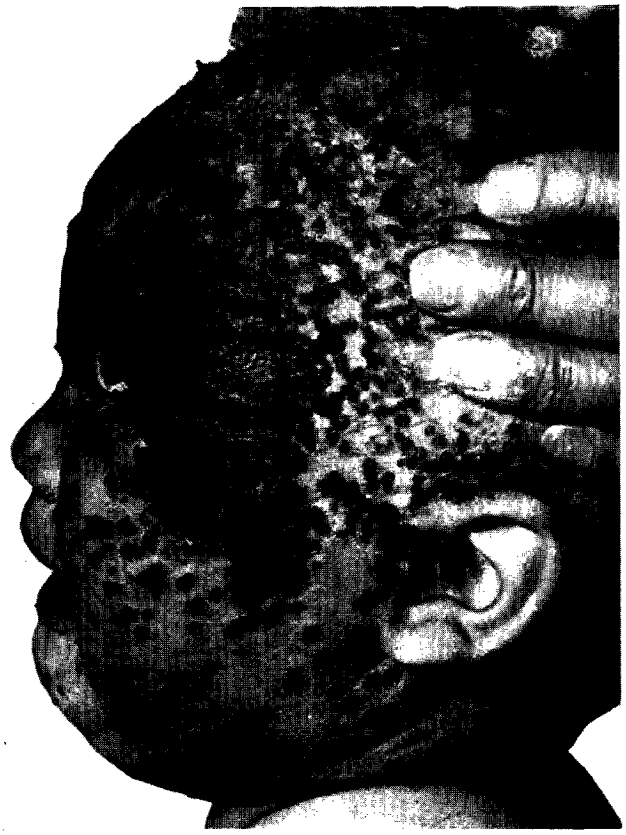


FIG. 187. Eczema vaccinatum.

rash at all, and the characteristic centrifugal distribution of smallpox is absent, although the rash may be more developed on the limbs than on the trunk. The abrupt change in density is probably more characteristic than anything else. Although the rash on the face at first sight resembles smallpox, the absence of rash on the tip of the nose (see Figs. 140, 186) compared with the density on the cheeks rules this out. Although the rash tends to occur in one crop, further lesions may appear during the next week. If the patient recovers, there is severe scarring. The mortality of genuine cases of this kind in children is exceedingly high, possibly in the region of 80 per cent, although mortality figures of 40 per cent and even as low as 10 per cent

have been quoted, but here the writers have included many mild cases of auto-inoculation on an eczematous area, without true generalization in their series, and have also included benign generalized vaccinia, which has a good prognosis. In most series of cases reported, it is noticeable that the mortality is higher in those who have been accidentally infected than in individuals who have been vaccinated and who develop this form of generalization as a complication. In the case shown in Fig. 140, that reported by Good and McLachlan (1950), the child complained of severe headache; within four days the rash had spread over the body, toxaemia was very severe, a confluent pustular mass covered the face from the eyes to the chin, there were a few scattered circular pustules with a slightly indurated base on the forehead. Scalp, mouth and eyes were clear of lesions. A semiconfluent pustular rash covered the extensor surface of both forearms, and discrete lesions were present on the outer side of both upper arms. The lesions on the extensor surface of the forearm much resembled variola, in that they were circular and umbilicated, and had slightly indurated bases. These lesions extended along the backs of the hands to the fingers, but there were none on the palms. On the trunk were three or four circular umbilicated pustules scattered across the shoulders, on the back, and two on the chest, but none on the abdomen. There were several similar lesions on the genitals and on the legs. The appearance and distribution of the lesions was similar to those on the arms. No lesions were found on the soles of the feet. The temperature continued between 103 and 105°F. (39·4 and 40·6°C.) and four days later signs of pneumonia appeared. The temperature rose to 107°F. (41·6°C.) and the child died. Although generalized vaccinia is different from the early stage of vaccinia gangrenosa (see below) in that the virus is blood-borne, it seems probable that some defect in antibody and the immunity mechanism is responsible. In a case described by Lewis and Johnson (1957), no neutralizing antibodies were detected, and although many of these cases are treated with large doses of gammaglobulin, some appear to respond while others do not. Martin (1954) points out that the globulin absent in cases with agammaglobulinaemia is the gamma-two fraction, and antibodies may be associated with other serum fractions. Hutchinson (1955) reported a case of agammaglobulinaemia, in which a child had passed through an apparently normal vaccination, without any untoward effects.

PROGRESSIVE VACCINIA, VACCINIA GANGRENOSA

On very rare occasions, the growth of vaccinia virus in the skin is not halted at about the eighth to tenth day by the development of antibodies and the cellular reaction against the virus. The virus continues to grow for many weeks, producing large, destructive ulcers, the advancing edge being studded with typical primary-type vesicles, apparently growing in a fully susceptible skin. Although in the first few weeks the lesion may be limited to progress from the primary site, towards the end of the condition, which may last as long as three or four months, numerous secondary lesions occur on the face and on other parts of the body, which are most probably blood-borne, but may also be inoculated, and these again have all the appearances of primary vaccinations. Investigation of these cases, which unfortunately so often progress to ultimate death (Figs. 188, 189 and 190), has shown that the condition is probably due to some abnormality of serum proteins interfering with immunity. The hypoglobulinaemia is, in the opinion of Janeway and Gitlin (1957), a transient physiological stage of infancy, and this may well account for some milder cases recovering suddenly, after a number of weeks of progressive growth. It also makes difficult the assessment of the value of hyper-immune

FIG. 188. Vaccinia gangrenosa, primary and satellite lesions, three weeks after vaccination.

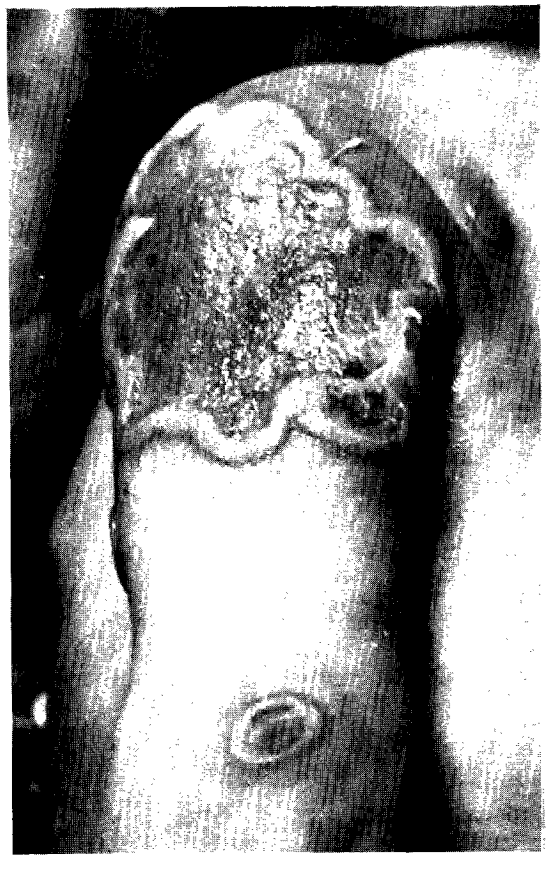


FIG. 189. Vaccinia gangrenosa, primary lesions five weeks after vaccination.

gammaglobulin, which undoubtedly should be given in these cases, although in a number there is practically a normal amount of gammaglobulin present in the serum (Galloway and MacBean, 1958). In a case reported by Barbero *et al.* (1955), gammaglobulin in a five-year-old boy was within normal limits, but the serum contained no neutralizing antibodies against vaccinia. In addition to skin lesions, a biopsy confirmed that vaccinial osteomyelitis of the metacarpal bones was present. Five doses of gammaglobulin derived from recently vaccinated persons were given over a period of six weeks. Complete healing was only obtained some

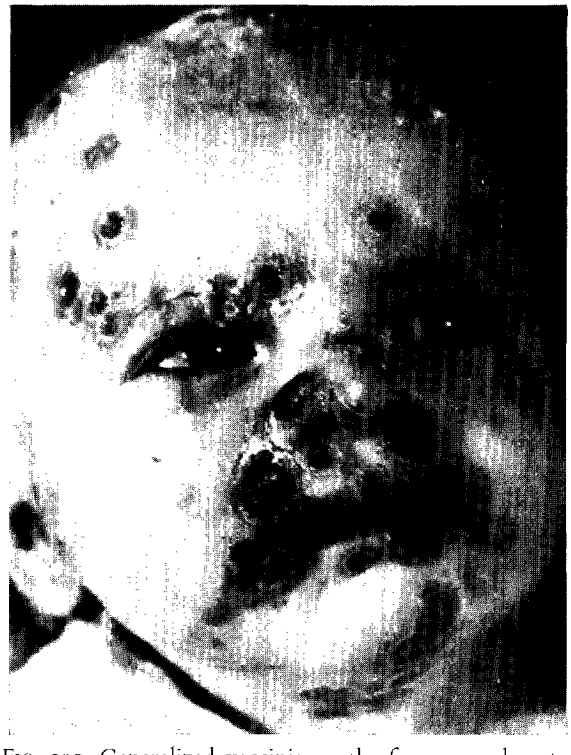


FIG. 190. Generalized vaccinia on the face, secondary to vaccinia gangrenosa, five weeks after vaccination.

four and a half months after the commencement of treatment. It has been suggested (Lewis and Johnson, 1957; Blake, 1958) that in some of these cases there is dysgammaglobulinaemia. Somers (1957) suggests that agammaglobulinaemia may be an inherited sex-linked Mendelian trait, but although the condition appears to be more frequent in males, it is by no means confined to this sex. In spite of treatment with gammaglobulin in large doses (250 milligrams daily for nine days), cases often die. The failure of this form of therapy supports the view that the condition is not wholly due to abnormality of gammaglobulin, as it has been shown that some individuals who have agammaglobulinaemia have unknowingly been vaccinated, and have had a perfectly normal, self-limiting infection (Hutchinson, 1955). There is some similarity between this condition and foetal vaccinia. Although vaccinia gangrenosa is rare, cases are being

reported from an increasing number of countries, and in view of the possibility of some being due to an abnormality only likely to be present in early infancy, particularly in premature infants, it is a further point to be considered by those who advocate universal infant vaccination, irrespective of the risk of smallpox. It seems highly probable that a number of the cases of so-called vaccinial syphilis of the nineteenth century, including the celebrated Leeds case, were really cases of vaccinia gangrenosa.

POST-VACCINIAL ENCEPHALITIS

This syndrome has always been called "post-vaccinal encephalitis" in British literature, although vaccinial is probably more correct, as it occurs during an infection with vaccinia. It is "post-vaccination" rather than "post-vaccinial", in that the condition occurs most commonly about the tenth to twelfth day in the evolution of vaccinial infection. Although Heine is credited with recording the first case in 1860, some claim that Sacco mentioned nervous complications about 1810. As discussed in the chapter on the history of vaccination, it seems just possible that the wild charges of change to a bovine personality, so beloved by the early anti-vaccinators, may have had a little substance if encephalitis and resultant personality changes actually did occur. As the condition has occurred after human cowpox, it does not seem impossible. In the early days, many adults and older children would have had a primary vaccination and mental changes if occurring might well have been detected, whereas later in the century the majority would have been done on infants. The earliest unequivocal case is, according to the Rolleston Committee (1928), considered to be that seen by Comby in France in 1905. The first recorded case in England occurred in July 1912, but the disease did not become a recognized or admitted risk of vaccination until 1922, when a number of cases occurred in England and in the Netherlands between 1923 and 1927. Many investigations were done, culminating in the special committee of the Ministry of Health in 1926. Its findings (Rolleston *et al.*, 1928) and the problems of post-vaccinial encephalitis in relation to vaccination policy and the control of endemic or epidemic smallpox are discussed in Chapter 14.

From the clinical point of view, the syndrome does not differ from encephalitis following some other infections. The incubation period, that is from the performance of vaccination, or the date of infection of naturally acquired cowpox (Schreuder *et al.*, 1950) to the commencement of the nervous symptoms, is about ten days in children, possibly slightly longer, eleven to fourteen days in adults. In the majority of cases, signs of cerebral, midbrain or medullary lesions occur. In the remainder, about 20 per cent, it is predominantly a myelitis, with or without symptoms of encephalitis. There is some variation in the clinical picture in different cases, and as they commonly occur singly the clinician is apt to emphasize one or other aspect of the picture, but the review of the committee of the Ministry of Health (1928) summarized previous cases in the literature and twenty-five new ones, and gave the following general picture:

"The disease is a disorder of the nervous system, in which the initial symptoms are headache, vomiting, drowsiness and pyrexia, occurring usually about the tenth to twelfth day after successful vaccination or revaccination. The onset is commonly sudden, and some of the cases in their subsequent courses appear to be indistinguishable clinically from encephalitis lethargica" (which was epidemic at the time). "Some are mild, and apparently recover completely in about a week, whereas others develop extensive spastic paralysis, and pass rapidly into coma

and death; paralysis is almost invariably of the upper neurone type. Between these extremes, severity and duration of the disease vary greatly. A paralytic case may last for weeks, and ultimately prove fatal from some intercurrent infection. Nearly one-half of the cases terminate fatally, and most of the deaths occur within a week of the onset of the illness. The cardinal symptoms, headache, vomiting, drowsiness and pyrexia, are very constantly present and severe, and rarely absent in mild cases. These may be the only symptoms present, even in fatal cases. Paralysis when it occurs is at first generally spastic in type, but later it may be flaccid. It is uncertain whether the flaccidity is due to an associated spinal lesion, or to lack of muscle tone, dependent on the cerebral lesion. Paralysis may be extensive, but more commonly it is localised and may be transient; the occurrence of trismus has led to a diagnosis of tetanus. Incontinence and retention of urine is common. Convulsions, general or localised, athetosis, tremor and choreic movements have been observed. Irritability, photophobia and delirium may occur, and in some cases severe pain, especially in the legs, arms and shoulders, has been noticed. Cerebro-spinal fluid is commonly under pressure, but is sterile. Cell count shows a moderate increase, chiefly of mononuclears. There may be a slight increase in chloride content, and sometimes sugar, but there are no features which are diagnostic." It seems probable that cases with flaccid paralysis are not as rare as supposed, and are incorrectly diagnosed as poliomyelitis (Linneweh and Oehme, 1958).

There have been three principal theories as to the cause of post-vaccinial encephalitis. The first, that the vaccinia virus itself causes the encephalitis, was at one time supported by Blaxall, because vaccinia virus could occasionally be recovered from the brain. Virus can be recovered from many other tissues of the body at this time, without giving rise to symptoms. Today, nobody seriously considers that the vaccinia virus itself directly causes the pathological condition.

The second theory is that there is activation of another virus carried by the individual. The pyrexial attack caused by the vaccinial infection activates this latent virus to give rise to encephalitis. This theory assumes a similar mechanism to encephalitis following infectious disease and other immunological stimuli, and is supported by the occurrence of more than one case in a family, and the high incidence in certain countries. As no one has yet isolated this virus, in spite of rapid advances in this field, this argument is much weaker than it was a few years ago. Herpes simplex virus has been isolated from time to time, but it seems much more likely to be a contaminant, as it is frequently found in human tissues.

The third theory, which is one that has gained popularity over the past few years, is that encephalitis is an allergic phenomenon. This is supported by some experimental work, but not by the epidemiology. None of the theories satisfy all the findings.

In the light of our ignorance of the cause of post-vaccinial encephalitis, treatment has to be arbitrary. Anti-vaccinial serum was suggested by Horder in 1929. Béclère (1931) recommended the use of calf serum instead of human serum, and in the case reported by Anderson and McKenzie (1942) anti-vaccinial horse serum was used, without a successful result. Davidson and Thomas (1942) used pentothal sodium and convalescent human serum obtained three to four weeks after vaccination but, although the case recovered, it would appear that the pentothal sodium was as important as the serum. Marsden (1943) pointed out that the serum from convalescent cases of post-vaccinial encephalitis might be of more value than that derived from ordinary vaccination, but its supply would obviously be difficult. There is no record of its use. Fyfe and Fleming (1943) used serum of recently vaccinated persons in doses of 150 to

200 c.c., and Ligterink (1951) treated a child with ACTH, 75 mgm. in the first twenty-four hours in six divided doses, continuing in progressively diminishing doses until 10 mgm. was given on the eleventh day. This patient recovered. Nossel and Rabkin (1956) reported two cases, one following revaccination, which recovered following ACTH therapy. It is difficult to understand the rationale of purely anti-vaccinial serum; in the majority of cases vaccination has all the appearance of being normal, and there is no evidence of abnormality of serum protein. ACTH therapy is based on the theory that the condition is an allergic vasculitis (Miller, 1951). Due to the rarity of the condition and the entirely unpredictable outcome of the disease without any treatment, the assessment of any remedy is extremely difficult. Cases which appear to be moderately severe may prove fatal, and others where the prognosis appears to be hopeless make a dramatic recovery without treatment. The prognosis of these cases where myelitis is the predominant site of injury tends to be better than those with encephalitis.

Focal epilepsy and varying degrees of hemiplegia have been recognized as commonly following the acute attack and although it has often been stated that post-vaccinial encephalitis left no mental sequelae, of twelve cases traced, which were under the supervision of the Andrews Committee, three were found to have mental changes. The Ministry of Health Report (1928) described these as slight, but I think today they would be regarded as very serious disabilities. O'Neill (1957) found that in post-infectious encephalitis, although recovery seemed complete on discharge from hospital, a follow-up done some months later showed that personality changes had often occurred. In the series presented by Miller (1953), nine out of twelve cases had psychiatric sequelae. I feel that this aspect of post-vaccinial encephalitis has not been given the attention it deserves. In countries where vaccination is compulsory, there is often great reluctance on the part of the authorities to admit that post-vaccinial encephalitis occurs at all, and in some countries private practitioners, having dealt with this unexpected complication of a simple procedure, are unwilling to focus attention on it by follow-up, which might well increase the chance of adverse criticism from the patient or relatives. Although much is made of the fact that the incidence of post-vaccinial encephalitis appears to be less in children under two years than in older children or adults, it is often forgotten, although pointed out by Conybeare (1948), that case mortality in infants under two years of age is about 70 per cent, which is very much higher than in later childhood or adult life, when the figure is approximately 40 per cent. Personality changes, however, are much less likely to be noticed by the parents or the doctor. The epidemiology in relation to vaccination policy is discussed in Chapter 14.

OTHER COMPLICATIONS

Vaccinial osteomyelitis may arise insidiously, with little or no systemic upset, swelling of the joint or temporary weakness of the limb being the only indication. It may therefore be confused with poliomyelitis. It may remain undiagnosed in its early stage, but deformity may arise later from destruction of epiphysial cartilage. Elliot (1959) described one case and reviewed four earlier ones. All were one year or under in age. The X-ray showed bone destruction, in his case, of both ends of the humerus with periosteal new bone formation. Lesions appear to be associated with any joints of the body, and not related to the arm in which vaccination is done, and must therefore be blood-borne. In one case (Barbero *et al.*, 1955) there was abnormality of serum proteins, but this did not occur in the case reported by Elliot.

Rosen (1949) pointed out that iritis and central serous retinopathy occur as a complication of vaccination, and considers that they have an allergic origin similar to encephalitis. He also points out that vaccination sometimes appears to precipitate clinical manifestations in pre-existing eye disease. Kisch (1958) reported a case of Guillame Barré syndrome, apparently the third recorded. Cangemi (1958) recorded a case of acute pericarditis, apparently occurring some twenty days after primary vaccination. This was thought to be of an allergic nature. A great variety of complications have been listed as occurring after vaccination, but many would appear to be purely chance association.

CHAPTER 8 | *Cowpox*

Cowpox is the common name given by farmers in many parts of the world to any vesicular or semi-vesicular eruption occurring on the udder or teats of the cow, and transmissible to man, giving rise to cutaneous lesions, usually on the hands. It was known before the time of Jenner, but he described two conditions: genuine cowpox, which might well be called Jennerian cowpox, which gives immunity against smallpox, and spurious cowpox, including what is now called "milkers' nodes", which gives no such immunity.

Confusion in terminology, however, still exists. Although milkers' nodes is a well-recognized condition in many parts of the world, particularly in Norway, where Danbolt (1949) claims there are over 10,000 cases a year, in the United States of America, milkers' nodes is described by Nomland and McKee (1952) as being caused by "natural cowpox" in cows, as distinct from "genuine cowpox" of cows, giving rise to Jennerian cowpox in man. In New Zealand, farmers and the medical profession regard milkers' nodes as cowpox, but Jennerian cowpox almost certainly does not exist. Jennerian cowpox and milkers' nodes are both virus infections, but there is no cross-immunity to one another.

Veterinary textbooks contain very little information on the subject, as it is of no economic importance to the farmer, who regards it, at any rate in the cows, as trifling, and only slightly reducing the milk output. He is usually not bothered by an outbreak, and is not anxious for an investigation to be made, for fear of having his milk supply stopped. Becker (1940) suggests that both diseases may be more common than is supposed, but the differential diagnosis between these and foot-and-mouth disease, and from the coital vesicular exanthemata, is not always easy. Most outbreaks are discovered because of the occurrence of human cases, not because of detection by veterinary surgeons.

Jennerian cowpox appeared to be fairly common in the early nineteenth century, although doubtless farmers did not pay any particular attention to it. During the following years, writers frequently referred to the disease as being less common than previously. Ceely, in 1840, thought that cowpox was not seen so commonly as forty or fifty years before. In England and Wales one outbreak was reported in each of the years 1887, 1888 and 1902, two in 1903, three in 1909, two in 1911, and one in 1913, 1915 and 1919. Nine outbreaks appear to have been recorded in the last twenty years in England and Wales, between 1938 and 1958. It would seem that in the first fifty years of this century the incidence has probably not varied very much. More outbreaks appear to occur in Holland, Dekking (1956) having isolated some thirty-six strains in the last few years. Cases have been reported from Germany, Poland, and Uruguay and the United States of America, but the true incidence is unknown.

Cowpox is of great interest because the virus producing it is so similar to vaccinia produced in the laboratory for vaccination against smallpox, but there are a number of points of difference. Serological observations made by Davis, James and Downie (1938) and by Downie (1939*b*) show that although there is a very large antigenic overlap, there are minor antigenic

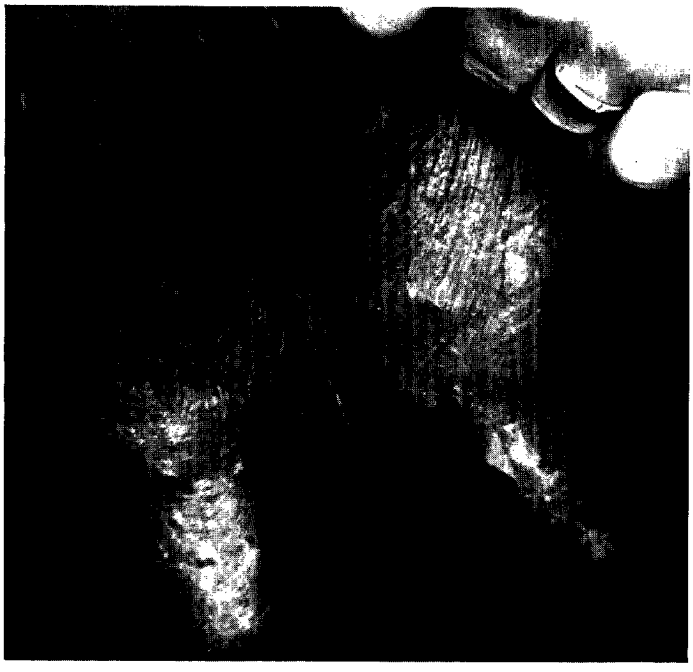


FIG. 191. Early cowpox lesions.

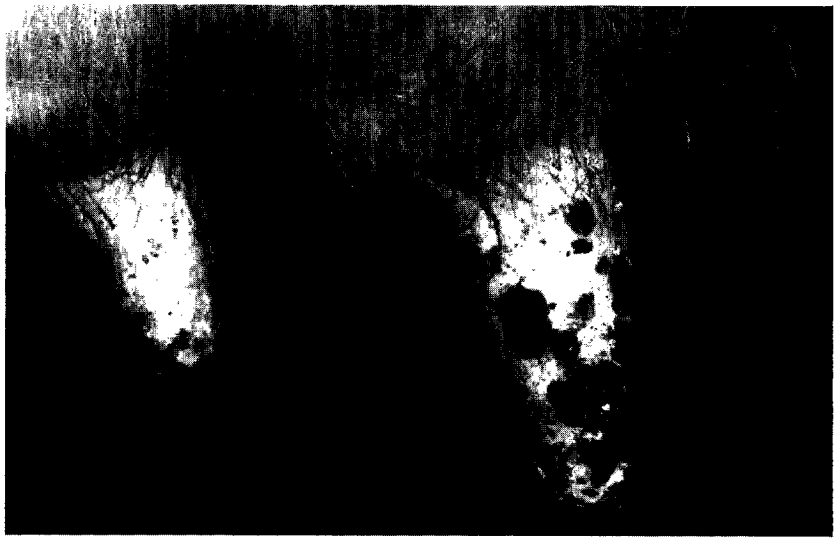


FIG. 192. Late cowpox lesions.

differences. Growth in the chorioallantois is also different. Cowpox virus produces epidermal thickening, and there is less rapid necrosis of the epidermal cells, and a greater tendency to involve deeper tissues, with a characteristic haemorrhagic appearance (Downie, 1939*a*; Dekking, 1950). In vaccinia, the lesions are not normally haemorrhagic. Downie and Haddock (1952) and van Tongeren (1952) both found variants in cowpox in which haemorrhagic lesions do not occur, and which have many of the characteristics of vaccinia. In laboratory studies, Fenner (1958) supports Ledingham (1935) and Downie (1939*a*, *b*) in their conclusions that cowpox is essentially a different virus from vaccinia.

The problem, however, is a complex one, and an examination of outbreaks of cowpox in cattle reveals a number of points of interest. In an outbreak described by Reece (1921–2) amongst eleven affected farms with 410 cows, 52 per cent of the animals were attacked. Forty-four persons were employed as milkers, of whom no less than 50 per cent became infected through attendance on farm animals. At one farm, forty out of forty-three cows became infected, five out of six farm horses, and a pony, six out of seven of the milkers, and the boy who was in sole attendance on the pony. Frenkel (1930) also reported a number of outbreaks, having seen five in one year in Holland. In each of these, all or nearly all of the milch cows in each herd were affected. Although this may be partly due to the fact that infection is not recognized in the herd until milkers are affected, and therefore infection may have been present in the herd for a considerable time without any preventive measures being taken, it would appear that cows are very susceptible to this virus. All cows on a farm would not be affected, if it were not for the fact that mode of infection is by milking. Cory (1898) wrote: "It does seem likely, if cows were not milked and horses were not shod, their respective variolous diseases would cease, as far as we can see, to exist." The disease only appears in non-milch cows and steers when very gross infection is present in the herd, and a poor level of husbandry. It is of interest that cases of human cowpox do not arise in slaughterhouse workers. This would suggest that cowpox is not a natural disease of bovines. The rarity of the condition, and the very long periods of freedom in an area, suggest that the reservoir of infection, wherever it may be, is not in these animals. Although dried scabs from a case of cowpox could under optimal conditions contain live virus for many months, it seems unlikely that a pasture could be infective for many years before giving rise to a new infection.

There would appear to be three possibilities. The first, that cowpox virus is a natural virus, the reservoir occurring in some other mammal or bird, where it produces symptomless infection. In support of this, it can be stated that both cowpox and vaccinia are unusual in the pox group of viruses in being capable of producing infection in a wide range of hosts. They are also both capable of producing variants. There would have to be some mode of infection, possibly by the digestive tract in cattle, a mild general infection, with localization on the skin of the udder, to produce local lesions capable of secondary, mechanical transmission through the herd, the whole episode being rather a rare infection or an unusual event in an otherwise symptomless infection. There is always the possibility of infection transported from this hypothetical source direct to the cow's udder, by flies. The presence of small sores on the udder, common from milking, would be both attractive to flies and increase the chance of a small amount of infective material being inoculated during milking. Although cows are very susceptible to the virus, in some parts of the world calves used for the production of calf lymph are sometimes found to be refractory.

A second source of infection is from vaccinia virus, inoculated onto the udder from a person

who has been recently vaccinated. Although Downie and Dumbell (1956) state that all the recent outbreaks in England have been due to "genuine" cowpox virus, Dekking (1956) stated that in eight of the thirty-six outbreaks in Holland, vaccinia virus was apparently the cause of clinical outbreaks of cowpox in both cattle and man. Similar outbreaks have been described (Boerner, 1923; Abente, 1949; Otte and Mockmann, 1955; Rozowski *et al.*, 1956). In many of these cases the identification of the source, an original vaccination, is unequivocable, but in some the identification is based on laboratory differences between vaccinia and cowpox. It seems possible that present-day cowpox outbreaks in countries where smallpox is not endemic, even those labelled genuine cowpox, on laboratory differentiation, may be quite recently derived from vaccinia. It would seem that the official *pox virus bovis* strain described by Fenner and Burnet (1957) and originally derived from a case of cowpox in Brighton in 1938 may be in this category.

The third possibility is inoculation of the udder of the cow with smallpox virus, which undergoes mutation, possibly not on first passage, but after a number of passages through cows by way of the milker's hands, so that ultimately a typical cowpox lesion results. This is the way that vaccinia virus is reputed to have been obtained from smallpox virus by many of the older workers, and is discussed in the chapter on clinical vaccination. (Chapter 7).

Downie and Dumbell (1956) doubt very much if this did occur, and quote more recent unsuccessful attempts (Nelson, 1943; Buddingh, 1949; Downie, 1951) to change variola virus into vaccinia. These investigators feel that as vaccinia is highly infectious for laboratory animals, earlier workers only infected their animals with vaccinia. However, the clinical descriptions of the early removes of this material to man suggest a virulence and clinical effect quite different from current strains of calf lymph, and I personally feel no reason to doubt that some of these attempts were successful. Copeman (1921) claimed that although it was extremely difficult to infect the calf directly from human smallpox of the ordinary variety, it was quite easy to convey the inoculated form to the calf. Variolation had, however, disappeared from many countries before the middle of the nineteenth century, and was made illegal in England after 1840. However, in view of the changes in smallpox virus that were likely to occur by repeated passage, using the Dimsdale or Sutton technique of inoculation, similar to the changes in virulence of vaccinia, seen in long-term arm-to-arm vaccination, it does not seem unreasonable to suppose that changes in smallpox virus might occur, rendering it better able to adapt itself directly onto the skin of the udder.

Another possibility is that the virus from the respiratory tract of the milker in the initial stage of smallpox might be able to give rise to a symptomless general infection in the cow, with occasional blood-borne localization on the udder, due to trauma in milking. In Jenner's day, outbreaks commonly were seen in the spring. Possibly the recently delivered cow is unduly susceptible, but it might require a number of passages on the skin of the udder to produce a typical cowpox lesion. Respiratory virus from the milker could also contaminate small abrasions on the udder of the cow. The close proximity of the milker's head would undoubtedly assist in this.

Laboratory evidence does not help very much, variola, vaccinia and cowpox are very closely related to one another. Although vaccinia and cowpox have common features of wide host range, serologically variola is more closely related to vaccinia. On the other hand, vaccinia shows considerable variations amongst its many strains, in tissue tropism and virulence. "Genuine" cowpox virus appears more virulent for man than vaccinia, but vaccinia virus

appears more virulent for cows than does the "genuine" cowpox. This may be merely due to the change from accustomed to an unaccustomed host.

From a practical point of view, the cause of many "spontaneous" outbreaks of Jennerian cowpox in cattle still remains somewhat of a mystery. In England and Holland, where outbreaks occur from time to time, sufficient infant vaccination is done to provide a source of virus. On the other hand, in New Zealand, where cowpox does not occur, infant vaccination

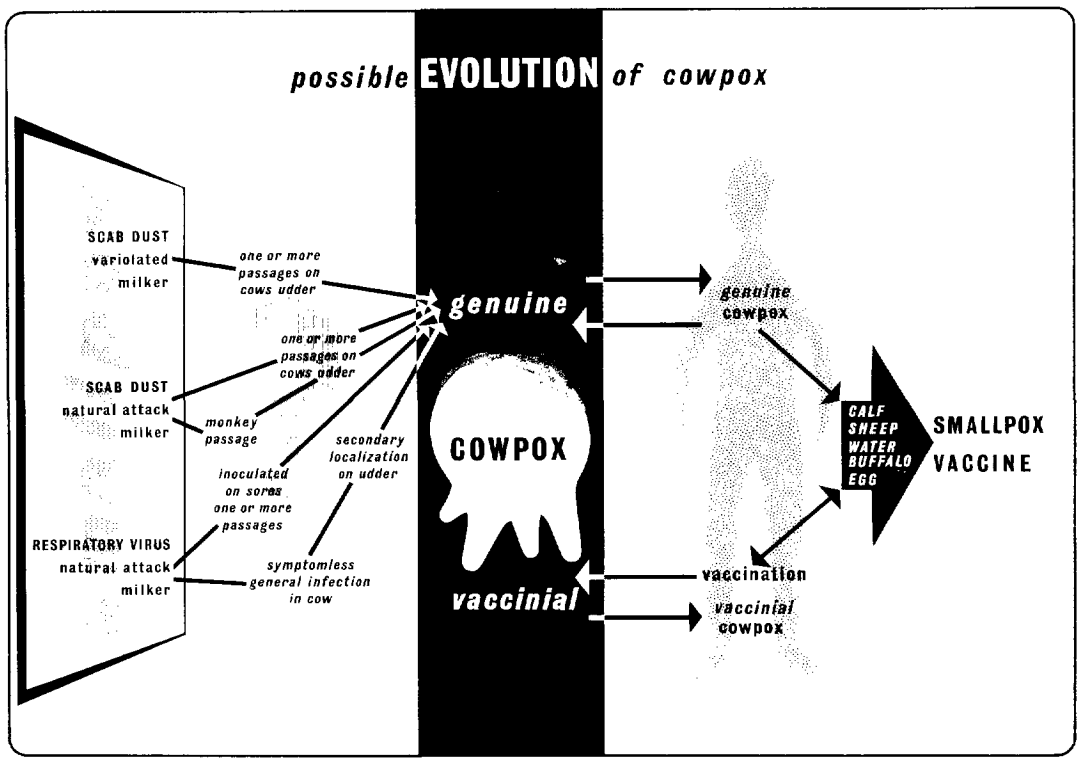


FIG. 193. Diagram showing possible origin and mechanism of spread in cowpox.

is only rarely done. Vaccinia could not of course have been the source in Jenner's time, but the cowpox virus of Jenner's day might have shown differences in its laboratory characteristics from current strains of cowpox, as the latter appears to from the current strains of vaccinia used in the commercial preparation of smallpox vaccine. In my opinion, cowpox is not a natural disease of bovines, and in Jenner's day was derived from smallpox virus, whereas today the infection will have come from vaccinia virus, either by direct passage, or after passage through bovines or other animals. It then assumes the "wild" properties of *pox virus bovis*.

Cowpox may affect a number of domestic animals, of which the most important is the horse. Although Jenner imagined that the disease known as "grease" in horses was the source of his cowpox in cows, as early as 1800 Lupton of Thame pointed out that the disease of the horse which was analagous to cowpox and was communicable to the cow was not the grease but a disease regarded by harriers as widely different from it, to which they gave the name

"scratchy heel". This was apparently common in carthorses, having long hair on the lower parts of the leg. The exudate from the lesions matted the hair and produced irritation, causing the horse to rub one leg against the other. The chance of man being infected from the horse appears to be very slight.

Control of cowpox in a herd is a veterinary problem. Suffice to say that removal of human cases is important and the isolation and separate milking of infected from apparently uninfected animals. Good milking hygiene, and possibly the use of potassium and permanganate solution, which has good virucidal properties, should help.

Human cowpox lesions are not very common. They usually occur on the hands, forearms and face; but more rarely on other parts of the body. The lesions occur on sites which are subject to mild trauma. There is no evidence that the virus enters the unbroken skin. Once infection has taken place, nothing may be seen for two or three days. A papule develops which enlarges, becoming vesicular about the fourth to fifth day. By the seventh to eighth day the vesicle is quite large and may be secondarily infected due to occupational injury. Considerable oedema of the surrounding parts may develop. Sometimes there is much erysipeloid erythema. Cowpox lesions arising from "spontaneous" cowpox in a herd appear to be more severe than those following single passage of the vaccinia virus to the cow. Most cowpox lesions of both virus types are more severe than routine vaccination lesions. This may be partly due to the larger area of skin involved, but there also seems to be a greater reaction in the skin of the hand, possibly due to greater vascularity, mobility of the parts and restriction of swelling. It is not without interest that when vaccination is accidentally performed on the hand, it appears to take well, even in a person with considerable residual immunity (Horgan and Haseeb, 1944; Lyons, 1954). The cowpox lesion passes through its stage of development like that of vaccinia, apart from the more severe and more rapid reaction. The discharge often has a peculiar and offensive smell, described by Jenner and noted by other observers, including Laurence (1955). The constitutional effects may be considerable, and are usually greater than in vaccination. The temperature will rise to over 100° F. (38·8° C.) and the patient may feel quite ill and show signs of toxaemia. Epitrochlear and axilliary glands are enlarged, the latter more than in vaccination. The scab will remain until about the twenty-first day, and a permanent scar will remain, which will usually distinguish it from milkers' nodes. Scarring on the hands, however, as in smallpox, is likely to be of the rather superficial, non-pitted variety, which is seen more clearly by exposing the hand to extremes of heat or cold. Scars on the lower arm or face, particularly the latter, will leave foveated, depressed areas, the same as vaccination. Vaccination may modify the cowpox lesion, but it should be noted that quite severe attacks may occur within six or seven years of a successful vaccination. Second attacks of cowpox after an interval of years are not uncommon. Björnberg and Björnberg (1956) report the frequent occurrence twenty-one days after cowpox of a secondary eruption, consisting of red and reddish-brown papules on the hands, forearms, and legs below the knees, accompanied by itching. Although allergic eruptions occur in cowpox as in vaccination, other writers have not drawn attention to this syndrome. Cowpox is usually regarded as a benign infection, but Jansen (1949) reported a fatal case of encephalitis following an attack of cowpox, and Leroy *et al.* (1952) reported fatal generalized cowpox secondary to infantile eczema, and also cowpox lesions on the mouth and tongue, associated with considerable toxaemia, including an erythema. Verlinde (1951) also reported a case of generalized cowpox in a patient with infantile eczema.

The diagnosis of a cowpox lesion in man is based on its appearance, the time it has taken to

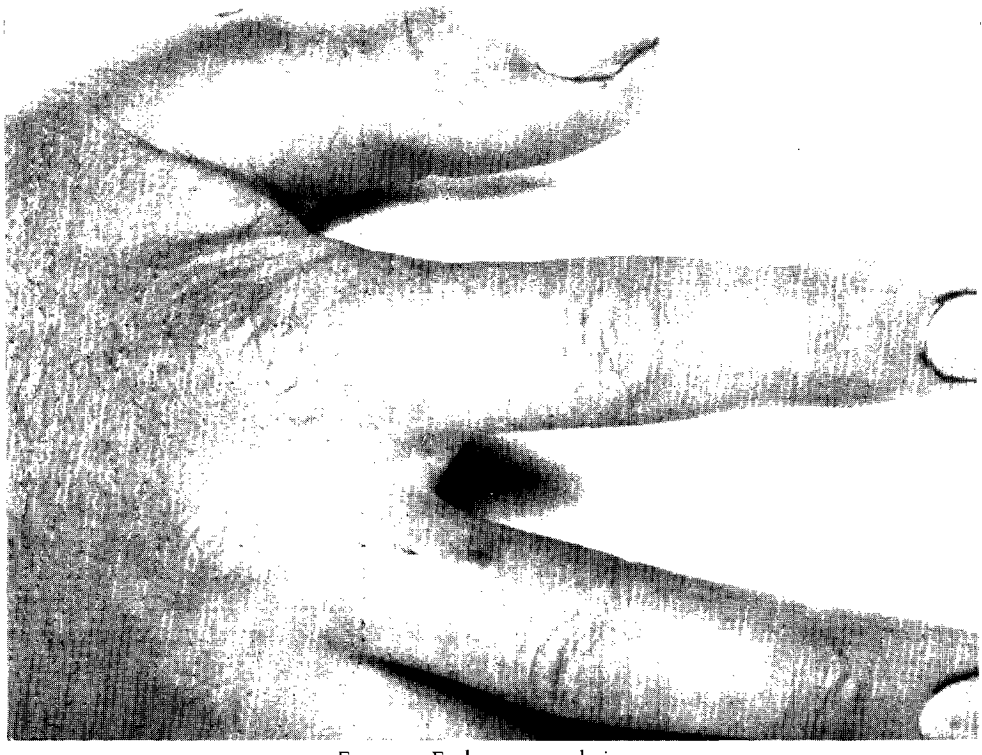


FIG. 194. Early cowpox lesions.

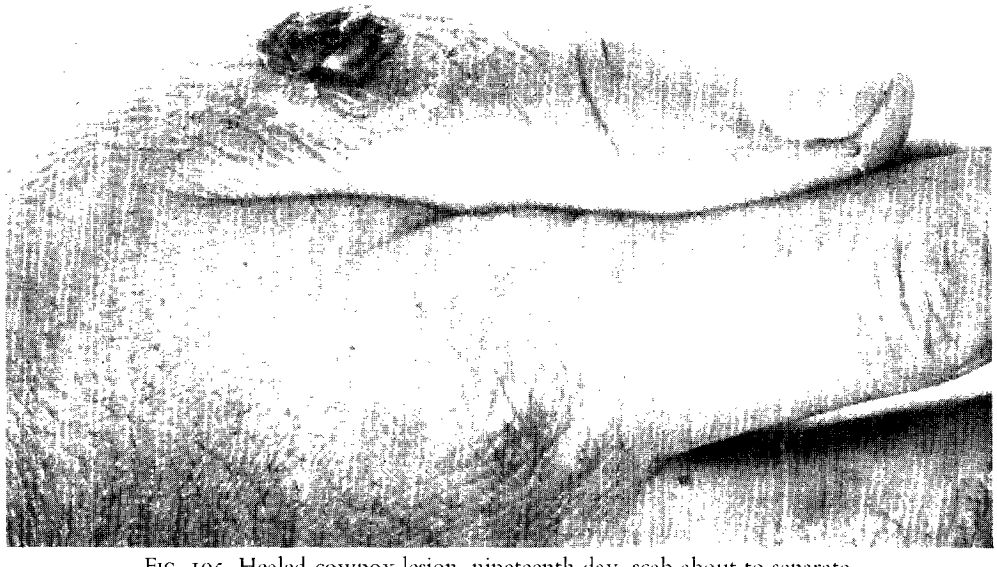


FIG. 195. Healed cowpox lesion, nineteenth day, scab about to separate.

grow in relation to its size and structure, and the vesicular nature, with the bluish tinge at the edge of the vesicle, as described by Jenner. The vesicle fluid will contain virus, and this can be readily identified in the laboratory, as having the characteristics of cowpox or of vaccinia. Antibodies should be detectable from the eighth to tenth day onwards, and retrospective diagnosis is possible by serological examination, assuming, of course, that the vaccinial history is in keeping with the deductions made therefrom.

Treatment is entirely expectant unless secondary sepsis supervenes. Generalized cowpox in infantile eczema can be treated with vaccinial gammaglobulin. Diagnosis is important, to

FIG. 196. Milkers' nodes.

avoid accidental infection of other persons, particularly those suffering from eczema, and also because on more than one occasion lesions of this nature have been subjected to surgery, in the belief that they were of different origin. Largely because the lesions are on the hands, human case-to-case infection also occurs, in the family, in those who have had no contact with bovines. Early diagnosis will prevent this, and also might prevent such widespread infection in the herd (de Stoppelaar, 1953). If diagnosed early, vaccination of other milkers will give protection by the eighth day, and modification if infected some days before.

Occasionally a lesion appears on the hand of a milker that clinically has all the appearance of a typical cowpox lesion, and yet inoculation of calves or other animals with the contents of the vesicle fails to give rise to cowpox lesions, and subsequent vaccination of the patient

three or four weeks later gives a perfectly normal vaccination reaction, although a person who has had cowpox should be immune. Reece (1921–2) cites a case of this nature in which he noted that no infection of the herd was apparent at the same time. Such occurrences only emphasize the difficulty facing the early vaccinators in selecting material.

An entirely different condition is called milkers' nodes, and doubtless gave rise to confusion in the early days, as it still does in some countries, due to it also being colloquially known as

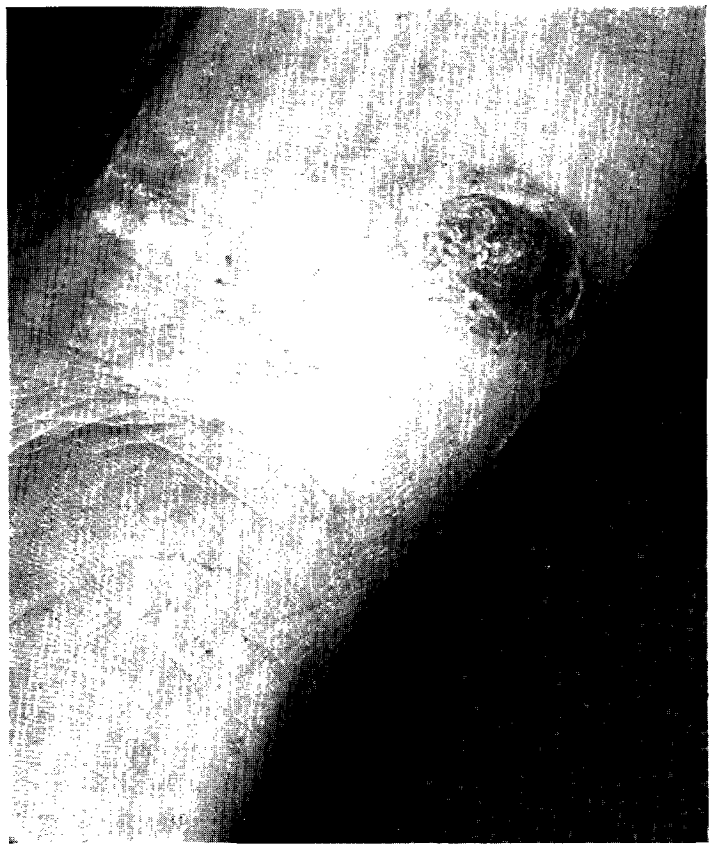


FIG. 197. Orf, lesion on the wrist about the sixth day.

cowpox. Milkers' nodes in man is derived from a virus infection occurring on the udder of the cow, producing small, papulo-vesicular lesions. They are not like typical cowpox lesions in that they are relatively chronic, and also tend to recur. Cowpox lesions themselves, however, can be considerably altered by the trauma of milking. The infection in cattle is probably fairly widespread. Danbolt (1949) suggested that there were over 10,000 cases a year in Norway, and that Norwegian country doctors were all very well aware of milkers' nodes in man. Cawley, Whitmore and Wheeler (1953)believe that no more than twenty such cases have been reported in the United States. The infection is very widespread in New Zealand, where it is

regarded by the medical profession and the lay public as cowpox. The two infections are, however, quite different, and as Berger (1955) showed, there is no cross-immunity between the virus producing cowpox, and that producing milkers' nodes.

In man, solitary or a small number of firm, bluish-red nodules develop on the fingers and hands, after an incubation period of about four to eight days. The lesions progress very slowly, and after several weeks there are small scabs over shallow ulcers. The condition usually lasts from five to six weeks, and slowly heals, usually without secondary infection, and leaves no permanent scar (Bonnievie, 1937). Allergic rashes sometimes occur, and may be quite severe (Danbolt, 1949), with diffuse oedema of the hands and forearms. The duration of immunity is unknown, but in many countries reinfection appears to be frequent. Secondary cases in human contacts, non-milkers, do not appear to occur. Treatment is symptomatic.

A further disease likely to cause confusion in the diagnosis of cowpox is infection in man with the virus of contagious pustular dermatitis of sheep. This condition, otherwise called Orf, can arise from handling infected sheep or sheepskins. After an incubation period of three to four days, a papular lesion occurs on the hand or wrist, particularly the latter. It grows so that after three days the central white area resembles a vesicle, but contains semi-solid material. It is surrounded by a hyperaemic area. The patient experiences no pain from the lesion (Webster, 1957). The lesion gradually regresses without any treatment, and heals without the formation of a scar (Fig. 197).

CHAPTER 9 | *Pathogenesis and Immunity*

PATHOGENESIS

Although accurate identification of the causative agent in smallpox has only been made quite recently, many of the older clinicians and even laymen (Colman, 1722) had a fair idea of the mode of infection and of spread within the body. "I lately met with a treatise on the Small Pox, wherein the Author advances this Rule of Maxim, 'That all venomous Particles do first enter the Body thro' the Pores of the Skin, and so croud into the Humours and Juices, and thence into the sanguine Parts. From hence he accounts why the Face and Hands and Feet are usually fullest of Pocks, because those Parts of the Body are more open and exposed, for the Admission or Entrance of those venomous Particles.'

"But if one Hypothesis or other may be at all admitted, with this farther and most reasonable Thought upon them, that these venomous Particles or Animalcules do also flow into our Nostrils, Throat and Blood, by our Breath; then may they not give us a Reason, why the Small Pox communicated by Incisions in the way of Inoculation, does not produce so many Pock and such a Flame and Corruption in the Body, as in the common Way of Infection it ordinarily does? Because in this Way not so many enter, nor immediately into such Parts of Hazard and Distress, as in the Nostrils, Throat and Inwards?"

In spite of research work in the human and experimental fields many gaps in our knowledge still exist today. It is perhaps idle for the epidemiologist to speculate on the cause of events when he has no proof, but medicine is becoming increasingly specialized and the experimental virologist may have little personal experience of smallpox in man so that field observations may perhaps be of value as a lead to experimental investigation.

The rather spectacular eruption has had much attention, so much, that many older writers, although recognizing the existence of an initial phase, rather regarded it as prodromal in character and spoke of the patient "having the smallpox" only from the time the rash appeared. As late as 1892 there were clinicians who still regarded smallpox as purely a skin disease (Birdwood, 1891). Ricketts (1908) went to the other extreme and regarded the rash of smallpox almost as a complication. He stated: "The rash of smallpox is to the disease as the bronchopneumonia of measles is to that disease." In the light of his wide knowledge of the disease and his masterly writings on such subjects as the distribution of the rash, this is a surprising statement, but perhaps it indicates the lengths to which Ricketts had to go to convince contemporary clinicians of the whole picture.

Smallpox and vaccinia viruses are identical in appearance under the electron microscope and are seen in dried films as brick-shaped objects about 200 × 300 millimicrons (Fig. 163). In tissues they may be ellipsoidal in shape.

Although the standard works on virology contain much on the effects of chemical and physical agents on vaccinia virus, all strains do not behave the same, and purified laboratory

suspensions react differently from commercial smallpox vaccines. Comparatively little work has been done on smallpox viruses and it seems wrong to assume, as is often done, that their behaviour must be similar to vaccinia.

The virus is only derived directly or indirectly from human sources. The epidemiological aspects are discussed in Chapter 14. Although the public to some extent still regard smallpox as contagious, the normal mode of infection is for the virus, suspended in the air in droplets or in dust particles, to enter the respiratory tract. The evidence is, however, only circumstantial, but many records exist of a person's only contact with smallpox being the breathing of air contaminated with virus from a smallpox patient or from clothing. The virus can be ingested; older writers relate cases of apparent infection by drinking water contaminated by smallpox material, and variolation has occurred from individuals eating smallpox crusts (Eimer, 1853). Although infection could theoretically arise from infected food it is not a route of any practical importance.

There is no evidence that smallpox virus enters through the conjunctiva, but the observations of Papp, Molitor and Öry (1956) in measles, raises this possibility. That virus can enter through an abrasion of the skin is well known and described under *Variola Inoculata* (Chapter 6), a local lesion being produced at the site of inoculation which passes through the stages of development similar to the benign smallpox lesion.

Whether the virus can enter the skin without producing a local lesion is more difficult to verify. Some writers believed that this did not occur, although in experimental animals (rabbits) vaccinia virus can apparently enter through the skin of the external auditory meatus (Gordon, 1925). The older accounts of inoculation suggest that in some cases of inoculation a primary lesion did not develop, although secondary symptoms and rash did. In some, infection was introduced so deeply as to be subcutaneous and without a dermal lesion. Others might have been infected by the respiratory tract. Whether this occurs in natural infection with smallpox is not known but is a possible explanation of the shortened incubation period which has been recorded in some cases.

From the moment the virus enters the body nothing is known of its whereabouts until its presence in the blood-stream at the time of the onset of the fever and symptoms of the initial stage. It had been suggested by the older clinicians that a "primary" lesion would be found in the lung, but in spite of much careful searching by many pathologists in the nineteenth century who had such a wealth of material, the "proto vesicle", as it was called, has never been discovered. It is not without interest that in smallpox the tissue which shows practically no effect of virus infection is the lung, although modern cytological investigations have not been done. The possibility of a different mechanism in hyper-immunes is discussed later.

In inoculation variola, as in vaccinia, a primary lesion occurs in the skin which reaches its maximum development just after the onset of general symptoms. Dissemination of virus occurs, but only in variola does it commonly produce secondary skin lesions.

It is tempting to assume and many writers have assumed that the pathogenesis of natural smallpox is the same as that of *variola inoculata*, although, clinically, they are so different. In natural smallpox, infection of a group of susceptibles with variola major virus gives rise to a high proportion of severe cases with an overall case mortality of about 30 per cent, but in variola inoculata using the variola major virus (although derived from the skin) the mortality is less than 1 per cent. In the inoculated disease the infecting dose is probably many hundred times the size of that experienced by the naturally infected patient who, records show, may

have a fatal attack from only breathing for a few minutes the air of a room occupied by a patient. When the virus in the form of crusts is introduced into the nose a relatively mild disease results. The comparison is, however, made more difficult as, in the one, "respiratory" virus infects the respiratory tract of the patient, whilst in the variolated, "skin" virus is introduced to the patient through the skin or through the nose.

I have previously suggested (1948) that the virus extruded through the skin and shed in the form of scabs may be different in some way from the virus exhaled from the respiratory tract during the initial phase. As discussed in the chapter on epidemiology, the epidemic potential certainly seems different. Perhaps there is some difference in the ability of the skin virus and the respiratory virus to grow at the site of primary development.

We have four possible combinations of source and route. (1) Respiratory virus can give rise to the usual respiratory infection, or (2) it could be accidentally inoculated into the skin and give rise to an inoculated type of smallpox. (3) Skin virus derived from scab dust can give rise to respiratory infection, but my *impression* is that milder cases result, or (4) when inoculated into the skin relatively mild inoculated smallpox.

I am well aware that I have no proof of my suggestion that event (3) is different from event (1). It is likely to prove difficult to elucidate this problem as many instances occur when infection could occur from *either* source simultaneously. Has respiratory virus a greater infective potential for the respiratory tract and less for the skin, and skin virus a greater infective potential for the skin than the respiratory tract? It seems quite possible.

Fenner (1948) has shown that in ectromelia in mice, a disease closely related to smallpox, the virus introduced through the skin first multiplies at this site and after reaching a maximum level infects the lymph glands. From here the infection passes into the blood-stream, whence it is removed by the macrophages of the spleen and liver. Further multiplication occurs and the virus is then again released into the blood-stream in large amounts. Focal infection of the skin and other organs then follows and after further growth visible skin lesions are seen.

Fenner (1948), Downie (1951) and Bras (1952*b*) consider the pathogenesis of ectromelia is a valid model for smallpox, but it must be remembered that in ectromelia the normal route of infection is through the skin, whereas in smallpox this is quite exceptional. In *variola inoculata*, as in vaccinia, the virus travels to the regional lymph nodes which enlarge at the time the primary lesions are bacteriologically sterile. Fenner's work on ectromelia is most fascinating, but I feel that although his explanation of the pathogenesis of vaccinia and of variola inoculata is probably correct, there are serious gaps in our knowledge of the early stages in natural smallpox which are important in understanding infectivity.

Although in ectromelia Fenner was able to sacrifice his animals and detect virus in the tissues and in the blood at the various stages, we have no similar opportunity in man.

It is very exceptional, and the older writers with wide experience agree, for the patient to have any symptoms, even slight malaise, during any part of the incubation period; so if there is a viraemia as the virus passes from upper respiratory tract epithelial cells, possibly via the glands to the liver and spleen, nothing occurs comparable with the viraemia of the initial clinical stage.

However, it is almost certain that great multiplication of virus occurs in the cells in the reticulo endothelial system in the liver and spleen and possibly also in other organs such as the lung (Downie, 1951). The liver probably enlarges slightly at this stage, but cannot be detected clinically and gives rise to no symptoms.

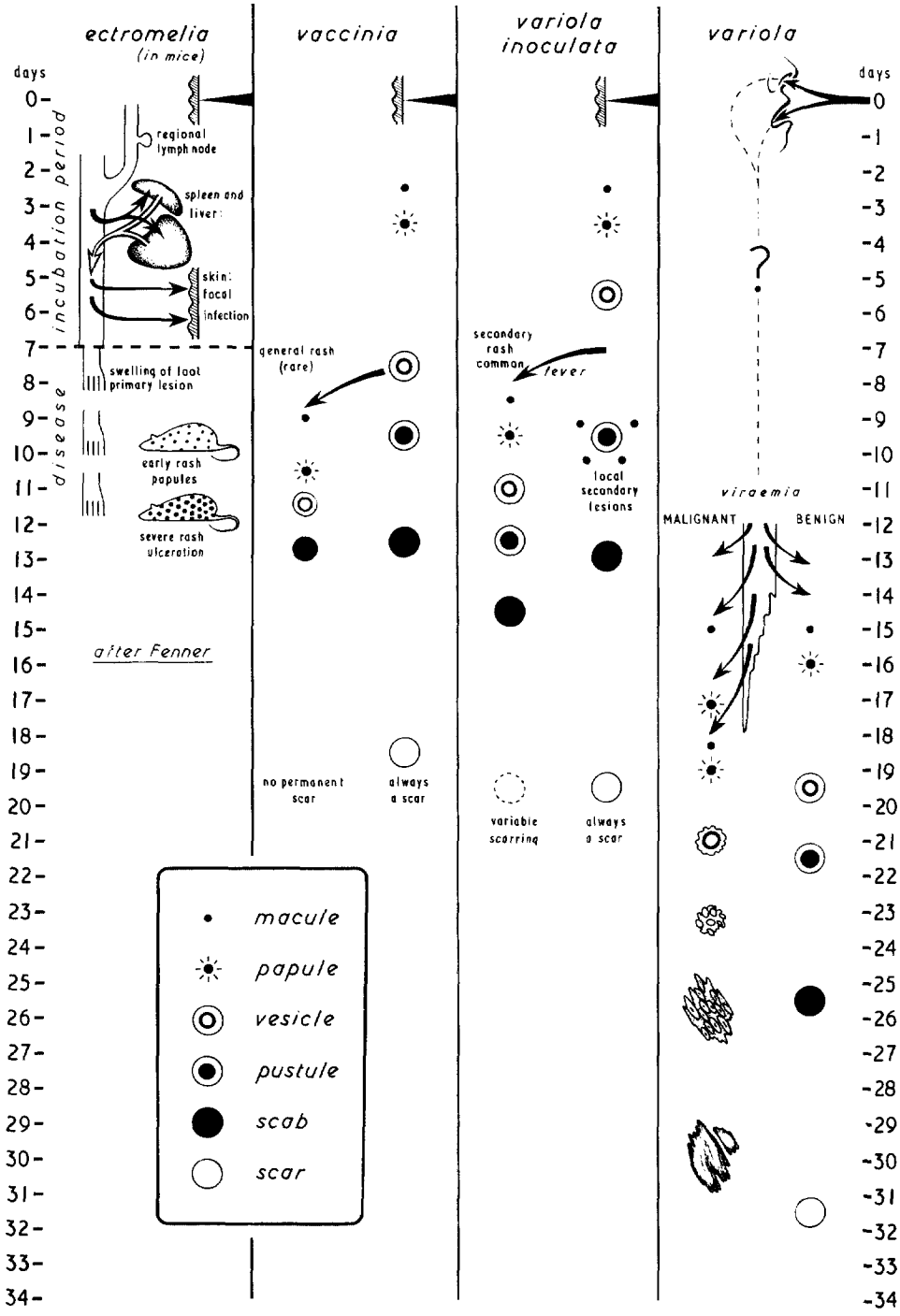


FIG. 198. Possible pathogenesis of some pox virus infections.

Figure 198 shows Fenner's diagram of events in ectromelia, and my own diagram is based on this to suggest the course of events in vaccinia, variola inoculata and in natural smallpox.

We are hindered by having no convenient experimental animal which contracts smallpox with a clinical syndrome similar to that occurring in man. Inoculation with smallpox and even more with vaccinia produces effects so essentially different from the natural disease that experiments in this field should not be interpreted too freely.

As already mentioned, it is quite exceptional for any fever or feeling of malaise to occur during the incubation period. Although the person may be mechanically infectious on the day of infection, there is no epidemiological evidence that once invasion has occurred the respiratory tract remains infectious. The next event is a sudden viraemia, usually on the twelfth day from the date of infection. Of all diseases the incubation period of smallpox is perhaps the most constant, and although the period of exposure is only rarely limited to a few minutes, over the years many cases have been recorded where this has actually occurred. In a very large proportion of cases the incubation period is then found to be closely around twelve days. More frequently, and this applies particularly to the records of cases in the many outbreaks in the nineteenth century, it may be impossible to decide which is the day of infection within three or four days. Curschmann (1875) felt that in less than 1 per cent of cases could the time of infection be determined exactly. Claims to incubation periods of nine or eight days, and even by some as short as five days, followed by normal clinical attacks, should be regarded with considerable scepticism. It is possible for a person to have been infected at the normal time from an unknown source, when it is remembered that the first known case is rarely the first *real* case in an outbreak. Incubation periods of nine or ten days have been recorded in patients with diseases of the skin (Eastwood, 1955), and although no primary lesion occurs it is possible that entry might be through sites of abnormal skin. His cases, which were very mild, had concurrent vaccinia and the pyrexia denoting onset of attack may have been vaccinial not variolous. Conybeare (1939) suggested that in vaccino-modified attacks perhaps there was some acceleration of primary growth analagous to vaccination. In some cases with shortened incubation periods the attack is fulminating and this may be the reason for the different onset. An alternative explanation for these *really exceptional* cases would be the omission of one stage in the hypothetical scheme of development of virus during the incubation period. This would seem feasible if there were constitutional or immunological factors operating.

Even when *variola sine eruptione* occurs, the usual twelve-day incubation period is followed by a brief viraemia, pyrexia and malaise with complete recovery within twenty-four hours and no rash. Although this type of case has been recognized since de Haen's (1775) time, it is also today somewhat euphemistically called "illness of contact" (Conybeare, 1939; Boul and Corfield, 1946). Although syndromes which might fit this description, with a twelve-day incubation period, are common, particularly in high-level immunes, another quite different syndrome also appears to occur. After an incubation period sometimes of five to eight days but also of eleven to fourteen days, the patient has a pyrexial attack, but rather less sudden onset, accompanied by signs of a "virus pneumonia". Resolution is slow, and in some cases convalescence protracted. The majority of these cases have been recorded in medical and nursing personnel. If they occur singly, it is common, in spite of the smallpox contact but because of the vaccinial history, to assume that they are genuine virus pneumonia of unknown etiology, which doubtless, as chance infections, they well may be. However, Howatt and Arnott (1944) recorded seven cases occurring simultaneously in a military hospital. The

clinical syndrome was that of a virus pneumonia which was supported by the X-ray appearances. Pickford Marsden (personal communication) has also shown me the X-ray of a smallpox contact who developed a "virus pneumonia" under similar circumstances. On the other hand, in more than one case with which I am acquainted, in spite of a clinical diagnosis of virus pneumonia in a smallpox contact, the X-ray appearance was negative. In the cases described by Conybeare (1939) where the incubation period seemed about seven days, at least one of the cases was a frank smallpox (type 8) and the remainder had not been successfully vaccinated for over three years. Respiratory symptoms were not noticed, and headache, backache, nausea and vomiting—symptoms much more characteristic of genuine smallpox—were present.

There therefore appear to be two possible syndromes: *variola sine eruptione*—with a pyrexial attack of sudden onset accompanied by headache, backache, nausea, but no rash. This initial stage may last as long as three days or only a few hours, but is indistinguishable from the initial phase of smallpox where a scanty rash does occur, but there is rapid recovery. The second syndrome, which at present is nameless, has a more insidious onset, with respiratory rather than toxaemic symptoms. The incubation period seems to be more variable generally shorter, between four and ten days, and rarely, if ever, the full twelve days. The disease process is at a different tempo, slower onset and terminated by lysis with some persistence of symptoms for many days, usually about two weeks.

The fact that so many of these cases occur in medical and auxiliary medical personnel, where the authenticity of old vaccination records, etc., can often be questioned, makes it difficult to get accurate, unbiased accounts.

Three possibilities appear to exist. Firstly, that isolated or even small outbreaks of virus pneumonia have occurred by chance in those who happened to be smallpox contacts and are recognized in those individuals because they are under surveillance, although similar cases might be occurring in the general population. Although this appears possible, there have been occasions where, as in an army unit under surveillance, only those who came into contact with smallpox developed any illness.

A second possibility, and on epidemiological evidence the most unlikely, is that the smallpox virus itself infects the lung, giving rise to a smallpox pneumonia.

The third, and the most likely explanation, as it would also fit the shorter incubation period, is that the smallpox virus enters the upper respiratory tract, multiplies and is liberated into the blood-stream, and in hyper-immunes is filtered out principally by the lung. An antigen-antibody reaction occurs, and this gives rise to oedema, to the clinical syndrome and X-ray appearances similar to a virus pneumonia.

To differentiate it from the "illness of contact", with a definite twelve-day incubation period, which is the same as *variola sine eruptione*, this syndrome had perhaps better be given a separate name, such as "smallpox pulmonary allergy". Although the problem is complicated by the fact that most of their contacts are also immunes, there is no evidence that these cases are infectious to other people, and they can be nursed without any special precautions. The occurrence of this syndrome makes one wonder whether some of the mild "bronchitis" seen in some outbreaks of smallpox in the well-vaccinated might not have an allergic pulmonary element superimposed on the normal virus cycle.

Variation in host susceptibility is often regarded as the reason for shorter or longer incubation periods, but in smallpox there is no evidence that the more severe infections tend to have shorter incubation periods or the milder cases longer.

Many claims have been made that the incubation period is often longer than twelve days; thirteen, fourteen and even as long as seventeen days (Ricketts, 1908). Proof of this is usually more difficult as a number of possibilities can occur. Although the patient may only have had contact on one occasion, infection may really have been indirect, by respiratory infection from the dust of the individual's own clothing which was originally infected on the day of contact with the case; or the virus on entering the nose and throat remains dormant for a day or two before entering the cells where actual multiplication can occur. It is commonly stated that in variola minor there is a longer incubation period, but Marsden (1936), with great experience of this disease, states that no real evidence has been produced to substantiate this. The incubation period in smallpox is, however, of more than theoretical importance as quarantine must depend on it.

Due to difficulties of this kind and to the general recognition of the rash as the most important single sign of smallpox, many of the older clinicians counted the incubation period from infection to the day of the appearance of the rash. Although in epidemiological investigations recording the day of appearance of the rash has some advantage in tracing field contacts, it is unscientific, tends to lead to neglect of the important initial stage, and gives rise to just as many difficulties as it attempts to avoid, as in the very severe types the onset of rash is ill defined, and in the mildest type of smallpox no rash occurs.

At the end of the incubation period the virus is liberated from its final site of multiplication in the reticulo-endothelial system, as a result of the bursting of infected cells. The virus shower probably commences just before the sudden rise in temperature and onset of symptoms of the initial phase. Blood culture is probably positive just before the onset of pyrexia, but only recently with egg culture has a really practicable method of isolation been available and many more observations are required. Virus is thus able to disseminate to all parts of the body with the possible exception of the central nervous system, although Puntigam, Orth and Kabin (1952) have identified by electron microscopy vaccinia virus in the cerebrospinal fluid of calves used in preparing calf lymph.

It is often stated that the explanation of the different types of smallpox is simply and solely due to the amount of virus liberated. This takes no account of the views of the clinicians over two centuries, that in the fulminating and malignant types the initial phase is different from that of the benign. Even more telling is the existence of semi-confluent malignant types quite distinct, and with a different prognosis from benign confluent and semi-confluent. The positive blood culture and presence of soluble antigen for some days in the malignant cases is in contrast to the short duration of positive blood culture and absence of soluble antigen in the benign. The reaction in the patient is so different that some different mechanism appears probable.

The most spectacular effect is on the skin (Figs. 18–23, 32–37, 49–54 and 55–60). Councilman (1904) suggested that the lesion in the skin occurs first in the epidermis. Using vaccinia and not variola as a model, Ledingham (1924) concluded that the lesions were first formed in the dermis. Bras (1952*b*), who carried out the most recent and possibly the most complete study of the pathological findings of smallpox, has paid particular attention to the histology of the skin lesions. Unfortunately he lost the opportunity of clarifying a number of points by trying to classify the cases on an impossible system (Nothnagel, 1895): (1) *variola vera discreta;* (2) *variola vera confluens;* (3) *purpura variolosa;* (4) *variola pustulosa haemorrhagica.* Bras states: "A sub-division between *variola vera discreta* and *confluens*, however, was quite impracticable

because nearly all patients of the variola vera group had discrete and confluent pocks at the same time, the latter usually on the face." (Of course, it is quite normal for confluent cases to have discrete lesions on some parts of the body.)

"Furthermore, it is sometimes impossible to determine whether a case of *variola pustulosa haemorrhagica* had started as a purpura variolosa or not. Again, haemorrhage can be so slight that classification of the case as *variola haemorrhagica* was doubtful. For instance a patient can have generalized *variola vera* eruptions but with haemorrhages only on the back, in and under the vesicles. Also when patients have been tied to the bed by the wrists and ankles because of restlessness, haemorrhages may be seen under these areas, traumatic in origin." A state of confusion which entirely supports my view that the word "haemorrhagic" should be deleted from smallpox terminology.

Examination of the brief clinical notes of his cases shows that many called "*purpura variolosa*" are in fact typical malignant smallpox, and interpreting the histological findings by reclassifying the cases shows that in fulminating and malignant smallpox there is "violent hyperaemia of the corium vessels" which "is not limited to the sub-papillary network. The deeper plexuses are simultaneously affected, though the cutaneous net is not. In addition there are localized haemorrhages between the collagen fibres of the *stratum reticulare corrii*, but occasionally extravasation of erythrocytes occurs in the stratum papillare corrii or even in the epidermis. The perivascular infiltrates are present though often masked by haemorrhages. Changes in the epidermis appear above the haemorrhages in the corium. As a rule they are not yet developed at the time of death" (presumably in the fulminating which die in three to five days; malignant cases usually die between the tenth and fourteenth day), "changes when present assume either the characteristics of reticular or of ballooning degeneration slightly varied, however, from the aspect in *variola vera*" (benign case). "Reticulation is not restricted to the middle and upper layers of the *stratum spinosum* but may also occur in the basal layer. Small irregularly scattered epidermal cavities may be formed, rarely a typical vesicle, with surrounding zone of swollen cells as in variola vera. Leucocytic immigration in the epidermis does not seem to have sufficient time to develop."

I would suggest that it is not a question of time, but that there is an intense and persistent leucopenia in the malignant case.

In benign smallpox (*variola vera* in Bras's account) he finds no effect on the corium except perivascular infiltration round the sub-papillary vessels, the effects in the uncomplicated lesion being confined to the middle layer of the epidermis.

Bras feels "that all types of smallpox, haemorrhagic and non-haemorrhagic, have no essential differences" and "the usual clinical classification is evidently founded only on a different development of parts of this pattern".

The confusion which the "usual clinical classification" produced, with the obvious mixing of some of the cases of benign confluent with the malignant confluent, prevented Bras appreciating these differences between malignant and benign. I feel, however, that this valuable piece of work confirms the view that although the virus is obviously growing in the skin and the histological changes amongst cells, to some extent, follow a "common basic pattern", the differences between malignant and benign are considerable and are in accordance with the clinical findings (skin close-ups, Figs. 18–23, 32–37 and 49–54). In the malignant there is a diffuse destructive process primarily in the dermis with little or no tissue reaction on the part of the host. In the benign there is localization in the epidermis, a tissue reaction and proliferation

surrounding the area of cells undergoing degeneration—an active defence mechanism. Unfortunately, the study of post-mortem material can never give the complete picture of changes in smallpox lesions as a large proportion of the milder types will not die. Deaths occur, with very few exceptions, at certain well-recognized times, either in the first four or five days of attack, between the tenth and fourteenth day, or from complications from the eighteenth day onwards.

It is generally agreed that the virus must reach the skin by way of the blood-stream. In the malignant cases changes in the corium indicate its presence at this level before it occurs in the epidermis, producing feeble vesiculation. The clinical effects already mentioned and illustrated suggest that the virus is present in large areas, possibly in all parts of the corium, and that vesiculation is an added and perhaps almost chance phenomenon. In the benign cases, as has been seen, the skin in between the lesions appears completely normal, and as one passes down the scale of severity to the milder cases it is almost certainly normal and free from virus. The typical pock or virus colony in benign smallpox is most probably formed by a virus-leucocyte embolus. Work on vaccinia (Smith, 1929) suggests that virus may become attached to cells and infective material be absent from the plasma of rabbits within a few hours. The idea of infective emboli as the cause of the virus colony in the epidermal pock in smallpox is a very old one and was used by Ricketts to explain his theories of distribution referred to later.

The reason for the different type of reaction in malignant and benign cases has not been explained. It is sometimes assumed that it is all a question of quantity of virus. In recent outbreaks, however, virus has not always been recovered in greater quantity from the blood of malignant cases than of the benign. In some malignant cases even when blood samples were taken early the virus has only been recovered on subculture, whereas type 7 cases have shown a positive first culture. If in the malignant case at the time of the virus shower there was a liberation of some toxic substances, possibly of the nature of hyaluronidase, this might assist the virus to diffuse and grow in the dermis. At the same time, there is an intense agranulocytosis and this might have something to do with the lack of localization.

As we have seen, the malignant lesions are in the true dermis; in the benign more superficial. Although in unmodified smallpox the discrete (type 6) and mild (type 7) attacks may have progressively fewer lesions, they are similar in size and depth, but in those with partial immunity the lesions are more superficial so that in a mild (type 7) in the unvaccinated a few normal depth lesions will occur, whereas a vaccino-modified (type 6) will have more numerous lesions but they will be more superficial. Once again the simple explanation that the mere amount of virus liberated determines the rash does not satisfy.

Why the vaccino-modified rash, particularly the later lesions, should be so superficial (Figs. 59–64) is not known. Virus is disseminated through an appreciable layer in the epidermis and in intercellular spaces. Possibly at the lower levels it is unable to grow owing to the effect of antibodies, whereas the more superficial virus particles are unaffected. What is also very noticeable is that the superficial lesions are much less liable to secondary infection with pyogenic organisms. The older writers recognized that one of the most beneficial effects of some residual vaccinial immunity was in saving the patient from the risk of septic complications even if the rash was fairly extensive, and this was also one of the virtues of *variola inoculata*. Ledingham in 1924 showed that in vaccinia the action of contaminating cocci was "stultified if the virus was rendered impotent by neutralization with anti-vaccinial serum". Possibly a similar mechanism operates in man.

Ledingham also noted that in experimental animals oedema around the lesions was necessary to induce active secondary infection. In human smallpox oedema occurs when there are large lesions, particularly on the face, in benign confluent and semi-confluent. In the vaccino-modified, however, due to the superficial nature of the lesions, cuticular oedema is very slight or absent.

FIG. 199. Deep destruction of sebaceous glands and formation of a pit.

The vast majority of smallpox patients who recover from the disease and who were previously healthy are left with no sequelae save scarring but, particularly in the female, this is of great importance.

Although the scars may appear as profuse on the hands or arms as on the face, the character is different, those on the latter, particularly on the nose and cheeks, being much deeper. When the cases, however, are seen a year later the difference is even more striking. Whereas on the hands and arms the scar sites may be difficult to see and pass unnoticed by the casual observer, the scars on the face are more pronounced than when the patient left hospital; a fact frequently ignored by the hospital doctor assessing the effects of treatment on scarring.

Bras (1952*a*) recorded his studies on the differences in the scars on the face and other parts of the body and pointed out that although the sebaceous glands seem to be specifically picked out in smallpox, a fact recognized by other observers (Petzholdt, 1836), their relative paucity on other parts of the body means that, in spite of destruction of the gland and subsequent fibrosis, the end-result is practically invisible. On the face, however, the sebaceous glands are particularly numerous, closely set and relatively large and destruction here results in deep fibrotic pits (Fig. 199) in spite of the vascularity of the face and its particular ability in tissue repair. Bras was also convinced that secondary infection of the lesions played little if any part in the cause of permanent scars in smallpox, a view I entirely support (1948). Very ugly keloidal scars may be seen on the face following smallpox, complicated by chronic impetiginous lesions on the site of the smallpox ones (Fig. 85), but these are really the scars of chronic skin sepsis and are unrelated to the sebaceous glands and could be prevented by chemotherapy if not by adequate hygiene and nursing. I have seen some of these cases in Cambodia following mild attacks of smallpox where practically no smallpox scars were present. As mentioned in the chapter on *variola inoculata*, even when the secondary rash was quite profuse the more superficial nature of the lesions and the escape of the sebaceous glands often meant that the inoculated person had no appreciable permanent scarring except at the inoculation site. In generalized vaccinia of the benign type, scarring is also invisible after a year. On the other hand, accidental vaccination of the face or other part concurrent with a primary vaccination will give rise to a permanent scar on the secondary site.

The characteristic distributions of the acute exanthems has always fascinated writers and smallpox is no exception. It has been recognized for many hundreds of years that the density of the rash was greater on certain parts of the body and that this might be determined by mild irritation or injury. Colman wrote in 1722: "It has long been noted—the face and hands and feet are usually fullest of pocks because those parts of the body are more open and exposed." Ricketts (1908) seems to have been the first clinician to point out the centrifugal nature of the rash and the gradual change in density from the centre to the periphery.

Ricketts claimed that the production of lesions on sites of trauma was due to vascular stasis allowing virus-leucocyte emboli to adhere to the capillary walls, so allowing viral growth. If the trauma was very slight, no effect might be produced, and if it was very severe with considerable hyperaemia, capillary circulation might be increased and the normal or less than normal number of lesions might be produced. In my experience, malignant cases do not show this phenomenon to any great extent and the depth of the lesion may account for it. The theory is neither proved or disproved, but is certainly the best explanation of the very characteristic clinical findings.

Ricketts developed his theory further to account for the variation on certain anatomical parts. For instance, it is common for the foot to have less rash than the hand. The dorsum of the foot is much more affected than the plantar aspect. If, however, the person is a great walker, particularly in tight shoes, then the rash on the sole of the foot may be confluent, even in variola minor (Fig. 129). The centrifugal distribution on the limbs is particularly well shown in children (Fig. 80), who presumably use all four limbs fairly vigorously, but in the adult, particularly those in sedentary occupations, the arms are much more affected than the legs. When a patient is bedridden the legs may be scarcely affected at all, even in discrete or semi-confluent cases. It has been noted that the hemiplegic has much less rash on the paralysed limbs. From similar observations Ricketts assumed that the normal smallpox rash must be determined

by the same intrinsic causes that determine the varieties, "the operative causes are manifold; but the most potent factors are exposure to air and friction with clothing and to their efficacy every case of smallpox is a testimonial" (Ricketts, 1908) (Figs. 133, 134, 138).

Ricketts proceeded, by an analysis of the extent of the rash on the head, face and arms, trunk, etc., to show that the most mobile parts and the extensor surfaces are most heavily affected, those parts protected by clothes and immobile the least. All this is borne out in practice. If, however, this is the real cause, why is it that in vaccino-modified smallpox where the patient is less ill and more mobile during the initial and early eruptive stage, and may in fact continue at work, the centrifugal characteristic of the rash is less well shown than in the more incapacitated cases. It is in the very mild ambulant cases that all the lesions may be on the trunk. Although in Europeans the rash undoubtedly tends to occur on those parts of the body which are unprotected by clothing, there are in the world many people who wear no clothes at all. Smallpox in these people has, however, the same characteristic distribution as in Europeans (Fig. 84).

Another point, which rather spoils the explanation, is the fact that trauma will affect chickenpox lesions in a similar way, yet the normal rash of chickenpox is quite different. It is particularly unfortunate for those who hold the view that the pathogenesis of variola and vaccinia are the same, that in generalized vaccinia the skin lesions do *not* follow the characteristic pattern of the smallpox distribution.

Although I feel that Ricketts' theory as to the cause of the centrifugal distribution is not valid, we are indeed grateful to him for his clear enunciation of the principles of diagnosis based on the characteristic distribution and not on the appearance of the individual lesions which are alleged to be diagnostic. As Galen wrote about A.D. 131, "no cause can become efficient without an aptitude of the body". We know something of the factors affecting this aptitude, but we still do not know the cause.

IMMUNITY

The immunity mechanism in smallpox is imperfectly understood although much can be deduced from the study of the disease, particularly in persons possessing residual immunity from previous successful vaccination. As a result of observations of this nature I put forward some ideas on the immunity mechanism in smallpox (1948). As little has been published since to add to the subject, the following account is largely based on the previous description.

Any theory of immunity must attempt to explain:

(*a*) the different clinical types of the disease, including malignant and benign, and the rashes associated with them;
(*b*) the variation and extent and maturation of the rash, such as the distinction between few lesions with normal maturation and many lesions with accelerated maturation;
(*c*) modification of the rash in type and rate of maturation associated with previous successful vaccination;
(*d*) the mechanism of the immunity produced by vaccination, including concurrent vaccinia and variola.

There appear to be three distinct components: anti-invasion, anti-dissemination, and local skin immunity.

Anti-invasion immunity determines whether or not the virus entering the nose and throat multiplies in some part of the respiratory tract and after further stages of development

produces the initial fever, the primary clinical syndrome. This immunity factor determines whether or not active infection will occur and in "immunes" is at a sufficiently high level to prevent tissue invasion. Possibly it is a local cellular immunity of the respiratory mucous membrane. It may allow an individual to carry virus for a few hours in a purely mechanical way and so infect contacts, although the individual does not subsequently show any signs of a clinical attack. This type of immunity occurs in those with a recent successful vaccination, but it declines relatively quickly, while other forms of immunity may still be present. On the other hand, this cellular resistance to infection must also be present in those individuals who are apparently immune to smallpox as they suffer no attack on repeated exposure to respiratory virus, but who can be successfully vaccinated subsequently. This latter infection is, of course, introduced through the skin.

The loss of anti-invasion immunity accounts for types 7, 8 and 9 occurring in persons successfully vaccinated some three to ten years previously. Following a natural attack of smallpox this component is more persistent, in some individuals lasting for a great many years, even for life, but as secondary attacks occur, it must decline in the same way as that induced by vaccination. Variolation seems to occupy a middle position, the immunity component being more lasting than that derived from vaccinia, but less than that following a natural attack. Anti-invasion immunity seems to be a fairly independent factor, and from the practical angle is complete or absent, resulting in resistance or active infection. This is supported by the fact that the initial syndrome is no less severe in *variola sine eruptione* than in many of the more severe types. There is also no characteristic difference in initial syndrome in variola minor where the majority of infections will be mild. It is to be noted that length of the incubation period does not seem to be affected.

In all types of smallpox a viraemia coincides with the onset of the initial phase. Whereas in the fulminating and malignant the viraemia continues for some days, "soaking" the tissues with virus, at the other end of the scale in variola sine eruptione, it is short, possibly lasting only a few hours, and the patient may feel perfectly normal within twenty-four hours.

Until serial blood virus counts can be made on patients in the viraemic stage of the different kinds of smallpox, one can only hazard a guess at what is happening from the appearance of the skin and from the general condition of the patient, the pyrexia, malaise, etc. Judging from the number of lesions in the skin there would appear to be no great difference between the intensity of the viraemia in the malignant confluent and in the benign confluent. On the other hand, in the malignant semi-confluent the viraemia is less intense although of longer duration than in the benign confluent, and this is supported by the very scanty laboratory evidence available at present, that the blood in malignant semi-confluent may not show very profuse growth of virus. As discussed later, the effects may be due to some toxic action or some immunity characteristic of the skin.

It is postulated that another immunity factor, the anti-dissemination factor comes into play, and in some way neutralizes virus. It might be argued that no such factor is necessary, the intensity of viraemia determining all, or that skin immunity can account for the differences, the skin, in some cases, being sufficiently immune to prevent growth of virus. However, in clinical practice we see one patient who has a few lesions of normal size and rate of maturation and another who has a large number of lesions which are abortive and mature rapidly like an accelerated vaccination although the initial attack appears identical. This suggests that two distinct factors must be present, an anti-dissemination factor and a skin immunity factor.

In variola minor in which the pathogenesis would appear to be identical with variola major, we have a similar and not always milder initial phase followed by a feeble growth of virus colonies in the skin. Either the primary growth cycle provides less virus, which is unlikely from clinical and blood culture observations, or the virus is neutralized by a *natural* anti-dissemination immunity factor present in most individuals or is less able to grow in the skin. The rare, extremely susceptible person, as in other diseases, may get a severe type of attack. This natural level of anti-dissemination factor is sufficient to cope with the relatively feeble variola minor virus, but only in a small proportion of individuals affected with variola major virus. If it is sufficient to neutralize all the virus, there is no rash. Even variola major *sine eruptione* can occur in the unvaccinated person.

The anti-dissemination factor is produced by vaccination and, as it wanes, types 7, 8 and 9 occur. It persists in some individuals, however, for a very long time, fifty or sixty years, although in others it may disappear quite quickly. Why there should be such variation is not known, and this is further discussed in the chapter on clinical vaccination (Chapter 7).

Whereas only a small proportion of unvaccinated persons possess significant anti-invasion immunity, a larger proportion possess some degree of anti-dissemination immunity resulting in benign-type lesions from confluent to *sine eruptione* following infection with variola major virus and the discrete and mild lesions following infection with variola minor virus.

The skin immunity factor is independent of the other factors and appears to be low in the vast majority of people as confirmed by the ability to successfully vaccinate or variolate nearly 100 per cent of a previously unexposed population. However, the newborn infant appears slightly less susceptible, as greater trauma is necessary to both successfully vaccinate or variolate (Monro, 1764). There is also the small but extremely important group in which repeated vaccination fails, but the individual proves to be susceptible to "natural" smallpox. It has been frequently noticed that persons who are refractory to vaccination over a period of many years may become susceptible, as shown by an apparently normal primary vaccination after numerous failures. In countries where smallpox is endemic observations of this kind are affected by the possibility of previous sub-clinical infection producing immunity. Fortunately, this evidence has been obtained in countries where smallpox is rare.

Malignant cases, apart from their severity, are of peculiar interest from an immunological point of view. It is well-recognized that malignant cases occur with undue frequency in those vaccinated some twenty or thirty years previously.

Malignant cases also appear to occur with greater frequency in those persons who are insusceptible to vaccination on a number of occasions.

From limited personal observations of family outbreaks, malignant cases seem to occur amongst persons of the same physical type. Although the literature on second attacks of smallpox is most difficult to interpret, they are most likely to be of two kinds, very mild, or fulminating or malignant. This paradoxical effect causes much doubt of the facts when they are presented.

It would seem that factors conducive to the occurrence of malignant cases may be natural or acquired. Although anti-invasion and anti-dissemination factors will be minimal, it seems possible that some skin insusceptibility—some factor hindering localization and growth of virus in the skin—might be present. The minimal mortality from natural smallpox, observed before both variolation and vaccination were introduced, is in the age-group five to fifteen, and suggests that perhaps some hormonal factors may determine the apparent frequency of

malignant types over the age of twenty years whether vaccinated or not. From a practical point of view the story of repeated failure to vaccinate successfully, followed by a malignant attack, is as common as it is tragic.

It seems possible that where an individual has previously come into contact with variola or vaccinia virus in a new infection there may be interference in the development of the virus at some stage, particularly the blocking of certain more susceptible tissues and some deviation from the site of primary multiplication. Perhaps all the virus is then filtered out by tissues such as the lung, and this gives rise to gross antigen-antibody reaction, producing dysfunction in the lung and giving rise to the "virus pneumonia syndrome", better called "smallpox pulmonary allergy".

Although the mild types of smallpox can occur in the unvaccinated and the course of infection must thereby be determined by some natural form of immunity, types 6 and more frequently 7 and 8 are very common in the vaccinated with alteration not only in the number of lesions, but in their maturation in the skin. As mentioned in the clinical chapters, occasionally, after a quite "normal" initial stage, a person may have a profuse eruption which does not proceed beyond the papular stage. This sudden abortion of the lesions is quite dramatic and can only be explained by a rapid immunological response in the skin of a previously sensitized person. As previously discussed under pathogenesis, the superficial granulomatous lesions in the vaccino-modified do not occur in unmodified smallpox, even in variola major in the unvaccinated when there are only a few lesions. Some immunity factor in the skin must be the cause of this reaction. In some individuals it is very persistent.

When vaccination or variolation is performed, virus inoculated into the skin, grows in this tissue first and not until relatively late in the development of the vesicle, about the ninth day, are antibodies present in sufficient amount to prevent further infection with vaccinia or with smallpox virus entering the respiratory tract.

There is some variation in different individuals but immunity of practical value is established much earlier than the maximum serological response which is delayed for about three to four weeks.

Immunity, sufficient to modify the eruption, occurs before immunity is sufficient to prevent an attack (Wilkinson, 1942). In Tripolitania (1948), twenty-one cases vaccinated successfully after contact with smallpox between the first and fifth days of the incubation period were of types 6, 7 and 8, whereas in thirty-one cases where vaccination was performed between the sixth and tenth days, eleven were types 2 and 3 and there were five deaths.

It seems that anti-invasion and anti-dissemination immunity may be completely lost, whereas the skin immunity factor probably never declines quite to the level in the unvaccinated subject; although in practice many revaccinations after twenty or thirty years do have all the appearances of a primary infection.

According to Ricketts, positive vaccination can occur in smallpox even when done on the second and third day of the eruption. Although this is possible, with acceleration of the vaccinial lesions similar to the effect of further vaccinating during the course of a developing primary vaccination, I would suggest that some of these apparent vaccination responses may be accelerated variola lesions on the vaccination site. On the other hand, there is probably complete dissociation between the anti-invasion, anti-dissemination and the skin immunity factors. This would allow trans-cutaneous vaccinial infection to proceed independently of the general variola infection, at any rate for a short time. As far as can be determined, once vesi-

culation has occurred in the skin, that is by the fourth or fifth day of the rash, successful vaccination will be impossible. Previous successful vaccination which does not usually modify the initial fever causes considerable changes in the affinity of the skin even when dissemination is fairly widespread, as in type 6. More rapid maturation of the skin lesions occurs, showing a sensitized skin immunity mechanism. All variations are seen, down to the abortive case where the lesions may not become vesicular.

Entry of the virus through the skin as in vaccination or variolation is likely to produce immunological changes of different type and magnitude from those produced in the natural disease with entry of virus through the respiratory tract. The course of events in inoculated smallpox and also in generalized vaccinia suggests that, depending on the type of infective agent and the level of immunity of the host, the inoculated disease can approach closer and closer to the natural disease, but a transcutaneous infection will always be different from a respiratory one. In successful vaccination the natural susceptibility of the skin to virus is neutralized by a successful take not only at the site of the lesions but to a lesser extent over the whole skin surface.

A person whose skin has always been refractory to vaccinia by regular failure to obtain a successful vaccination with good lymph, is not necessarily insusceptible to smallpox. If infected, the disease is usually of types 1, 2 and 3, or 7, 8 and 9. In some individuals the skin is apparently highly susceptible to vaccinia, produces a primary-type lesion even within one year of a typical primary vaccination, but we do not know whether this susceptibility to vaccinia parallels susceptibility to smallpox. Ricketts believed it did, but I feel that although parallelism exists in a fair proportion of individuals a great many exceptions occur. The problem has been oversimplified by assuming that the pathogenesis and immunological process in vaccinia and in natural smallpox are the same.

Successful vaccination may not, however, result in the skin affinity being neutralized completely in all parts of the body. The skin may be refractory to further virus at the site of the primary inoculation, but successful vaccination may occur accidentally on other parts of the body such as the hand (Horgan and Haseeb, 1944). A revaccination on the arm may fail to take and the individual may subsequently come into contact with smallpox without apparently becoming infected but may still be susceptible to vaccination on a more receptive site such as the finger (Lyons, 1954).

Immunity factors can be summarized as follows.:

Anti-invasion factor. Determines infection or not. Occasionally present naturally. The factor first lost as effect of successful vaccination wanes.

Anti-dissemination factor. Natural or acquired from vaccination, the latter lost more slowly than anti-invasion, but more quickly than skin immunity. Affects the number of skin lesions. In malignant cases other causes present, possibly a "spreading" factor, hormonal factors or abnormal state of the skin.

Local skin immunity. Occasionally natural, more frequently acquired from vaccination previously or concurrent—causes lesions to be more superficial, mature rapidly or even abort in the papular stage.

The three immunity factors deduced from clinical observations have not been proved to exist by laboratory investigations.

Because of its ease of handling and growth, vaccinia virus has been used as a model for a great amount of study on antigens.

It has been shown by Craigie (1932) that vaccinia has two antigens, one heat labile (L), being destroyed at a temperature of 60°C., and the other heat stable (S.). These two antigens part of a complex L.S. antigen is apparently specific for vaccinia and variola viruses and is the basis of the serological test. There is also another antigen, which is nucleo-protein (N.P.). Haemagglutins are also present (Nagler, 1944; Nutt and Gilding, 1944), apparently distinct from the L.S. antigen (Chu, 1948).

All these antigens are present in vaccinia, cowpox, variola major and variola minor viruses, and *in vitro* serological tests show no definite antigenic differences between them, although minor differences could be demonstrated by the use of absorbed sera (Downie and McCarthy, 1950).

Downie (1951) has surveyed the evidence concerning antibodies against variola and vaccinia. Complement-fixing antibody and anti-haemolysins are laboratory "indicators" which are not directly related to immunity to natural infection. This factor can be measured to some extent by virus neutralization shown by the reduction of the pock count in the chorioallantois. Although it had been hoped that this technique might at least give us a practical method of measuring an individual's protection against smallpox, Downie (1951) quotes a case of mild smallpox in a nurse vaccinated two years before in whom a considerable titre of this neutralizing antibody was present in a specimen of blood taken just *before* she was exposed to infection.

In a small series of persons who had had smallpox one to eight years previously, Downie found complement-fixing antibody was absent and anti-haemagglutin low, whereas neutralizing antibody remained high. Similarly, following vaccination the maximum levels are attained at three to four weeks, although not so high as after smallpox. After a year complement-fixing antibody and anti-agglutinin are usually absent, whilst virus-neutralizing antibody is still present, although showing much variation in different individuals. Downie (1951) is forced to conclude that some at present elusive factor of avidity must account for the discrepancies between quantity and quality of antibody in preventing smallpox infection. We must therefore admit that we have no method at present of measuring the immunity of an individual to smallpox either basically or following vaccination, other than the traditional method of deduction from the imperfect picture of the response to vaccination or revaccination. The practical aspects of this subject are referred to both under laboratory diagnosis of smallpox and under field problems in vaccination.

Failure to obtain a successful vaccination after repeated attempts with good lymph and a good technique in a person who has *never* had a successful vaccination means a skin, at least, temporarily, insusceptible to vaccinia, *but not necessarily any immunity to natural infection with smallpox*. Failure to obtain a successful vaccination in persons with a good primary scar although using good lymph and technique, even when done more than twice, does not *prove* they are immune, although this is probable. The fact that persons show an active infection with vaccinia on revaccination, although indicating skin susceptibility, does not *prove* that at the time they would necessarily have been susceptible to variola, although it is often assumed by patients.

Much of the difficulty in national and international vaccination procedure is due to our inability to measure the degree of immunity against smallpox possessed by an individual at any time.

CHAPTER 10 History of Smallpox, Variola Major and Variola Minor

In attempting to trace the history of smallpox, it is necessary to interpret accounts by many writers, who although using well-known terms rarely give sufficient clinical description to allow one to be certain of the real identity of the disease. At all times contemporary writers assumed that their readers would be familiar with the disease they named, but there is no guarantee that such a disease is the same condition in different countries, or at different periods of history. Due to the widespread practice of borrowing medical knowledge, particularly from Arabic sources, it is probable that the name smallpox was applied to a local disease which appeared to best fit it, although it might have been entirely absent from the particular community. Smallpox is particularly difficult to study, due to the confusion with chickenpox, which existed in some parts of the world until the late nineteenth century.

The nomenclature is confusing. The first accurate description of the disease was given by Rhazes, physician to the hospital of Bagdhad, who died about A.D. 923 or 930. As the disease did not occur in either Greece or Rome, there is no original Greek or Latin word for it. When Rhazes' writings in Arabic were translated into Greek, smallpox was rendered "loimic" disease, and when tranlated into Latin the corresponding term was "pestis", a word often used with a much wider meaning. The word "variola" was first used by Marius in A.D. 569, but may not have been applied to smallpox at all, as there is no clinical description. Constantinus Africanus (1020–87), who translated some of the Arabic medical works into Latin, first uses the term variola for the disease described by Rhazes. The present Anglo-Saxon word "smallpox" is derived from "pocca", a bag or pouch, whereas the word "variola" is thought to have been derived from the Latin word "varius", which means spotted, or from "varus", which means a pimple. Although in A.D. 961 the word "variola" and "poc" or "pocca" were used together, this does not prove that the disease named was the same as that described by Rhazes. Creighton (1891) takes great pains to show that, in the sixteenth century, "les pocs" in French might refer to "la petite vérole", which was taken to mean smallpox, or to the "great pocks" or syphilis. Similarly in many English accounts the word "pockes" is frequently used, and only subsequently with the appearance of syphilis have writers conveniently prefixed it with the word "small". In Latin, smallpox was sometimes described as "variola minuta", the pustules being small as compared with boils, or more particularly with the bubos which accompanied true plague. The French also called smallpox "poquote". The German names "pocken" and "blattern" are borrowed respectively from the Dutch "pocke", meaning a pocket or purse, and the German "blatte", meaning a blister. The German prefix "klein", as with the French "petit", came into use after the appearance of syphilis in Europe in 1494.

In describing smallpox, Rhazes stated that hardly anyone escaped having it, and when in

the tenth century this was translated into Greek, it was rendered "every man is born liable to it". Isaac the Jew, who lived in the ninth century, thought the disease was inevitable, as it was a process of purification of the child from the retention of menstrual blood during pregnancy. Rhazes believed it was a process natural to children, because the blood is like new wine and must ferment. It is difficult to appreciate that the inevitability of some diseases was at this time regarded as an almost physiological event, like the eruption of teeth. In more recent times we have seen some sections of the population accept a discharging ear as being a normal occurrence. European physicians, however, reading the Greek or Latin translation of Rhazes, were more than likely to think that measles and chickenpox, being so common in infancy, would fit the description well enough, and so give rise to the statement that smallpox and measles were common conditions in childhood and of no consequence.

Between 800 and 1400 the terms "variola", "vayrola", "veyrola", "vayrora", "variolas", and "morbis varicus" were used at various times. Confusion, however, was common, as Creighton (1891) points out. Phaer, writing *The Regiment of Life* in 1553, talks of smallpox and measles, but translates "variolae" as "ye measles" and "morbilli", "called of us ye smallpox. They are but of one nature and proceed of one cause." In an English-Latin glossary of 1570 by Levins, "ye maysilles" is translated by "variolae".

Much has been written on the history of smallpox, including complete works, such as the *History of Smallpox* by Moore (1815), the *History of Inoculation* by Woodville (1796), and extensive chapters in books by Hirsch (1883), McVail (1893), and more recently by Goodall (1934) and Rolleston (1937). Many others have written on this subject, often drawing on Moore's original source material. Creighton (1891, 1894) investigated much of this and also thoroughly reappraised the original work, and devoted a large amount of space to the history of smallpox in his classic *History of Epidemics in Britain*. Although much of the later history is coloured by his anti-vaccination views, his survey of the early history constitutes a standard work on the subject. I have drawn freely from many sources, and have attempted to reassess some from a twentieth-century viewpoint, but much is a matter of opinion rather than fact. The inherent probability of any occurrence tends the closer to zero the further in time we get away from it.

The origin of smallpox is unknown. The frontispiece to this book is a picture of the mummified head of Rameses V, *c.* 1160 B.C. His death was thought to have been due to smallpox by Elliott Smith (1912), Ruffer (1921) and Warren Dawson (1953), and my own examination of the large photographs of the mummified body and head leads me to support this view. Moore (1815) stated that smallpox was known in China in the Tcheou dynasty, 1122 B.C., the Chinese name for the malady being "tai-tou". Inoculation was first described about 590 B.C. in the Sung dynasty, using nasal implantation of virus from seeds. According to Holwell (1767), the disease had been present in India for many thousands of years, and according to von Schrötter (1919), evidence of variolation was contained in a Sanskrit text "Sacteya" attributed to Dhanwantari. In the Brahmin mythologies a special god, Kakurani, was recognized for this disease. Smallpox appears to have been present in India from the earliest times, and also in China for nearly as long. Although this might suggest that smallpox had its origin in Eastern Asia, it should be remembered that many parts of the world have no literature as old.

The most striking thing about smallpox is its absence from the books of the Old and New Testaments, and also from the literature of the Greeks and Romans. Such a serious disease as variola major is very unlikely to have escaped a description by Hippocrates if it existed. It is

possible that the observations on Rameses V are wrong. On the other hand, smallpox is a disease in which there is no carrier state, and if communications were poor, it would be quite easy for it to die out. The extremely slow pace of sea travel, because of the absence of the mariner's compass, meant that smallpox could not be easily spread by sea. It was more likely by land, where relatively large migrating groups could travel. It seems possible that Alexander the Great's army which travelled down the Indus was attacked by smallpox: "as the scab attacked the bodies of the soldiers and spread by contagion." It could, of course, have been scabies or some other skin disease. The fact that it was not brought back to Asia Minor suggests that it was something that could burn itself out.

Although some think that the description given by Ko Hung (A.D. 265–313) in his *Handbook of Emergencies* is smallpox, it would seem to be more like impetigo. The disease described by Eusebius occurring in Syria in A.D. 302 and recorded by Willan (1821) sounds more genuine. "It was characterized by a dangerous eruption which unlike the true plague spread over the whole body and which also affected the eyes and often resulted in loss of sight, which had the effect of protecting against a second attack of the same disorder, and whose eruption was, according to a later writer, accompanied by a very offensive smell."

The next appearance of a disease regarded as smallpox was recorded in Arabia during the elephant war of A.D. 569, when infection was thought to have been brought from Abyssinia. An outbreak occurred amongst troops at the siege of Mecca, illustrated by the story: "Large birds appeared, which dropped stones the size of a pea on to the persons, and they were killed." This has usually been interpreted to suggest that some skin condition occurred. Abraha and the remains of the army fled, and he himself died from the disease, and "as they brought him along the retreat, his limbs fell off piece by piece, and as often as a piece fell off, matter and blood came forth". This might well be a description of the shedding of the skin in malignant smallpox. There was, however, considerable confusion between smallpox and measles. Both could produce a high mortality when occurring in a new population. Bruce of Kinnaird quotes a manuscript of El Hamesy, *Travels to discover the Source of the Nile*, in which he states that smallpox and measles broke out in Arabia and almost destroyed the army of Abraha. The story of the birds was thought to have been added later, to boost Mahomet and to make the whole occurrence appear a miracle, as a large army of Abyssinians was unable to take Mecca, which was held by a handful of frightened citizens (Creighton). Infection was thought to have spread from Arabia into Egypt in 572, or, according to Gibbon, in 569. This fits in with the first writings on smallpox, by Aaron of Alexandria, who apparently flourished during the life of Mahomet. Although we have no direct accounts of Aaron, he was quoted extensively by Rhazes some three hundred years later.

At the beginning of the seventh century, Chosroes the Persian invaded the Roman Empire, and overran Palestine and Egypt, and this doubtless increased the likelihood of the introduction of smallpox in this area. In 622 Mahomet collected the wandering tribes against the surrounding nations, and very large numbers died, many as the result of disease. The Arabs carried their wars eastwards along the North African coast. Three of the early caliphs were apparently pitted with smallpox; two had a white spot in each of their eyes. In 647 Tripoli was captured, and the conquest continued westwards. One source of smallpox in Europe was through Spain, by its conquest by the Moors in 710. In 731 the Moors crossed the Pyrenees and invaded France. Much disease was recorded about this time under the general title of plague. Even true bubonic plague was sometimes called pustular plague, which further confused the issue.

It seems probable, however, that the disease was already present in Europe, as the often-quoted account of Gregory of Tours in 581 indicates. Willan translates the description as follows: "A person, after being seized with a violent fever, was covered all over with vesicles and small pustules. The vesicles were hard, white, unyielding and very painful. If the patient survived to their maturation, they broke and began to discharge, when the pain was greatly increased by the adhesion of the clothes to the body. The lady of Count Eborin while labouring under this pest was so covered with the vesicles that neither her hands nor feet, nor any part of the body remained exempt, nor even her eyes were wholly closed up by them." The description would fit smallpox well, but the disease was not given a special name, although Willan (1821) thought that it was likely to be the same as an epidemic referred to by Marius, the Bishop of Avenche, in A.D. 570, to which the name "variola" had been given. However, no clinical description exists to show what sort of disease this really was.

Smallpox is thought (McVail, 1893) to have existed in Ireland under the native names of "bolgach" and "galar breac" and was first recorded in A.D. 675 and at intervals over a number of years until 778. No clinical descriptions appear, however, to exist, and although both terms are still used in Ireland today to describe smallpox, this does not prove that the name has always been applied to the same disease.

Jenulf, writing in 923, said: "It is shocking to hear the groans of the sufferers, to see parts of their bodies as if burnt, dissolving away, and to smell the intolerable foetor of their putrid flesh." In 944, "pestilence of fire occurred in Limosin, where innumerable bodies of men and women were consumed by visible fire, and also in Aquitaine". In the eleventh century, "the people died miserably from their limbs being burnt black from a sacred fire". The description of invisible fire and burns applies particularly well to malignant smallpox, as the photographs in the clinical section show. The remark that the limbs were burnt also suggests a peripheral distribution. In 907, Princess Elfreda, the daughter of Alfred the Great, contracted smallpox and recovered. In 961 her grandson, Baldwin, Earl of Flanders, died of smallpox, and the disease was called by the physician "variolas sine poccas". This is the first instance where the two words "variola" and "pock" are used together to suggest that they meant one and the same thing.

The Harleian Collection of manuscripts in the British Museum contains a prayer, "Defend me from the fire and power of smallpox, and against the loathsome pox",which Woodville (1796) suggests indicates that the inhabitants lived in continual dread of this disease. Amulets were also worn by nuns and others from the tenth century. St. Nicaise, who was Bishop of Rheims in the fifth century, was regarded amongst many others as a patron saint of this disease. Moore (1815) suggests that when a new disease appeared, a suitable saint was found, and to make the case more satisfactory, stories were then invented that he had suffered from the disease at some time in the past, which could not be verified and was quite likely to be untrue. It has been maintained that smallpox was brought into Europe by the Crusaders returning from the Middle East, which did not occur until 1096, but it seems more likely that smallpox had been in Europe at least two and possibly four centuries before this. No doubt smallpox was brought back by the Crusaders as well.

Simon (1857) quotes some of the epidemic history of Iceland. An outbreak in 1241–2 caused several thousand deaths. In 1310–11, 1,600 people died. There is a continuity of records up to 1707, when, amongst a population of about 57,000, some 18,000 people died. A large number of deaths at intervals in a small and isolated population shows that it was a killer disease, almost

certainly imported from Denmark from time to time, and because of its mortality most likely to have been smallpox.

In the book on leechdoms by Cockayne (1865) there is a reference to Bald the physician in the tenth century, describing the treatment of a pock disease, which was "to delve away each one of them with a thorn". There is also a description of a "pock in the eye", which possibly refers to injury to sight by smallpox. The puncturing of the pock with a thorn greatly strengthens the suspicion that the disease was smallpox, as this form of treatment has never been advocated for chickenpox, which rarely leaves a deep scar, but is almost constant in the world folklore for the treatment of smallpox. Although Irish manuscripts mention "galar breac" as epidemic in 1327 and 1368, there is a manuscript in the British Museum that states that in 1366 "also that time fell a sekness that men called ye pokkes, slogh both men and women thorgh ther enfectyne". In this instance the age of attack is suggestive of smallpox. One must, however, emphasize the almost certain confusion between smallpox and chickenpox. There was also a great tendency to exaggerate the effects of medical treatment, and it was therefore greatly to the physician's interest to call chickenpox smallpox, and claim his ability to cure it. John of Gaddesden (1280–1361), who claimed to have cured the King's son, was treating chickenpox, and not smallpox. References in the fourteenth century are very scanty, but in 1512 Sir William Sidey, the eldest son of Lord Lyle, was reputed to have suffered from the disease, and in 1537 there is a reference to so-called smallpox in a noble family. This was Henry Brandon who at the time was an infant of some twenty months. He did not die of the disease which could therefore have been smallpox, chickenpox or measles.

In October 1562, at the age of twenty-nine, Queen Elizabeth I suffered a severe attack of smallpox from which she nearly died. The Council even considered nominating the Earl of Huntingdon, descendent of the Duke of Clarence, as her successor. According to Halliday (1956), the Queen sent for Dr. Burcot, who was reluctant to attend but went. He wrapped the royal patient in scarlet, the usual form of treatment, and was paid 100 marks for his services. Elizabeth became bald as a result of the illness, and thereafter wore red wigs, and was concerned about the disfiguring marks on her face. She had another illness in 1572, which was first thought to be smallpox, but was probably chickenpox. Lord Darnley was murdered in 1567 when he was reputed to be recovering from an attack of smallpox.

Creighton makes no mention of these facts, and he is extremely doubtful of the existence of smallpox in England in the early part of the sixteenth century. He regards the first recorded case of smallpox in English as that of Master Richard Allington, who died in 1561. Due to a troubled conscience, he had made the statement: "Seeing that I must needs die, which I assure you I never thought would have come to pass by this disease, considering that it is but the smallpox. . . ." This remark suggests that if he did die of smallpox, the disease which he had previously thought to be so mild was probably chickenpox. In 1568, Dr. Gilbert Skene, writing from Scotland, remarked on the pock, a pustular disease, being frequent not only amongst children but in older age groups, and in 1591, in Queen Elizabeth's court, advice was given that Her Highness should "remove from that place where the smallpox were", although she is reputed to have had the disease in 1562.

McVail (1893) felt that smallpox had been present in Europe and therefore probably in England from the seventh century. This view is hotly opposed by Creighton (1894), who considered that the slender evidence, the supposed case of Richard Allington in 1561, gave stronger support than earlier descriptions to the sixteenth century being the earliest occurrence in England.

I feel that Creighton was blind to earlier evidence to justify his emotional conviction that smallpox and syphilis, introduced in 1494, were closely related. It is not, however, impossible for the disease to have been present sporadically in Europe and England before the eleventh century, only to disappear and not recur in England until the late fifteenth or early sixteenth century. The lack of spread would be in keeping with the experience of the seventeenth century, and even of the mid-twentieth century, although communications were extremely poor and would hinder it. It has perhaps been too readily assumed that the pattern of spread of smallpox in urban England in the mid-nineteenth century was the norm for this disease.

Although the first cases were recorded in the nobility, and smallpox characteristically has little respect for social class, outside London we have no knowledge of its incidence in humbler folk, as their deaths would not be recorded. Confusion with syphilis was considerable. Generalized rashes occurred in a much larger proportion of cases than at the present time, and unfortunately it also became a habit to use the term "la petite vérole" euphemistically to describe what was known to be syphilis in the nobility. Deaths in infants under the age of two from a disease labelled "smallpox" are notoriously inaccurate, with the high infant mortality rate of the period, and throw little light on the possible incidence of this disease.

Smallpox appears to have been introduced into the New World in the West Indies in the year 1507, some fifteen years after the discovery of America, and was so disastrous that whole tribes were exterminated. The disappearance of the Lucayan Indians is chiefly ascribed to smallpox. The disease reached Mexico in 1520 with troops from Spain, and it has been estimated that 3½ million people died in a short time. It first appeared in Brazil in 1563, again exterminating whole races. According to de La Condamine, in the province of Chito about 100,000 of the population died.

According to Creighton, it was not until the latter half of the sixteenth century that there were real epidemiological records of smallpox on the Continent, in works by Donatus on smallpox at Mantua in 1567, and by Betera (1570, 1577 and 1588) in which the more severe types of smallpox were seen.

In England in the seventeenth century the disease begins to figure considerably in the records, domestic and other. In 1625 the famous composer Orlando Gibbons died in Canterbury, according to some of the plague, but in the opinion of others from smallpox. In 1628, Lord Dorchester in a letter called it the "popular disease". In another letter, of 9 June 1628, from Gilbert Thacker to Sir John Coake, quoted by Creighton, it is stated that "Mrs. Ellweys was sick with us of the smallpox 12 days or thereabouts. Before she was out of the smallpox, she was taken in labour on June 15, and died the next morning at 5 o'clock". There is little doubt of the diagnosis here. In 1631, in a letter from Dr. Donne, Dean of St. Paul's, there is reference to smallpox and the fact that he stayed away from a case for a fortnight and was aware of the disfiguring nature of the disease. 1634 was reputed to be a year of high incidence and the Chester parish register has a note opposite 1636 which says: "For this two or three years divers children died of smallpox in Chester." It is quite obvious that either the children died of some other condition or, if the children did die of smallpox, then the adults must have been immune to the disease as a result of previous contact with it, and that it must have been present for a number of generations. In 1641, the attendance in both Houses of Parliament was poor because of the presence of smallpox. In 1649 smallpox was epidemic in London, with 1,190 deaths. Willis says that the epidemic was also in Oxford during that year, "yet most died of it owing to the severe type of the disease". He was, however, at first uncertain of the

diagnosis, because "the smallpox had never been in that place". It would seem that smallpox was not endemic in England at the time, but occurred from the introduction of infection from abroad and therefore tended to occur first in the nobility. It seems probable that in some areas chickenpox and measles were called smallpox, and were credited with a number of deaths in small children. In 1660 the Earl of Anglesey died, and Lord Oxford had an attack and recovered. In the same year, when Charles II came from The Hague to receive the English crown, his two brothers accompanied him. Four months after arrival, the Duke of Gloucester was seized with an illness, which at first was thought to be between smallpox and measles. By the seventh day, he was "in a good condition for one that has the smallpox", but a day or two afterwards the condition deteriorated, he had epistaxis and became unconscious, and had considerable haemorrhages from what was obviously a malignant attack. In the middle of December, the Princess Mary of Orange, who had arrived in September, also had smallpox and died. Much blame was attached to the doctors and to the treatment, which suggests that the disease was relatively new. In 1661 the disease seems to have been present in many other parts of England, both in Oxford and some of the rural villages. London, however, appeared to be particularly unhealthy. This was noticed in Pepys' diary. Both smallpox and plague were present until the plague burst forth in the unprecedented epidemic of 1665. The authors of the time were surprised that smallpox was behaving in a way so different from the past. "Smallpox and measles are wont for the most part to terminate favourably." Dr. Walter Harris, writing in 1689 the first English work on acute diseases in infants, emphasized the mildness of smallpox by saying: "Smallpox and measles in infants, being for the most part a mild and tranquil effervescence of the blood, are wont to have often no bad character, where neither the helping hand of physicians are called, nor the unbounding skill of complacent nurses is put in requisition." The apparent low mortality in children could be explained if one grouped chickenpox and smallpox together and bore in mind that quite a high infant mortality would have been regarded philosophically as of relatively minor importance. Although Creighton makes no mention of the possible inclusion of chickenpox, he does point out that by the eighteenth century, when we have figures of age at which death from smallpox occurs, the whole of the mortality is below the age of ten. This continued into the nineteenth century, where the age affected was again altered, due to vaccination. What seems clear is that this state of affairs did not exist in the seventeenth century. John Evelyn, of diary fame, had smallpox when abroad. His two daughters died in early womanhood, and the fiancé of one died from the disease about the same time. Morton (1692-4) gave sixty-six clinical histories, of which twenty-three cases were under twelve and forty-three cases over twelve years of age.

In the latter part of the seventeenth century, the major controversy was over treatment, with Sydenham sponsoring the cooling regimen, although he carried out blood-letting in the early stage. His opponents carried out more vigorous blood-letting and purging, and although many patients with smallpox were killed by treatment, this was not the cause of the apparent increase in mortality from the disease which was reputed to have been benign and previously only present in children. The controversies were dropped until the re-occurrence of epidemics in 1710-14, and in 1719 the celebrated fracas occurred between Woodward, Professor of Physic, and Dr. Mead. Sydenham undoubtedly made a major contribution to the treatment of smallpox, by at least advising no treatment for those with discrete attacks.

The epidemic in London, 1667–8, was of interest because, as Sydenham says: "The disease was regular and of a mild type. It cut off comparatively few among the immense number of

those who took it." However, perhaps this was relative to the recent heavy mortality from plague. Pepys, writing in 1668, also noticed "the excessive number of people to be seen up and down the streets newly come out after the smallpox". Included amongst the victims was the King's mistress, Frances Stewart, Duchess of Richmond, who was the model for the figure of Britannia on the English penny. Although she had some facial scarring, the King did not lose his ardour. As Creighton rightly points out, this was the beginning of a change in attitude towards smallpox, with much emotional emphasis, and a great tendency to exaggerate its horrors and residual disfigurement. By examination of the "Wanted" notices in the *London Gazette*, Creighton deduced that the number of pock-marked persons in the London population of the lowest social class was probably about 12 per cent. This makes an interesting comparison with a figure of 22 per cent in Army recruits between 1844–51 (Simon, 1857) and 6 per cent in the general population of Sheffield in 1887 (Barry 1889). Cases occurring in adults were more likely to be noticed, particularly by the change in looks and appearance of the women, whereas smallpox scarring in childhood, although at first severe, does improve over the years. The assumption that smallpox always led to severe pitting of faces was an idea which commenced at this time, and remained in the minds of some right to the present day, along with the idea that smallpox was a frequent cause of blindness. While the epidemic of 1667-8 was reputed to be of the fairly mild type, that of 1760–72 included much of the severe or malignant smallpox. Creighton felt that the years of high mortality might be due to the association of other diseases, particularly measles and infantile diarrhoea. On the other hand, this would have played no part in the mortality amongst adults. It is tempting, of course, to suggest that possibly some outbreaks were due to smallpox virus of the minor type, but it is more likely for mortality to have been affected by the age-group upon which the main weight of attack fell. The age-group 10–15 would give a low mortality, whereas 0–5 or over 25 would tend to give a higher case mortality. The inclusion of chickenpox with smallpox in some years would also reduce apparent mortality. The clinician's skill was not of a very high order, not only for the pox diseases, but typhus and typhoid had yet to be differentiated, and diphtheria from scarlet fever.

In the last thirty years of the seventeenth century, smallpox appears to have visited many towns, including Norwich, Halifax, Leeds and Taunton. It is of interest that both Norwich and Taunton were centres of clothmaking and would have been visited by buyers from the Continent, and from the middle of the century a considerable growth of industry occurred in the London district. Doubtless as communications improved, there was much greater opportunity for the spread of disease. Although the Great Plague occurred in London in 1665, and the Fire in 1666, neither appeared to interfere appreciably with the increasing frequency of epidemics of smallpox. Its interference with the social and educational activities of the country was such that advertisements were put in the paper that Bath was "wholly free of contagious distempers", and the Vice-Chancellor and two doctors of medicine of the University of Cambridge had to advertise and contradict a report that smallpox was prevalent in the University.

An event of considerable interest and importance was smallpox in the Royal Family. The description of the clinical features of Queen Mary's illness was related by Bishop Burnett. "On the third day from the initial symptoms, the eruption appeared, with a very troublesome cough. The eruption came out in a manner that the physicians were doubtful whether it would prove to be smallpox or measles. On the fourth day the smallpox showed itself on the face

and the rest of the body under its proper and distinct form, but on the sixth day in the morning the variolous pustules were changed all over her breast into the large red spots of the measles. That evening many livid round petechiae appeared on the forehead above the eyebrows and on the temples. One physician said these were not petechiae, but sphacelated spots, but next morning a surgeon proved by his lancet that they contained blood. During the night following the sixth day, Dr. Harris sat up with the patient, and observed that she had great difficulty in breathing, followed soon after by a copious spitting of blood. On the seventh day the spitting of blood was succeeded by blood in the urine. On the eighth day the pustules on the limbs, which had kept the normal variolous character longest, lost their fullness and changed into round spots of deep red or scarlet colour, smooth and level with the skin, like the stigmata of plague. She died on the 28th of September 1694, on the ninth day of her illness." A typical case of malignant smallpox. The confusion with measles in the early stage still occurs today. From 1695 to 1710 smallpox was at a low ebb. As Creighton suggests, a state of war in Europe on more than one occasion produced a low incidence in England. This supports the view that smallpox was frequently being imported into the country and therefore primarily affected the large towns. The disease, however, was continuously present in London, as it was from then on till the end of the nineteenth century, and undoubtedly constituted a source of infection to the rest of the country. By the turn of the century the continued presence of smallpox in the Capital stimulated interest in the subject by members of the Royal Society. Their action in this matter is described in the chapter on the development of inoculation (variolation). The death in 1700 of another Duke of Gloucester, this time the son of Queen Anne and heir to the throne, precipitated a constitutional crisis which resulted in the Act of Settlement. Not only did smallpox change the course of history by its effects on the English Royal Family, but the Emperor Joseph I of Germany, Louis XV of France, William II of Orange, Peter II of Russia, the last Elector of Bavaria, all died of the disease, while Queen Anne of England, Louis XIV of France, and William of Orange, afterwards William III, all had very severe attacks.

Perhaps the most important advance in knowledge in the seventeenth century, apart from Sydenham's improvements in therapy, was the assertion, not held by Sydenham, of von Helmunt (1578–1644) and of Boerhaave (1668–1738) that smallpox was an infectious disease.

During the eighteenth century smallpox was present in most of the major towns in Europe, epidemic years occurring from time to time. In England, in the latter half of the century, a great deal of controversy centred around the effects of variolation. Although this gave a lower case mortality than the natural disease, it was principally used amongst the wealthy and, in the main, without sufficient care to prevent the spread of infection. On the other hand, as Haygarth (1784) described in Chester the common people frequently exposed their children to the natural disease, with a view to contracting it and so getting it over. It would seem that a very fatalistic attitude to smallpox developed in the towns. It was assumed that everybody would contract the disease and this did much to favour its continuance. On the other hand, in country districts smallpox might be absent for many years; for example, in much of Dorset it was virtually absent for forty years, and in a rural part of Kent only ten deaths were recorded during twenty years. The village of Ackworth in Yorkshire, had only one death from smallpox between 1747 and 1756. In London, however, inoculation progressed and from 1746 more and more attempts were made to procure the inoculation of the poorer classes. These charitable efforts hardly had any effect on the immunity of the population, and as the century went on the pattern of smallpox in the cities became more and more a disease of infants and

young children, the majority of older children having already had the disease. In 1767, Dr. Maty, and in 1775 Dr. Lettsom, pressed for the inoculation of young children as a means of eliminating smallpox from the community, an idea which probably influenced Jenner and has persisted in some quarters till the present day. Gratuitous inoculations were given in Chester in 1779, in Liverpool in 1781, and undoubtedly did much to maintain infection in these towns.

On occasion general inoculation was used much more intelligently, sometimes either at the beginning of an epidemic, where all the inhabitants of a small village who had not already had smallpox would be inoculated, and this would bring the outbreak to a rapid close, although possibly constituting a source of infection to any travellers who might visit the place at this time. Although many local reports suggest that inoculation was general, this was probably far from the truth amongst the lower classes. Inoculation was done in Leeds in 1781, and again in 1788. It was thought that smallpox subsequently appeared to be less frequent and less fatal. London was in a peculiar position in that continuous immigration occurred, particularly of susceptible young adults, and this considerably enhanced morbidity and mortality. Many of the accounts of the time were exaggerated. In the epidemic in Blandford in 1766, it was estimated that 700 persons in a town of 2,100 had not had the natural smallpox, i.e. one-third, and a general inoculation was resolved. "A perfect rage for inoculation seized the small town", and 384 were done, which was only just over half the susceptible population. Although the smallpox was reputed to be of a very malignant type, the total deaths for the year only amounted to forty-four. In 1731, an outbreak of smallpox had occurred in which time sixty families had the disease with 150 cases, and only one died.

Although it was a standing rule from 1749 that children admitted to the Foundling Hospital should be inoculated, in 1762 there was an epidemic of sixty cases with four deaths, which at least should have produced a fairly immune population, but in the following summer nineteen cases occurred, of which eleven were fatal. One wonders whether these were really smallpox.

The period from 1721 to 1730 was one of epidemics of smallpox in a great many of the provincial towns of England. Figures for these were collected both by Nettleton of Halifax and subsequently by Creighton, to make a considerable list showing a case mortality between 15 and 25 per cent. The outbreak in Plymouth in 1724–5, described by Huxham (1725), was particularly severe, and a number of attacks occurred in adults, including an old woman of seventy-two, who died from the disease, and he regarded this as quite exceptional. He also pointed out that apart from a large number of haemorrhagic cases, there were many instances where mothers, who had had smallpox before, were locally infected with smallpox pustules on the face or hands, from attending their children. Another interesting outbreak was that at Aynho, near Banbury in Northamptonshire, a small town in which the age of attack of both cases and deaths is given for an outbreak spread over some fifteen months, 1723–4. Out of 132 cases, none occurred under two years of age, a few between three and ten, 33 (one-quarter) between ten and fifteen, 12 between thirty and forty, and 10 between forty and fifty. Eighteen of the twenty-five deaths occurred over the age of twenty. It is of great interest that this age incidence is more akin to seventeenth-century smallpox, and to some extent similar to variola major in England within the last twenty years, even in areas with relatively unvaccinated child populations. It is, however, totally different from the picture which occurred in the latter half of the eighteenth century and the early half of the nineteenth century.

The comparative absence of smallpox in some towns is also interesting. In Boston, Lincolnshire, an important town, there were no smallpox deaths between 1750 and 1753, none in 1759,

1761, or between 1765 and 1768. This was ascribed to it being a healthy town, and having "no narrow streets or crowded houses, or want of medical assistance". The deaths in Kilmarnock, where outbreaks occurred every three or four years, show the typical age distribution that one would expect where the disease was virtually endemic, and in complete contrast to Aynho. In Kilmarnock from 1728 to 1763 there were 622 deaths; 118 were under one year, 146 one to two years, 136 two to three, 101 three to four, 62 four to five, and only 50 over the age of five years.

In 1753, Salisbury had an epidemic of smallpox with 1,244 cases and 165 deaths, possibly due to general inoculation having been done between August 1751 and February 1752, some 422 being inoculated. The outbreak went on until the end of 1753, and notes given in the *Gentleman's Magazine* of 1751–5 by Dr. Fothergill throw an interesting light on the general practitioner's impression of smallpox. In some years smallpox was described as of the "bad type". In 1752 it was, on the whole, mild but so widespread that not many escaped who had not had it before, and the children of one to three years suffered most. It would seem probable that chickenpox and smallpox are being considered together and it makes it difficult to assess possible variations in severity. It must be remembered that Heberden did not differentiate between them for the medical world until 1767, and his views were not universally accepted for more than a hundred years The prevalence of smallpox in adults newly arrived in London is also seen from the figures of the London Smallpox Hospital. From 1746 to 1759, 3,946 cases were admitted of which 1,040 died, the Annual Report stating they were mostly adults, and admitted when there was little hope of cure. Although smallpox was increasing in incidence in many of the more populous cities of the country towards the end of the century, the figures from Boston from 1769 show that although there were seventy-eight deaths in 1770 and fifty-five in 1775, the disease was present practically continuously until 1781. Between 1786 and 1789 there were no deaths, only three between 1790 and 1795, inclusive, and after an outbreak in 1796 only one between 1797 and 1800 inclusive.

Smallpox in Ireland behaved as one would expect in an essentially rural country. No special mention is made of it except during the famine of 1740 and in 1745. In 1766 smallpox was noticed which was the year in which it was very prevalent in England. It would seem probable that the disease occurred when brought by sea from England, and affected coastal towns on the east coast, but due to the poor communications many of the central and western areas might escape a visitation for a great many years.

During the first few years of the nineteenth century the country was at war with France. There was considerable poverty, but smallpox occurred less than in the latter part of the eighteenth century. Although outbreaks occurred in towns such as Boston and Norwich, it was not until 1817–19 that large-scale outbreaks occurred, possibly partly due to the migration of Irish peasants, because of the appalling conditions in Ireland. There was a great deal of unemployment in England in 1816, and much movement about the country in search of work, a sociological event very likely to lead to the spread of smallpox. The effect of the wearing off of vaccinial immunity induced in the first ten years of the century, probably left the community more susceptible to infection than for many years past. An outbreak in Ulveston in 1816 was of considerable importance as a number of cases of smallpox occurred in people who had been vaccinated, and these were called "hornpox", or what we would now call "modified smallpox". This increased the chance of spread of infection. The outbreak at Newton-Stewart in Scotland in the autumn of 1816 is historic in that it was the first recorded

where smallpox was introduced by a girl from London, suffering from hornpox, who had been vaccinated some years earlier. This occurrence caused much confusion. In some areas hornpox cases were the centre of interest and the normal smallpox cases hardly noticed, whilst in Norwich hornpox cases were not counted in as smallpox at all. The interest of the hornpox cases in Edinburgh led Thomson (1818) to coin the name "varioloid", for which we have suffered much since. He thought varioloid was smallpox modified by vaccination, but that this disease and chickenpox were different manifestations of one disease entity. Of 556 cases given by Thomson (1820), 205 were reputed to have had hornpox, although unvaccinated or unvariolated. Although he thought the extreme severity of the outbreak had caused the cases in the vaccinated, he caused further confusion by saying that some deaths were due to malignant crystalline water-pox. However, Bent (1818) stated that the disease was the same in those cases who had never had coxpow, as in those who had passed through that disease satisfactorily. One suspects that Dr. Bent was an antivaccinator, and his statement propaganda, as the publication of the report caused considerable correspondence from Jenner's friends. Creighton states that smallpox traversed the country and arrived in Norwich by June 1818, having been brought from York by a girl travelling with her parents, but it turned out to be of the fatal type. The "anomalous disease", as it was called by doctors in Derbyshire, occurred also in London and other places.

It seems probable that modified smallpox had begun to occur some ten years earlier. The first cases were probably reported by Dr. Adams of Forfar in 1813–14. Cases were also seen in 1817, at Mittou in the South of France, and in Switzerland in 1818. The first case of varioloid in Baltimore occurred in August 1821, and at first confused Dr. Horatio Jameson, until he looked at the accounts of varioloid received from Europe over the preceding few years, when he had no difficulty in recognizing the condition. Jameson noticed, however, cases occurring not only in persons who had been vaccinated, but in those who had been inoculated and who had previously had natural smallpox. The disease, however, was introduced from the ship *Pallas*, which had recently arrived from Liverpool, and the investigation carried out by the mayor and Board of Health on Thursday, 3 January 1822, makes an interesting story which would have delighted Killick Millard by showing the difficulties which have arisen with the spread of much modified and thereby missed smallpox, in persons who have been vaccinated.

The extract from the records of the Board of Health is as follows: "Captain Otis of the ship *Pallas* stated that the crew and passengers enjoyed good health from the time of the ship's leaving Liverpool, until her arrival at this port on August 15, with the exception of seasickness; and that but one death had taken place on board, in the person of a child who had died of teething; that previous to the ship's leaving Liverpool a Scotch family applied for passage to this place, on the face of a girl belonging to which, a trifling eruption was perceptible, which he was informed was the result of swine pock, (so-called in Scotland) which had subsided; that Thompson, one of his crew, who died on August 28 with smallpox, was in perfect health when he was discharged from the ship at the quarantine roads; that a slight eruption was visible on the face of one of Mrs. Purviance's children, which its mother informed him was the rash; visited by the mayor, board of health and consulting physician on September 15, when it was found, in a convalescent state after smallpox, as per the consulting physician's report of October 4; and finally that every soul on board of the ship was mustered on the quarter deck for the inspection of the health officer. Dr. Hamilton stated that he saw Mrs. Purviance's children and Thompson with the remainder of the crew and passengers and

believed them all to be in a sound state; that the ship was remarkably clean, and that after having gone through the usual routine of examining vessels, and having been firmly persuaded that no disease was on board, he permitted her to come into port. From the foregoing affirmations etc., the mayor, Board of Health and consulting physician are under the impression that no concealment of any of the crew or passengers was effected by Captain Otis; that Dr. Hamilton fully performed his duty as deputy health officer throughout the transaction; and that the introduction of smallpox into the city was owing entirely to the new appearances which it has assumed."

Statistics on the occurrence of smallpox in the vaccinated and the unvaccinated are now full of the bias of the reporter. Nowhere do we see the word "successful" qualifying the term vaccination, or attempts to eliminate those who have no scar, and we are continually up against the problem of "perfect" and "imperfect" vaccination. Although vaccination, like variolation, was probably practised to a fair degree amongst the upper classes for the first twenty years after its introduction, the amount of vaccination amongst poorer people was largely determined by the presence or absence of smallpox. It seems very doubtful whether even in the big towns more than 10 per cent of the infants would be vaccinated. In country districts this was probably very much less. Free vaccinations were done in a great many areas, but as the epidemic of 1819 subsequently showed, response was poor even though in 1812, at a time when a labourer's wage was about nine shillings a week, Dr. Rigby had persuaded Norwich Board of Guardians to offer parents a half-crown for each child brought to be vaccinated. Perhaps the most important change in the incidence of smallpox was not so much in its age incidence as its change in social class. Smallpox had become and continued throughout the nineteenth century to be primarily a disease of the lower classes, whereas in the seventeenth and early eighteenth century it had been a disease of the nobility. It is for this reason, amongst others, that for many years there was general apathy in Parliament and far less interest in the introduction of vaccination than occurred in other countries. The failure of vaccination to give lifelong protection against smallpox caused an increase in the amount of variolation done, which had never been entirely superseded by vaccination. This was particularly so in parts of Norfolk, Suffolk and Sussex. Even the London Inoculation Hospital, which had given up the inoculation of out-patients in 1808, had continued to treat in-patients until 1822. It is thought that many thousands of variolations were done.

The next outbreak of any magnitude was 1825–6 and, although records are not very complete, the demand for admissions to the smallpox hospital in London was quite heavy. Other information, however, suggests that the incidence was chiefly amongst the lower classes. Figures from the bills of mortality for London, which had been relatively accurate in the eighteenth century, were progressively less so due to the expansion of the city without inclusion of a great many new areas. It was therefore impossible to estimate how much smallpox there was, and the effect of vaccination. Gregory, writing in 1826, was possibly the first to have reasonably accurate figures to work on, and pointed out that the mortality for smallpox in the vaccinated was 8 per cent in the London smallpox hospital, while in the same year the rate in the unvaccinated was 41 per cent, a point glossed over by Creighton as being entirely due "to the different rate of fatality at different ages", although in the most favoured age group this was 20 per cent. The appalling conditions of the poor in the 1830's in such cities as Glasgow, probably the worst in the country, meant that much smallpox, being a disease of children, passed unnoticed, whereas cholera, affecting adults, was recorded with greater

accuracy and even excited the notice of Parliament. Although in Glasgow the majority of smallpox deaths were in infants, 7 per cent were above the age of ten, much higher than most other places, probably due to the continuous immigration of Highlanders in search of work.

The next epidemic, 1837–40, was of importance because the new registration of births and deaths coming into force in 1838 allowed for the first time some measurement of the death-rate in the whole country. The epidemic started in the west and south-west of England and spread across Wales into Lancashire, and ultimately into the eastern counties. From 1 July 1837 until 31 December 1840, it caused 41,000 deaths in England and Wales. No one knows the origin of this outbreak, but between 1825 and 1840 there had been a great boom, and enormous sums spent on railway construction, with large collections of Irish and other labourers moving about the country. The most important effect of the 1837–40 outbreak was the introduction of legislation dealing with vaccination, the first Vaccination Act of 1840, providing for free vaccination of the poorer classes at the cost of the ratepayers, and prohibiting the practice of variolation. Although the original Bill only sought to prohibit this amongst amateurs or empirics, Mr. Wakley, a radical in the Commons and proprietor of one of the weekly medical journals, succeeded in putting in an amendment that the practice should be illegal, even if performed by orthodox medical practitioners. The penalty was imprisonment for a term not exceeding one month.

In contrast with the English experience, the 1825 epidemic in Paris gave rise to many adult deaths, particularly amongst the nobility, and subsequently in 1829 the rapid increase in smallpox in adults prompted the German Government to resort to revaccination. In England, Gregory, writing in 1838, pointed out the need for revaccination, but this fell on deaf ears until some forty years later.

Smallpox epidemics occurred in 1844 and 1845, in 1847, 1852, 1858 and 1863–5, the earlier outbreaks being associated with a large amount of railway construction going on in England, and further waves of Irish immigration. The next outbreak of magnitude was the celebrated epidemic of 1871–2, in which some 42,000 people died. It was essentially an epidemic of the towns and industrial areas, rather than of the countryside. London had an increasing proportion, nearly one-quarter, of the total deaths from smallpox in the whole country. By this time the Metropolitan Asylums Board was in operation in London, and reasonably accurate figures could be obtained of those patients admitted to hospital. The case fatality rates were very high; 52 per cent in the age-group 0–5, with a minimum of 9·4 per cent in the age-group 10–20, and a rate of 25 per cent in those thirty and over, but it is obvious that as smallpox was not notifiable at the time, a very large number of minor cases, particularly in the vaccinated, would not be admitted at all. Creighton traces the change in fatality from 1870 up to 1902 from the figures from the M.A.B. hospitals, and says the change is remarkable, quite oblivious of, or unprepared to accept, the fact that with the increase in popularity of the M.A.B., there was an increase in the proportion of vaccinated cases admitted to hospital throughout this period. There is nothing mystic about it, although Creighton would like one to believe that there was. Creighton goes to some length to point out that the epidemic of 1871–2 was the first since the seventeenth century in which the deaths over the age of five were considerably in excess of those under five. He says: "When the epidemic of 1871 began, it found many in youth or mature years who had not been through the smallpox. It attacked a certain proportion of them accordingly." As he was an antivaccinationist, he makes no reference to the fact that in the

previous ten years the presence of much infant vaccination had probably not only reduced the number of young susceptibles in the community but had caused a decreasing proportion of adults to be exposed to infection, enough to boost their waning immunity from infant vaccination. Creighton takes the extraordinary view that the failure of so many infants to die of smallpox was not due to vaccination, but largely to numbers having been removed by suffering from scarlet fever in previous years. "But the fact that scarlatina had in a great part dispossessed smallpox among the factors for mortality under the age of five did not prevent the latter infection from attacking those of the higher ages who were susceptible to it, and were at the same time unvexed by any great epidemic malady proper to their time of life." "But in no state of the population or of the public health can we suppose that three years of excessive mortality of children by one kind of contagion (scarlet fever) would be followed immediately by two years of equally special mortality at the same age as by contagion of another kind. It is not only epidemiological science that tells us this, but also common sense." William Guy (1882), however, had a different explanation. "The storm of that year, overleaping all barriers, was speedily followed by a calm as strained as the tempest itself. That atmospheric condition, whatever it may be, to which our epidemics are due, was so favourable to attacks of smallpox, that the barrier of vaccination, though effective in ordinary years, proved insufficient in this. The more and the less susceptible were alike seized, and the population was swept clear for a time of almost all possible victims. Then vaccination, a protective in ordinary seasons, resumed its sway, and almost brought about the cessation of smallpox." As a pro-vaccinationist, Guy had to find some mystic influence to explain the apparent failure, quite oblivious of the changes in herd immunity.

However, a new factor had come into the smallpox picture, and that was the importation of infection from abroad, rather than the build-up of small epidemics at frequent intervals from an endemic reservoir. This route caused dissemination primarily amongst adults, and from them a general spread to the community. Perhaps this infection was a particularly virulent strain, *variola maxima* of Peters (1909) and Stallybrass (1931), but there is nothing to suggest that changes in herd immunity cannot account for its striking power. The infection is reputed to have come from France in October 1870, and began in the East End of London, from which it gradually extended in the next two years over England and Wales, giving rise to more than 42,000 deaths. In the immediate years following, the deaths from smallpox in England and Wales dropped to just over 2,000. This is not surprising in view of the increase in herd immunity which must have resulted not only from the clinical, but a very large number of unrecorded sub-clinical, cases in those possessing some vaccinial immunity.

The outbreak in Sheffield in 1887–8 was reported in great detail by Barry, (1889). He gives a mine of information on incidence as well as mortality, as a house-to-house survey of a very large part of the city was made, giving an epidemiological picture which was otherwise not possible until satisfactory notification was achieved in the early twentieth century. In this outbreak, in thirteen months, there were 6,088 cases and 590 deaths. The attack rate in vaccinated children under ten was 5 per 1,000, in the unvaccinated under ten, 101 per 1,000. The death-rate in the vaccinated under ten was 0·9, and in the unvaccinated 44. A very large proportion of the population had been vaccinated in infancy, and not subsequently, so that the attack rate at all ages was 230 per 1,000 in the vaccinated and 750 in the unvaccinated, but the death-rate in the vaccinated was 11 per 1,000 and in the unvaccinated 372 per 1,000. In the house-to-

house census it was found that 6·6 per cent of the population had suffered from smallpox previously.

The outbreak in 1893–4 further emphasized the high incidence in London and some southern counties and the increased incidence in Lancashire and Yorkshire. In 1895–6 the city of Gloucester suffered an outbreak of smallpox which has always been given considerable attention, as in 1886 a wave of antivaccination propaganda had swept the city, with the result that very few infant vaccinations had been done for eleven years, In 1895, when smallpox first appeared, it was estimated that there were about 10,000 unvaccinated children in Gloucester. It is of interest that the first case was in an unvaccinated child, who was thought to have measles, and whose illness was concealed from the sanitary authority, a not uncommon accompaniment of antivaccination policy, and probably accounting in no small degree for the widespread nature of the outbreak. Up to July 1896, there were 2,035 cases, of which 443, or 21·8 per cent, were fatal, including 281 unvaccinated children under the age of ten years. For years afterwards, this fact was made the basis of much propaganda in favour of infant vaccination. What is somewhat lightly glossed over is the fact that there were 102 deaths in 916 adults attacked who had been successfully vaccinated in infancy, according to the law and the accepted policy of the time, but of course they had never been revaccinated. Hospital accommodation was limited to forty-eight beds, although in the months of March and April there were 644 and 744 cases respectively. The fact that so many cases were not hospitalized contributed to much spread of infection. Trade in the town was paralysed, and it was estimated that the loss to Gloucester city, through fear of people even coming to do their shopping, was more than £150,000 (1895 values). It was recorded that some of the leading members of the Gloucester Anti-Vaccination Society contracted smallpox during the epidemic and several died. Other antivaccinationists had smallpox in their families, and they themselves were vaccinated or revaccinated, including the founder of the Society and its president. As usual, there was no lack of bias in the interpretation of the cause of this outbreak. The antivaccinationists claimed that it was the insanitary state of the city, but "expert advice", whatever that means, absolved the sanitary circumstances from having affected the epidemic in any way. Low (1918) states, somewhat naïvely, that the main factor was the unprotected state of the children, through the neglect of vaccination during the previous ten years, a result of misdirected zeal of the local antivaccinationists. As already mentioned, a frequent accompaniment of antivaccination policy is antipathy towards public health work of any kind, including notification, and failure of this probably had a considerable effect in preventing the early detection of smallpox and its effective isolation, which might have gone a long way to preventing the free spread of smallpox, as we know it can today. The fact that Gloucester had been free from smallpox for about twenty years prior to this outbreak was reflected in the high incidence in vaccinated persons and the high mortality. Of the 723 cases under ten years of age, 699 were unvaccinated, whereas of the 990 cases aged twenty and over, 916 were vaccinated, rather a pretty reversal of incidence. Although successful infant vaccination would have prevented the 281 deaths in children under ten years of age, many medical officers of health were sufficiently naïve to believe that if all the infants had been vaccinated, then smallpox could never have spread in Gloucester at all. Of this there is obviously no evidence whatsoever, and the occurrence of outbreaks such as London 1901–2, and those in the last twenty years, predominantly amongst adults, supports the view that smallpox epidemics could occur amongst adolescents and adults, even if 100 per cent of the infants were conscientiously and effectively

vaccinated. After the outbreak in 1893–4, in which nearly 4,000 cases of smallpox were notified in London, there followed a period of nearly ten years with relatively few cases. This was thought to be partly due to the removal, from 1885, of smallpox cases from M.A.B. hospitals in the densely populated parts of the city to the hospital ships at Longreach, owing to the current opinion that smallpox hospitals acted as centres for diffusing the infection amongst the population living thereabouts. The apparent calm was rudely shattered in 1901–2, particularly in the latter year, in which 7,796 cases occurred with 1,314 deaths, making a total for the two years of 9,496 cases and 1,543 deaths, a case mortality of 16·2 per cent. In the report of the medical officer of health, Sir Shirley Murphy, for 1902, the most striking feature is that, of 8,618 cases, no less than 6,120 occurred in persons who had been vaccinated. The fatality rate was very different, some 10·3 per cent in the vaccinated, including a large number, some 1,800 persons, thirty-five years and over, and 32·1 per cent in the unvaccinated. Liverpool had its largest outbreak in the twentieth century in 1903, and in Scotland 1901 and 1904 were peak years. Since 1904 variola major has never produced a large epidemic in Great Britain.

The term variola minor seems to have been used first in the Annual Report of the Ministry of Health for 1929. Mild forms of smallpox, although possibly confused with chickenpox, were described by Wagstaffe as far back as 1722, when he made the celebrated remark: "We have the sort in which a nurse cannot kill, and another in which even a physician can never cure." Jenner also described an outbreak of what he called swine-pox, with material from which he was apparently able to variolate his son and others, and which was recognized by the local practitioners as a distinct entity, although this term had been used by Heberden (1767) as an alternative term for chickenpox. Adams in 1807 also described a mild type, and Marson in 1866. Creighton, however, quotes Thomas Phillips who describes the journey of a slave-ship from Guinea to Barbados in 1694, during which apparently smallpox, although very prevalent, had a low mortality and an outbreak in Minorca in 1742 also produced very few deaths, but "every house a hospital". Again in 1752 in Barbados, Hillary remarks: "Smallpox, in general of a distinct kind, and in those few who have the confluent sort, they were generally of a good kind." It seems possible, however, that these outbreaks occurred principally in young adolescents between ten and twenty, in whom the mortality in any case would be low. In an age when death was so cheap, comments on high and low mortality are only relative. The first unequivocal description of a mild form of smallpox was that given in 1867 by Izett Anderson, on outbreaks in 1865 and 1866 in Jamaica, in which he called the disease varioloid varicella. In 1896 a very mild type of smallpox began to occur in the southern parts of the United States, probably introduced from the Caribbean area. In 1902–4, it was noted in Trinidad by Bridger (1903) and Dickson and Lassalle (1903). In South Africa it was thought to have been present amongst the Kaffirs for a great length of time, but I feel this is doubtful. It was first discovered in Brazil in 1910, and given the name alastrim, although Beaurepaire-Aragao (1911) suggested para-variola.

The problem of nomenclature became topical in the early 1920's, with its spread to Europe and although "atypical" smallpox was called amaas in South Africa, mild smallpox in America, and alastrim in Brazil, the term subtoxic smallpox was used by Cameron (Marsden, 1959), and Garrow (1922) suggested para-smallpox. Today there is little if any doubt that all these diseases are one, that they are a form of smallpox, and are best designated by the name variola minor, although Ricardo Jorge (1924) preferred the term alastrim, because this mild

form of smallpox and variola major breed true and are therefore two separate diseases. However, their clinical diagnosis, and in particular early diagnosis for administrative action, makes it imperative that both diseases are treated as one, at least in the initial stages of an outbreak.

The clinical descriptions and photographs of the disease are given in Chapter 3. Perhaps the most striking difference between it and variola major is the low degree of toxicity, once the eruption has appeared, but it must be borne in mind that some severe cases of variola minor are much less different from variola major than many writers will admit, and similarly variola major can on occasion, even in the unvaccinated, be just as trifling a disease as variola minor.

In 1896 a very mild type of smallpox began to occur in the southern parts of the United States. Mortality was very low, and it was at first mistaken for chickenpox, or for some new disease, and was called Cuban itch, elephant itch, Spanish measles, Japanese measles, Puerto Rico scratches, Manila scab, Manila itch, Filipino itch, kangaroo itch, Italian itch, bean-pox, water-pox or swine-pox. Most of the names indicate the general opinion that it was a new disease and, as is the custom, must have originated in foreign parts. Fifty-four cases of smallpox without a death occurred between November 1896 and June 1897, and in the surrounding country there were many more cases, also without deaths. Although variola major of the classical type had been absent from the area, Chapin (1913) thought that the new type was a sport or mutation from the normal. The disease spread to Alabama, and during the year ending 31 March 1898 there were 3,638 cases with fifty-one deaths. During 1898 this "new type" of smallpox spread into northern Florida and into Georgia. In these southern areas most of the cases were amongst negroes, and little attention was paid to the disease, but as they constituted the bulk of the labouring population they carried the disease from place to place. It occurred in Virginia in March 1898, and in Philadelphia in the same year. Reaching New York there were three hundred cases in forty different localities, but with only one death. Later in the year it spread to Michigan, and from Michigan to Ontario. By the end of 1898 a mild form of smallpox, called by Montizambert (1901) *variola ambulans*, was also prevalent in the province of Quebec, although it appeared to die out early in 1899.

The disease spread westwards, but in Texas it appeared alongside cases of variola major, due to infection imported from Mexico, where the disease was endemic. The mild smallpox spread in a somewhat leisurely and unspectacular manner over the whole of the North American continent. Although notification was very incomplete and only some 3,600 cases were recorded in 1898, the figure was nearly 11,000 in 1899, 20,000 in 1900, 48,000 in 1901, and 54,000 in 1902 (Chapin, 1913).

The case fatality, which was probably far from accurate, was 5 per cent in 1898, had fallen to between 2 and 3 per cent by 1905, and for the subsequent years it was between 0·23 and 1·7 per cent. In those years where the mortality was over 0·6 per cent, a number of cases of variola major may possibly have been included. At the extremes of life, deaths are recorded due to smallpox, although the attack of variola minor is a terminal event, not contributing appreciably to the death. The number of missed cases is also likely to be great, and this affects the case fatality rate. All the figures, however, showed that the disease was totally different in its severity from classical variola major, small outbreaks of which occurred from time to time, such as ninety-three cases with sixteen deaths in Arizona in 1899, and in the Charity Hospital in 1900, where there were 752 cases and 252 deaths, a case fatality rate of 33·5 per cent. In many there was clear-cut evidence of importation of variola major, but in New Orleans in 1899 and 1900, although the mild type appeared to be prevalent, in one area, Shrieveport,

there were forty-six cases in a month, of which twenty-three were confluent with six deaths, suggesting the undetected intrusion of variola major into a variola minor outbreak. It was confusing in that severe cases sometimes developed in amongst a large number of very mild ones, and where it could be reasonably certain variola major had not been introduced. However, if one regards variola minor as a variant of variola major, but with a lower pathogenicity for man, there is always the possibility that in particularly susceptible individuals even this mild strain may produce a very severe, even fulminating or malignant attack, and death. Although this was very rare in Pickford Marsden's (1936) very wide experience of variola minor in England between 1928 and 1935, in a population that might be described as inbred to resist smallpox for at least two and a half centuries, I do not think there is any doubt that these severe cases occur without having to postulate a sudden change in virulence of the infecting organism (see Figs. 114 and 115). It has been noted that the severe cases, even fatal ones, have not only been derived from very mild cases but themselves may give rise to secondary equally mild cases. Chapin states that during the fifteen years up to 1913 there must have been among the hundreds of thousands of mild cases several hundred and more likely several thousands of severe cases derived from them. If by severe he means those with confluent or semi-confluent eruptions similar to those illustrated in the clinical chapter, then I would certainly agree that several thousand is probably the more correct estimate. He gives no consideration to the probability that the "mild smallpox" was imported from the West Indies or from South America, but rejects wholeheartedly the suggestion that the people of the United States had acquired a partial immunity against the disease, either as a result of previous experience of variola major or as a result of vaccination. At the time (1913), Chapin regarded the United States as "the least vaccinated of any civilized country". However, from time to time variola major showed its power. An outbreak in Pittsburg in 1912 gave rise to 121 cases, and 33 died, case mortality 27·8 per cent; Los Angeles 1912, 119 cases, 17 or 14·3 per cent died; and in 1914 at El Passo, Texas, 191 cases of smallpox, 49 or 25 per cent died. Variola minor dominated the smallpox field in the United States for practically the first fifty years of the century. The peak years were 1920 and 1921, with over 100,000 notified cases in each year. The rate was over 30,000 until 1931, when after falling to 5,000 in 1934, it rose again to 14,000 in 1938, since when it has steadily fallen until 1950, when there were forty-two cases and no deaths. The majority of these were single cases, the largest being five at any one time in widely separated states, which suggests that some at least were chickenpox thought to be variola minor. On a number of occasions small outbreaks of variola major have occurred, such as in Seattle, 1946, and New York, 1947.

Although Hirsch (1883) makes the statement that smallpox occurred in Sydney, Australia, in 1838, it seems much more likely that these were cases of severe chickenpox. The first case in Victoria, an imported one, occurred in 1857, and in New South Wales there was one case in 1874, and a definite outbreak in 1877. The first case in South Australia occurred in 1882, in Tasmania 1887, and in Queensland not until 1892. Western Australia had cases in 1869, but there is some doubt as to the accuracy of diagnosis.

Cumpston (1914), who wrote the history of smallpox in Australia, quotes extensively from early writers. When white settlement of Australia commenced in January 1788, there was by 1789 an extensive epidemic of some disease amongst the aboriginal inhabitants. Large numbers died in and around the area of contact with the white settlers. Substantially the same description is given both by Collins (1804) and Tidswell (1898). They relate how the native population

were infected from the white settlers, and how they died in large numbers. This appears to have been partly due to the fact that, as it was a new disease, they were terror-stricken and abandoned the sick, who may well have died both of starvation and of the effects of exposure. Two points about this mysterious disease are interesting: one, quoted by Mair (1834), that the eruption was fully developed in twenty-four hours, and the other, that no cases occurred in the white population that were in contact, even amongst children and adults who were not vaccinated. In the following years, other outbreaks occurred and the disease spread rapidly amongst the aborigines but did not attack any of the white population who were in constant contact with them. Little attempt appears to have been made to investigate the disease, but Mair, who arrived late in an outbreak, successfully vaccinated three and they were subsequently not infected, although they would have been exposed for a long time before. The disease is reputed to have attacked one European, in the form of "secondary smallpox", whatever that is, and is supposed to have proved fatal to a child with symptoms resembling confluent smallpox. Dr. Getting, who had been sent to Streaky Bay, had informed Professor Tait "that he had treated the disease as smallpox, to which it had a close similitude, presenting similar symptoms, but he was not prepared to deny that it was not the smallpox". Confusion also arose with what was known as "native pox", and this appeared to be a form of impetigo, which may or may not have been secondary to chickenpox, producing considerable septic complications and scarring, owing to the hot climate and lack of hygiene. Many observers deduced that smallpox must have been present in aborigines some fifteen to twenty years previous to their visit, largely on the presence of facial scarring, and occasionally of blindness, which because of the current medical views of the time was always blamed on to smallpox. There was considerable confusion, however, in the use of the term chickenpox. According to Whittel, quoted by Lendon (1884), it was used vaguely for any pustular eruption which was not thought to be smallpox, and did not necessarily mean true varicella.

There are, however, records that some disease occurred which caused considerable reduction in population. Normal funeral rites were suspended, and in large mounds of earth, communal graves, scores of human skeletons have been found arranged in rows. All the Australian historians state that these were probably victims of smallpox. On the other hand, it could have been chickenpox introduced as an entirely new infection to a completely susceptible population living under very primitive conditions. It would doubtless not be sufficiently like chickenpox, as European doctors knew it, and yet they were not sure that it was smallpox, a disease with which all were familiar.

The other contact between Australia and the outside world was in the far north, where Malay prahus used to come to the Gulf of Carpentaria in search of *bêche de mer*, and had possibly done so for many centuries. They had considerable contact with the natives of those parts. A description given by Paul Foelsch (1882) said that the disease occurred in the dry season. There was a high fatality, and amongst those who recovered several became totally blind. This is a typical smallpox description, but it might easily have been applied by a man who, having thought it was smallpox, put the suitable description to it. On the other hand, there seems a much greater chance of it being smallpox, as this disease had been present in the East Indies and Malaya for a long time. Much of the supposed evidence of smallpox relates to people who had facial scarring or who were blind, not sufficient evidence in itself. It is perhaps of interest that Queensland, of all the parts of Australia, has had practically no smallpox in its entire colonial history.

The later history of smallpox in Australia, from 1887, is a succession of instances where the infection was brought by sea. Much detail is given by Cumpston, but perhaps the most important feature of these outbreaks was the realization, particularly by Dr. Ashburton Thompson (1887), that smallpox in Australia spread slowly, by direct personal contact, in spite of cities of over a quarter of a million inhabitants, with at least 100,000 unvaccinated persons below the age of twenty. In one outbreak no more than 154 cases occurred, although the infection was present and active for eight months. He based his methods of control on early diagnosis and quarantine, and on vaccination of contacts, rather than pressing for infant vaccination. Although official opinion, following orthodox British practice, asked for compulsory legislation, this was refused, and Thompson's views, written in 1887, show that in a new country some individuals could look at an old disease afresh, unsmothered by the need for orthodoxy, at the time the Royal Commission in England was still propounding the view that compulsory infant vaccination could alone prevent epidemics of smallpox in a community.

Classical outbreaks of smallpox occurred in Australia between 1868 and 1903, on six different occasions, giving rise to case fatality rates between 17 and 28 per cent, evidence that the infecting virus was classical variola major. In 1884 one outbreak occurred with sixty-four cases and only four deaths, a case mortality rate of 6·2 per cent, suggesting that this was an outbreak where a proportion of those affected had previously been vaccinated.

In April 1913, the mild strain current in the United States was conveyed to Australia and New Zealand. In Australia it occurred amongst employees in a clothing factory in Sydney, having been introduced by a ship's steward who had been infected in Vancouver. The epidemic continued until 1917 in New South Wales, by which time 1,073 cases had been notified. The complete number of notifications in the country was 2,400, with four deaths, of which only one was thought to be directly due to smallpox. One death was in a parturient woman, the other in an infant of twenty-three days of age. There were the usual difficulties of diagnosis, the disease being first mistaken for chickenpox, but in the report by Robertson (1913), who was chief quarantine officer, recent vaccination gave absolute protection against the disease, a fact which is important in view of the somewhat inconclusive results of laboratory experiments on the Australian virus conducted by Green (1915) in London. No cases were diagnosed in persons within thirteen years of a successful vaccination. There were 500 cases in persons under twenty-one years of age, all unvaccinated.

The infection was also introduced into New Zealand, and produced quite a different picture. Here the disease occurred principally amongst the Maori population, having been introduced by a Mormon missionary from Utah, who had joined a ship in Vancouver and arrived in Auckland in April 1913. The disease lasted until 1914, during which time 114 Europeans were attacked, with no deaths, and 1,778 Maoris, with fifty-five deaths, but it would seem probable that many more cases occurred, as medical aid was not often sought, and the assignment to smallpox as a cause of death might also be incorrect in a number of instances. In the clinical section, there are two photographs of deaths in adults (Figs. 114 and 115) which leave no doubt that variola minor introduced into some populations can give rise to some quite severe infections similar to variola major, and where death is primarily due to smallpox of this type.

Smallpox was introduced into South Africa in 1713, having been brought from India. Although the patients died on the voyage, clothing was brought ashore, and gave rise to smallpox

amongst those who washed it. Ultimately 570 were attacked and 200 died, which leaves little doubt that this was variola major. The disease produced a high death-rate in the Hottentots, many of whom fled inland, carrying the disease with them. Another outbreak occurred in 1775, the infection again having been introduced from Asia, this time from Ceylon. Nine hundred and sixty-three Europeans and over 1,000 of the native inhabitants died. Theal, in his history of South Africa, quoted by Mitchell (1922), stated that amongst some of the distant Hottentot tribes it differed in appearance so much from what was held to be real smallpox that the Europeans called it gall sickness. Whether this was really evidence of a mutation of the infection introduced in 1755, or whether smallpox had been smouldering in the centre of the country from 1713 or before, or whether the disease was atypical chickenpox, is not known. In 1767 infection was brought to the Cape, this time from Europe, with nearly 2,000 cases, 179 European and 396 native deaths, again leaving no doubt that it was variola major. Further outbreaks occurred at intervals throughout the nineteenth century, on each occasion severe and imported. One exception was an outbreak recorded in 1812, where only fifty cases occurred, and the disease was mild, with no deaths. Cases were slaves from a Portuguese ship; they may have been vaccinated, or perhaps the "nil" mortality was relative, less than usual.

In 1882, an outbreak of an unusual skin condition occurred in Kimberley, and this gave rise to difficulties in diagnosis, and was eventually called "epidemic pemphigus". An outbreak of a smallpox-like disease which is repeatedly referred to in the literature as one of variola minor, occurred in 1895 in Graaff-Reinet and was thoroughly investigated by Dr. [later] Sir George Turner, Medical Officer of Health for the Cape Colony. It is obvious from reading his report that the disease had all the characteristics of smallpox, except a lower mortality. This, however, was 6 per cent, and as the majority of cases were in vaccinated persons, I see no reason for supposing, as is done by Ricardo Jorge (1924) and others, that this was not variola major, a view which seems also to have been held by Sir George ,who stated that there was no essential difference in the cases from those which he had seen in the outbreaks in Europe in 1871 and 1872. Although the majority of the cases were in Kaffirs, it also attacked some Europeans and caused deaths.

Although variola minor undoubtedly occurs in South Africa today, exactly when and how it evolved is quite another matter. De Korte, writing in 1904, described the disease as a distinct entity, and in 1910 Spencer and Grant pointed out the continued existence of this disease. Mitchell (1922) described how the Bantu tribe had an accurate name for variola major, *ngqakaga*, meaning "face is spoilt", and they had another term for variola minor, which meant "younger brother to smallpox". The term *amaas* was apparently restricted to the Dutch-speaking population. Its origin is uncertain, possibly being derived from the Kaffir word *amasi*, meaning fermenting milk, and so is linked to the word milkpox, but more probably, in the opinion of Mitchell (1922) it is a corruption of the Dutch word *masels* or *mazelen*, meaning measles, although there is less chance of confusing measles with variola minor than with the early stages of some types of variola major. In Kimberley in 1905 some cases were seen by thirteen doctors, of whom nine thought the disease was smallpox, whereas the other four regarded it as *amaas*, or at any rate not smallpox. The danger lies in regarding the first few cases in an outbreak, if they are mild, as *amaas*, whereas they might well be cases of variola major, particularly in the vaccinated, until this is discovered by severe cases and deaths. Mitchell (1922) thought the mild type could become severe. He records one incident in 1900 in a leper asylum, where there was a case mortality of 38 per cent, but this must have been

variola major. In 1903, cases of smallpox of the "usual mild type" occurred, and the outbreak spread down a valley, eventually to the town of Port Elizabeth. Although the early cases were very mild, later ones were more severe. One cannot exclude the possibility that it was eventually a mixed infection with variola major, introduced through the port. Observations, particularly Marsden's very large series in London in 1936, show conclusively that in variola minor there is no tendency to change in type. Since 1900, outbreaks of variola minor have occurred in a wide belt across Central Africa.

In Jamaica, Izett Anderson (1867) used the title varioloid varicella in attempting to describe something which looked like smallpox, but had a case mortality more like chickenpox. In Cuba the same disease was called Cuban itch, and ultimately spread to the southern States and over the whole American continent. The disease had long been present in South America, and was first studied in São Paulo in 1910 by Rebas. The disease appeared to occur in labourers on coffee plantations, and was apparently very prevalent in the interior parts of the country. It was colloquially called alastrim, and this was the name which it was given by Rebas, and which has found its way into the medical literature of many countries of the world. According to Ricardo Jorge (1924), alastrim is a Brazilian word derived from the Portuguese *alastra*, meaning something which "burns like tinder, scatters, spreads from place to place". In Portugal a similar word, *andaço*, is used, meaning something which travels, not very apt as one of the mysteries of variola minor is that it does not travel as fast or as certainly as variola major.

A paper of Thomson and Brownlee (1898) is often quoted as describing an early outbreak of variola minor in Britain, but the original report shows that it was an outbreak on a ship amongst Lascar seamen who had recently been successfully vaccinated, and was almost certainly atypical chickenpox. The first authentic outbreak appears to be that described by Boobbyer (1901), occurring in Nottingham, where five cases of a very mild form of smallpox occurred in some adults between twenty-two and thirty-three years of age, four of whom were unvaccinated. Cases occurred in Leicester, Loughborough, Derby, Sheffield and Liverpool, without spread to secondary cases, but they had all been infected in Nottingham, due to attending a small Mormon conference, held on 24 March of that year. The infection was thought to have been introduced to the mission as it was frequently receiving large parcels of papers and other goods from Salt Lake City, where smallpox of the mild type was prevalent. Wilkinson (1914–15) refers to 800 cases of smallpox in Oldham between 1904 and 1906 without a death, claiming infection was brought from Yorkshire, but this seems doubtful. Copeman (1920), in describing the outbreak of variola minor in Suffolk, refers to its similarity with an outbreak he investigated in Cambridge in 1903. Examination of the annual report of the Medical Officer of Health of Cambridge for 1903, however, shows that although the early cases gave rise to considerable difficulty in diagnosis, as they were very mild and thought to have been chickenpox, the case mortality in the whole series was 8 per cent in the vaccinated and 25 per cent in the unvaccinated, which leaves no doubt that this was genuine variola major, occurring in a fairly well vaccinated community, and where just by chance all the early cases occurred in persons who had considerable immunity. Whether variola minor was common in England at this time, as suggested by Chapin (1913), seems more doubtful, and although outbreaks of smallpox at Oldham in 1913 and Milnrow in 1914 are normally stated (Rep. C.M.O., Ministry of Health, 1931*b*) to have been variola minor, examination of newspaper accounts in the *Rochdale Guardian* for 1914 suggest that the Milnrow outbreak at least may have been variola major.

The first recognized outbreak of variola minor seems to have been that described by Copeman (1920) which occurred in Lowestoft and Beccles in the summer of 1919. The infection was thought to have been introduced by the skipper of a steam trawler which came from Alexandria and stopped at Malta and Gibraltar, and infection may have been obtained from the latter place. As usual, the attacks were mild, and there was considerable confusion over the diagnosis, chickenpox being assumed at first. Infection spread from case to case in the usual way, except in its introduction into Beccles, where it was possibly conveyed by fomites—in this case coins. There was doubt as to whether patients suffering from the disease could be vaccinated in the period of convalescence, but some confusion probably arose over the interpretation of a successful vaccination. Wanklyn, however, who saw the cases, was quite convinced that they were smallpox.

In the report of the Ministry of Health for 1920, eighty-three cases of mild smallpox are included, with cases of variola major, and in that for 1921, although the table gives 322 cases as variola major, plus four as alastrim, the report shows that at least 277 of the cases were variola minor, 142 in Nottingham, 41 in Middlesbrough and 94 in the Colne Valley.

The course of variola major in the twentieth century in England and Wales is shown in the table in Fig. 200. Although notification has been compulsory to all local authorities since 1899, figures of notifications are only available in the records of the Registrar-General from 1911, emphasizing that until relatively recently the paramount interest was in deaths and not cases. It will be seen that, after 1905, in no year did the number of deaths exceed 100, but from 1919, and particularly from 1922, the number of notified cases was wholly disproportionate, due to the outbreak of variola minor, which is described subsequently. The number of smallpox cases in any one year was often small, but it was not until 1935 that a year occurred with no cases at all. In this year a case was notified by a medical officer of health, but was not considered to be smallpox by medical officers of the Ministry of Health. If this is accepted as a case, then 1939, is the first in which no cases of smallpox occurred. The pattern of infection has been one of introduction of variola major from abroad by persons usually entering by sea, but occasionally travelling over land and in the last few years by air. At no time have valid vaccination certificates been required for travellers entering the United Kingdom. From 1912, detailed tables were given in the annual reports of the Local Government Board and subsequently the Ministry of Health, showing that in each year between fifteen and twenty cases of smallpox had been diagnosed amongst foreign seamen arriving at the ports and who were infected abroad. From the 1920's the proportion of cases detected in seamen has got progressively smaller, probably due to more widespread vaccination, but the number of missed cases that constitute the source of outbreaks in England and Wales appear to have increased.

Variola minor first appeared in Switzerland in 1921, and produced 596 cases with only 7 deaths, and in England and Wales there was an abrupt change, from 1920, with 263 cases and 30 deaths, a case mortality of 11·4 per cent, probably mixed variola major and minor, to 1921, with 315 cases and only 5 deaths, a case mortality of 1·5 per cent. In 1922 there was a case mortality of 2·7 per cent, and from 1923 to 1930 it varied between 0·17 and 0·3 per cent. The figure for Marsden's 1936 series of over 13,000 cases was 0·25 per cent. The reduction in mortality a year or two after the first appearance of the disease may be largely accounted for by incomplete notification, many physicians at first regarding the condition as being chickenpox. Although in the years 1924 and 1928, the years in which variola major was not recorded

Year	Variola major			Variola minor		
	Cases	Deaths	Case fatality (%)	Cases	Deaths	Case fatality (%)
1911	295	23	7·79	—	—	—
1912	123	9	7·31	—	—	—
1913	115	10	8·69	—	—	—
1914	64	4	6·20	—	—	—
1915	90	13	14·4	—	—	—
1916	149	16	10·7	—	—	—
1917	7	3	42·8	—	—	—
1918	63	2	3·17	—	—	—
1919	294	24	8·16	36	—	—
1920	180	30	16·67	83	—	—
1921	45	5	11·11	277	—	—
1922★	78	24	30·77	895	3	0·335
1923	18	2	11·11	2,467	5	0·203
1924	—	—	—	3,765	13	0·345
1925	10	1	10·00	5,365	9	0·168
1926	5	1	20·00	10,141	17	0·168
1927	17	7	41·18	14,753	40	0·271
1928	—	—	—	12,420	53	0·427
1929	42	14	—	10,925	25	0·299
1930	—	—	—	11,839	28	0·236
1931	—	—	—	5,664	9	0·159
1932	—	—	—	2,039	3	0·147
1933	—	—	—	631	2	0·317
1934	26	4	15·38	153	2	1·307
1935	—	—	—	?1	—	—
1936	12	—	—	—	—	—
1937	3	?	?	—	—	—
1938	7	3	42·86	—	—	—
1939	—	—	—	—	—	—
1940	—	—	—	—	—	—
1941	—	—	—	—	—	—
1942	2	—	—	—	—	—
1943	—	—	—	—	—	—
1944	11	3	27·27	—	—	—
1945	4	—	—	—	—	—
1946	56	14	25·00	—	—	—
1947	78	15	19·23	—	—	—
1948	—	—	—	—	—	—
1949	19	5	26·32	—	—	—
1950	8	—	—	—	—	—
1951	27	10	37·04	—	—	—
1952	—	—	—	135	—	—
1953	29 (40)†	8	26·67	—	—	—
1954	—	—	—	—	—	—
1955	—	—	—	—	—	—
1956	—	—	—	—	—	—
1957	7	3	42·86	—	—	—
1958	5	1	20·00	—	—	—
1959	—	—	—	—	—	—

★ Estimated (C.W.D.).

† Lower figure number of cases "accepted" by the Ministry of Health. Compiled from official reports and information kindly supplied by Drs Bradley and Grant Nicol of the Ministry of Health.

FIG. 200. Table of cases and deaths and case fatality for variola major and variola minor for England and Wales, 1911–1959

in the country, the case fatality rate of variola minor appears slightly higher, the differences are not statistically significant. In some outbreaks of variola minor a rise in mortality suggests the intrusion of variola major, but the practice in England and Wales of crediting a death as due to smallpox, however it is mentioned on the death certificate, does include a number of cases where the disease has made little if any contribution to a terminal event, particularly in old people.

Figure 200 gives the incidence of the disease from the 1920's, from which it can be seen that it gradually increased to a maximum in 1927, with 14,000 cases, and then gradually declined, until by 1935 it was extinguished. Quite the most interesting feature of variola minor, and rather different from the picture of the disease in the United States between 1899 and 1905, was the very leisurely spread from the North of England to the South. The disease first appeared in 1919, practically simultaneously in the counties of Durham, the West Riding of Yorkshire, Lancashire and Cheshire. There is no real evidence as to where the infection came from, and as the earliest cases were mistaken for chickenpox, infection had in all probability been present in the areas for some months. Isolated pockets, however, occurred further south. There were the thirty-five cases in Suffolk in 1919, and seventy-five in Essex in 1920, but in each area no cases occurred in the following year. In Gloucester there was a large outbreak in 1923–4, which is described in Chapter 17, but except for these there was virtually no smallpox south of the line from the Bristol Channel, through Nottinghamshire to the Wash, until 1924. In 1923–5, Leicestershire, Northamptonshire and Warwickshire were involved. The extreme south was not affected until 1928, in which year smallpox appeared in London, some also in the home counties and in the south Midlands. This all suggests that variola minor is a disease of relatively low infectivity, and in spite of the ease of communications in a small country like England and the presence of the Wembley Exhibition of 1924–5, with hundreds of thousands of visitors from all parts of the country, its ability to spread appeared very limited, contrary to the view put forward by Ricardo Jorge (1924).

By 1935 variola minor died out, without spreading appreciably south of London and the home counties. During the period from 1922, some 80,000 cases of variola minor were notified, although the number of infections must have been much greater.

At this time, England and Wales was the only European country that had continuous weekly notifications of smallpox, and this led to international repercussions, particularly at the time of the "*Tuscania* incident", an introduction of variola major. In April 1929, the French Government, on the assumption that the 200–300 notifications of smallpox were variola major and not minor, asked all passengers from England to produce evidence of vaccination within five years as an alternative to fourteen days' surveillance. From time to time, demands were made at continental ports that crews of ships coming from British ports in which smallpox was reported should be vaccinated, a not unreasonable request at the time. The Ministry of Health forwarded every quarter to the International Health Office during this period statements of the clinical character, mortality and local spread of the disease, and stated that these declarations "have proved of great value in securing a satisfactory appreciation of the smallpox situation in this country by foreign administrations, which otherwise would be disposed to exact special precautions on the arrival in their territory either of passengers from England, or of goods which might be presumed to harbour smallpox infections" (Ministry of Health, 1931*a*). To some extent this was got over by the policy of medical officers of health informing the Ministry of contacts of smallpox who had gone overseas, so that the Ministry could

communicate with the foreign health administrations with a view to the continuance of the surveillance. Nothing is stated in the report of the many missed cases of smallpox who presumably also went overseas. It illustrates the attitude at the time of supporting compulsory vaccination of infants, although it did not protect the community from outbreaks of smallpox, but strenuously resisting the idea of compulsory vaccination of adult travellers for the benefit of other countries.

It is impossible to describe the interesting features of the history of smallpox in many other countries, but the subject of world incidence was dealt with by Hirsch (1883) and subsequently reviewed by Bruce Low (1918) and more recently by Stowman (1945), Fabre (1948) and Murray (1952, 1953). The problem of smallpox in the world can be assessed either from figures collected in various countries as to incidence, normally based on some system of notification, or on the records of deaths. Notification is far from perfect in probably all countries of the world. In many countries medical services are so poorly developed that notification can only be fragmentary, but even in those which are well developed there is a tendency to minimize the number of notified cases, because of national prestige. In some, cases of variola sine eruptione are excluded, and cases diagnosed retrospectively on serological examinations are not included, nor are cases which are diagnosed *post mortem*. In those countries that are proud of their medical services, smallpox has a certain stigma, and those that are developing are well aware that the figures of incidence are somewhat rough-and-ready.

It might be thought that figures for smallpox deaths would therefore be much more valuable as an indication of smallpox, but unfortunately we have the problem of both variola major and minor, and the fact that quite a large number of cases may occur in a community with a fair amount of infant vaccination, with relatively few deaths, whereas in an unvaccinated community, the natural mortality of variola major, about 30 per cent, may exaggerate the importance of some isolated outbreak.

To overcome some of the problems of measuring the risk of smallpox in the world in those countries with a high endemic level, Murray, in the *Epidemiological and Vital Statistics Report, 1953*, worked out an endemicity index for each country, by averaging the smallpox attacks or death-rates for the five years in which the lowest incidence of the disease was recorded during the period 1936–50. It has the disadvantage of not recording variola major and minor separately, and only gives a relative index, probably more significant in comparing the differences in parts of one country, rather than at the international level.

At present the main reservoirs of smallpox in the world are in India and Pakistan, Burma, and to some extent in Vietnam and Cambodia. All these areas are foci of variola major, and within recent years smallpox has flared up from time to time both in Indonesia and Thailand. Malaya and Singapore are also liable to be infected along the sea-lanes, but otherwise have medical services sufficiently well organized to remain free.

In Africa there are foci of both variola major and variola minor occurring in the Congo, Nigeria and Tanganyika, and of variola minor in parts of Central Africa. In the Americas, Mexico has been the last reservoir of variola major in the North American continent, but is now apparently free, while in the South American continent, Venezuela, Colombia, Brazil, Bolivia, Peru and Paraguay remain as foci of variola minor, although extensive vaccination campaigns have reduced the incidence considerably, and are part of the smallpox eradication programme in this area. Portugal appears to be the only country in Europe with a high endemicity rate, but this is probably incorrect, due to the fact that chickenpox

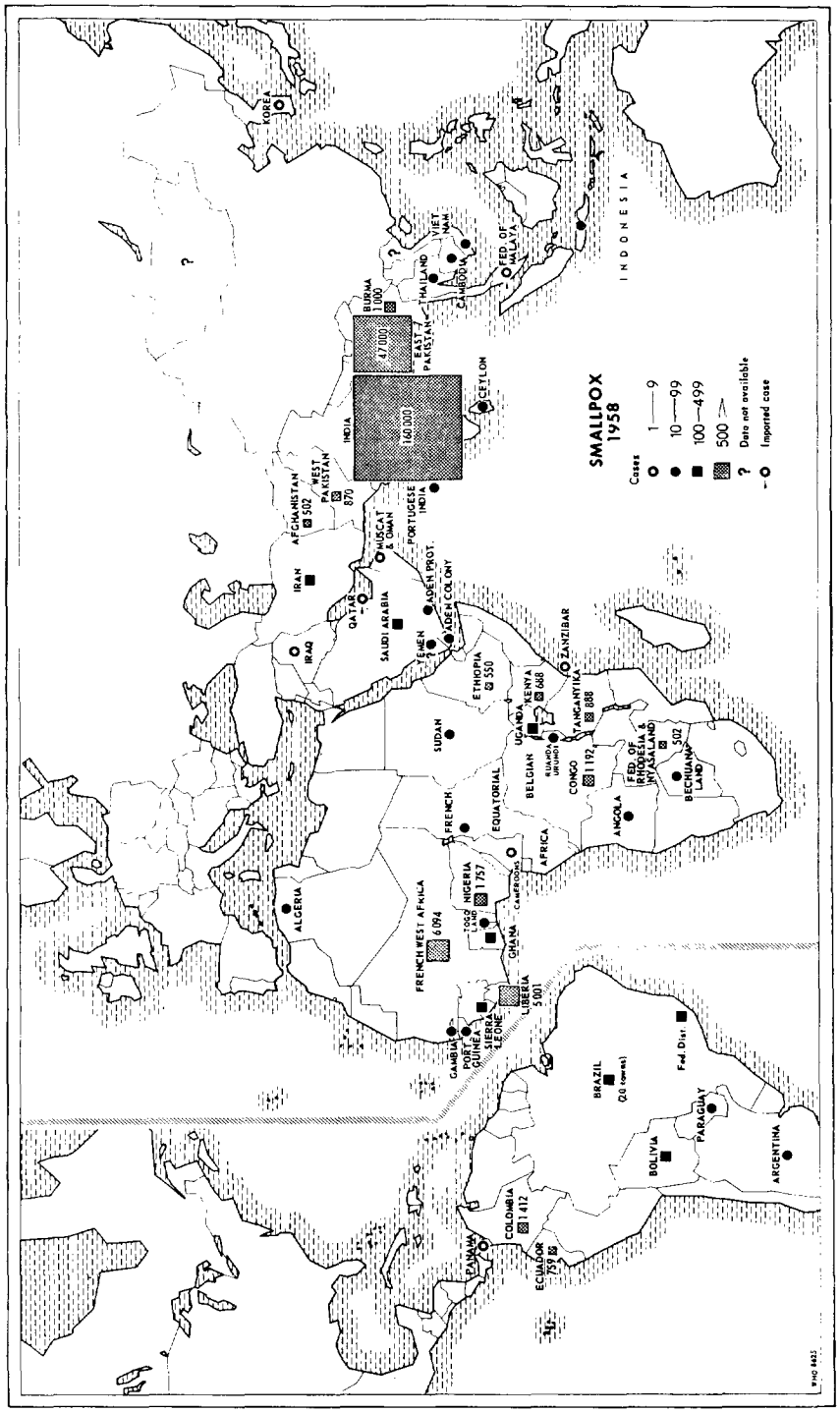


FIG. 201. Notification of cases of smallpox in 1958.

and variola minor have been confused in that country. However, no cases appear to have occurred since 1954, so perhaps the method of recording has altered.

In the Appendix (pp. 452–470), tables taken from the W.H.O. Reports are given for both cases and deaths, in a wide range of countries, but without an intimate knowledge of the medical and other services of the countries concerned, too much reliance should not be placed on these. More recent figures for smallpox incidence may be obtained from the publications of the World Health Organization.

CHAPTER 11 The History of Inoculation for the Smallpox

Once a discovery is made, exhaustive attempts are made by interested persons to show that the idea is not new. Inoculation for smallpox is no exception. As I shall discuss later, initial interest in and experiment with this practice by the medical profession belongs to the period 1700–25, although there seems little doubt that it occurred in folk-medicine practice in a number of places in Europe from at least 1650 and in the Orient possibly much earlier. In England it was fashionable in medicine, as in music, to adopt foreign experiments and styles, and many who had travelled embellished their accounts, often written many years after inoculation had been established, with stories from "eye witnesses" who had all affirmed that this practice had been known long before. We thus have statements that "buying the smallpox", the practice of obtaining smallpox scabs which were rubbed into the skin, had been a common practice in Poland (1671), and had also been used in Wales (P. Williams, 1723; Wright, 1723) and in Scotland (Kennedy, 1715; Monro, 1818), in Naples (La Condamine, 1754), parts of Africa (Colden, 1753), China (d'Entrecolles, 1718) and India (Holwell, 1767). Patrick Russell, admittedly writing in 1767, suggests that it was a common practice amongst Bedouins over a wide area in the Middle East, including Iraq, and had been for very many years, and that its general acceptance there would prevent its novelty being brought to the attention of the European traveller. Although some of these accounts may have been true, writers going to some pains to substantiate their statements, some were obviously false, such as La Mottraye (1727), who gave elaborate details of the practice in the Caucasus which could not be substantiated by quite reputable observers who had lived in the same region.

There is no doubt, however, that an important feature of much folk medicine in many parts of the world was the idea of transferring a disease away from the sufferer to a charm or deity or to a "brute" animal such as the sheep. The removal of such obviously evil material as the scabs and crusts in smallpox must have been quite common. It has occurred more recently in West Africa as part of the practice of Sokpono witch-doctors. Accidental cutaneous inoculation of mothers from nursing infected children, giving rise to primary smallpox lesions on the skin of the face, neck or breast, was well known and astute observers doubtless noticed that some of these individuals appeared to suffer from mild smallpox attacks. It was also a common practice to purposely expose children to mild cases in the hope that they, as direct contacts, would also develop mild attacks. A procedure uncertain in its result, but having the important principle of "arranging" for the disease when the individual was in good health to receive it, rather than by chance when possibly in a more unfavourable state.

It is possible that in some parts of the world small groups of individuals might have carried out the practice of inoculating the disease, particularly during an outbreak (it was necessary to have a source of virus), and this may have been done a thousand years ago in India where

smallpox probably existed, but in spite of Holwell's (1767) account suggesting very early inoculation in India, I think it is true to say that no community appears to have carried out *systematic inoculation* as a preventive measure in the way we understand it today, or in the way that it was developed in England and America from 1720 onwards.

Although life was cheap and pestilence common, the death of Queen Mary from smallpox in 1694, and its effect on William, probably influenced the court and circles of learning more than is usually appreciated. The death also from smallpox of the Duke of Gloucester, the son of Anne, in 1700 precipitated a constitutional crisis which resulted in the Act of Settlement, and to this day no King or Queen of England may leave the country without Parliament's permission.

These important events must have stimulated interest in the disease and its prevention, although at such a time progress was necessarily slow. The first evidence of interest in variolation by any scientific body was the report sent from China by Joseph Lister, dated 5 January 1700, to Dr. Martin Lister, a member of the Royal Society. The letter described the Chinese method of inoculation against smallpox by inserting crust material into the nostrils of the individual. There was a growing practice amongst the intelligentsia to correspond with persons in foreign countries, the further away the better, on matters of medical, botanical or general scientific interest. This practice was not only undertaken by medical men and "scientists" of the time, but was also a fashionable hobby of the nobility, some of whom may not have been searching for truth, so much as the opportunity of publicizing some new discovery or idea before their neighbours. On 14 February 1700, Dr. Havers presented an account to the Royal Society, but quite how he could have done this if Joseph Lister's letter was really dated 5 January 1700, is difficult to understand. In view of the fact that Dr. Havers was a colleague of Dr. Lister's, it seems unlikely that there were two different accounts. Possibly Joseph Lister may have sent his report earlier to Dr. Havers although there is no record of this. In 1711 the Emperor Joseph died of smallpox. This unexpected blow to the stability of Europe once again emphasized the peculiar position of smallpox amongst the great diseases in its ability to strike in high places.

The next person contributing something to the story is Edward Tarry, who in 1706 was in Pera and Galata, and claimed to have seen over 4,000 people inoculated. He apparently remained in Turkey until 1712 and then returned to England, setting up practice in Enfield. Discussion on inoculation took place in the Royal Society in 1713 and 1714, information being gained from merchants and others who had lived in Turkey, and possibly also from Tarry.

Timoni, who was physician to Charles XII wrote an account of the practice of inoculation in 1713, while he was in Turkey. A copy was sent in December 1713 to Dr. Woodward of the Royal Society, who reported its contents on 27 May 1714. Timoni, who was an Italian, had been in London in 1703 had obtained a degree at the University of Oxford and was made a Fellow of the Royal Society. He would have been aware of the report of Dr. Havers presented in 1700 on the Chinese method of inoculation and this may have sufficiently stimulated his interest in the practice to cause him to write an account and send a copy to Dr. Woodward for presentation to the Royal Society, Otherwise it must be assumed that it was only by chance that one of the many European physicians in Turkey decided to write an account and send it to London. On 3 June 1714 the paper was read in English at the Royal Society, and therefore its contents would become available to a large number of the Fellows of the Society, many

of whom were not medical practitioners. It so stimulated interest, which, because of the importance of the disease, had been sustained for many years, that at a discussion on 10 June 1714, additional information was requested, with the comment that "*it was needless to mention the benefits of this method*". The Secretary of the Royal Society, named Waller, therefore wrote to a William Sherard at Smyrna on behalf of the Royal Society. Sherard contacted Jacob Pylarini, whom he knew well, and with whom it is suggested he had discussed inoculation against smallpox some years before. Pylarini, who came from Cephalonia, had in 1701 been asked about inoculation against smallpox by a Greek nobleman who wished the operation

FIG. 202. Lady Mary Wortley Montagu.

carried out on his four sons. At the time Pylarini admitted that he knew nothing about the practice, but on being pressed as to whether it would be harmful or not, he at length admitted that it probably would be harmless and the nobleman's four sons were inoculated by a Greek woman at this time (1701). Sherard, having obtained information from Pylarini, did not write to Waller, the Secretary of the Royal Society, but to his brother, who was an apothecary, sending him a copy of a book which Pylarini had published in Venice late in 171[illegible] describing the whole technique of inoculation. This was received by the Royal Society on 24 May 1716, and reported in the Transactions. It seems difficult to understand why Sherard did not send this information direct to the Secretary of the Royal Society. Pylarini's account, although a useful exposition, did not appear to have added very much to the knowledge available at the time.

In 1715, Peter Kennedy, a Scottish physician, although he had never done an inoculation, observed, in another connection, that the practice was not to be doubted. How much correspondence on this subject went on between interested lay people is not known, but it was a very important scientific curiosity of the period. Charles Maitland, who was surgeon to the Embassy in Constantinople in 1717, was already "well acquainted" with the practice. In 1714, at a meeting of the Royal Society in London, Townshend (1714) had reported that he had seen at least two hundred persons done. Although it would appear that all these inoculations were done on the local inhabitants, the children of Europeans were almost certainly inoculated about this time. In 1713 the children of the French Consul in Aleppo were inoculated. So far London had only hearsay evidence of inoculation, and although discussed by reputable Fellows and correspondents of the Royal Society, it was not until late in 1716 that there returned to London two children, the sons of the Secretary to the British Ambassador in Turkey, who had been inoculated there on 7 March 1716. For the first time the results of the Turkish practice could have been inspected.

In 1716 Lady Mary Wortley Montagu, the wife of the British Ambassador to Turkey, travelled across Europe to take up residence there. Lady Mary was an unusual character who throughout her life loved the pompous and spectacular. She admired unorthodoxy for its own sake and was always searching for admirers of her intellectual activity. Two weeks after arriving in Turkey she wrote to Sarah Chiswell, on 1 April 1717, that on her return to England she intended to bring the usefulness of this fashion (inoculation) into common knowledge.

> "*Apropos* of distempers, I am going to tell you a thing that will make you wish yourself here. The small-pox, so fatal, and so general amongst us, is here entirely harmless, by the invention of *ingrafting*, which is the term they give it. There is a set of old women, who make it their business to perform the operation, every autumn in the month of September, when the great heat is abated.
>
> "People send to one another to know if any of their family has a mind to have the small-pox: they make parties for this purpose, and when they are met (commonly fifteen or sixteen together), the old woman comes with a nut-shell full of the matter of the best sort of small-pox, and asks what vein you please to have opened.
>
> "She immediately rips open that you offer her, with a large needle (which gives you no more pain than a common scratch) and puts into the vein, as much matter as can lie upon the head of her needle, and after that binds up the little wound with a hollow bit of shell; and in this manner opens four or five veins.
>
> "The Grecians have commonly the superstition of opening one in the middle of the forehead, one in each arm, and one on the breast, to mark the sign of the cross; but this has a very ill effect, all these wounds leaving little scars, and is not done by those that are not superstitious, who choose to have them in the legs, or that part of the arm that is concealed.
>
> "The children or young patients play together all the rest of the day, and are in perfect health to the eighth. Then the fever begins to seize them, and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty in their faces, which never mark, and in eight days they are as well as before their illness. Where they are wounded, there remain running sores during the distemper, which I don't doubt is a great relief to it.
>
> "Every year thousands undergo this operation; and the French Ambassador says pleasantly that they take the small-pox here by way of diversion, as they take the waters in other

countries. There is no example of anyone that had died in it: and you may believe I am well satisfied of the safety of this experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England, and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue, for the good of mankind. But that distemper is too beneficial to them, not to expose to all their resentment, the hardy sight that should undertake to put an end to it. Perhaps, if I live to return, I may, however, have courage to war with them. Upon this occasion, admire the heroism in the heart of your friend." (*Letters and Works of Lady Mary Wortley Montagu*, 1861.)

It seems reasonable to suppose that she knew a good deal about inoculation before going to Constantinople and so soon after arriving had convinced herself that it was an established practice and one worthy of being done in other countries. Although Lady Mary has been credited by some as showing great originality in wishing to introduce inoculation into England, it is obvious that by this time the practice was already reasonably well understood in theory, although few had seen it in practice. What probably strengthened her will to introduce it into England was the fact that she had suffered an attack of smallpox herself in December 1715 which had left her severely scarred. The year before, in December 1714, when her husband chose a house for her in Duke Street, Westminster, she not only thought it might be damp and unsound, but because some years before the occupier's wife and child had died of smallpox therein, she was afraid infection might remain. Her real fear of smallpox was made greater by the fact that her brother had died of it.

While ill she had been visited by none other than Sir Hans Sloane, afterwards to become President of the Royal Society, and another eminent physician, Dr. Garth. Lady Mary's feelings are shown in the verse she wrote after she recovered, commenting on the useless and incorrect advice of the physicians (Halsband, 1956):

"In tears surrounded by my friends I lay,
Mask'd o'er and trembling at the sight of day;
Mirmillo came my fortune to deplore, (Sloane)
(A golden headed cane well carv'd he bore)
Cordials, he cried, my spirits must restore:
Beauty is fled, and spirit is no more!
Galen, the grave; officious Squirt, was there,
With fruitless grief and unavailing care:
Machaon too, the Machaon, known (Garth)
By his red cloak and his superior frown;
And why, he cry'd, this grief and this despair?
You shall again be well, again be fair;
Believe my oath; (with that an oath he swore)
False was his oath; my beauty is no more!"

To her dying day she hated the orthodox medical profession. This may well have sprung from the fact that although knowledge of the practice of inoculation against smallpox had been available in England for some years, no physician had had the courage to carry it out and so

prevent the disease in persons such as herself in whom disfigurement was such a tragedy and such an injury to her pride. On 19 March 1718 she had the conviction to have her own son inoculated in Constantinople, although she arranged to have it done while her husband was away at the Grand Vizier's camp at Sophia and waited four days before writing to him about it. He was somewhat disinterested, and in a further letter she explains that her young daughter cannot be done as "her nurse has not had the smallpox", showing that Lady Mary was well aware that "*innoculated smallpox*" was *infectious*, although Maitland, the surgeon to the Embassy, appeared unaware of this fact even in 1721.

Maitland (1722) describes the procedure thus:

> "About this time, the Ambassador's ingenious Lady, who had been at some Pains to satisfy her Curiosity in this Matter, and had made some useful Observations on the Practice, was so thoroughly convinced of the Safety of it, that She resolv'd to submit her only Son to it, a very hopeful Boy of about Six Years of Age: She first of all order'd me to find out a fit Subject to take the Matter from; and then sent for an old Greek woman, who had practis'd this Way a great many Years: After a good deal of Trouble and Pains, I found a proper Subject, and then the good Woman went to work; but so awkwardly by the shaking of her Hand, and put the Child to so much Torture with her blunt and rusty Needle, that I pitied his Cries, who had ever been of such Spirit and Courage, that hardly any Thing of Pain could make him cry before; and therefore Inoculated the other Arm with my own Instrument, and with so little Pain to him, that he did not in the least complain of it. The Operation took in both Arms, and succeeded perfectly well. After the third Day, bright red Spots appear'd in his Face, then disappear'd; and thus interchangeably (as it commonly happens) till in the Night betwixt the Seventh and Eighth Day, he was observed to be a little hot and thirsty, yet remain'd so but a few Hours; and then the Small Pox came out fair: They became round and yellow, like those of the more gentle distinct kind; and the Red Spots which appeared first, were the fullest and largest of all: They began to crust a few Days after, and then gently died away; so that the young Gentleman was quickly in a Condition to go Abroad with Safety. He had above an hundred in all upon his Body; but without any the least Disorder but what I have mentioned: And they all fell off, without leaving any one Mark or Impression behind them. This Operation was performed at Pera near Constantinople, in the Month of March 1717."

Lady Mary left Constantinople in 1718, returning to England by sea. In the spring of 1721 a smallpox epidemic occurred in London with a high fatality amongst children. In April 1721, Mary Montagu junior, her daughter, was inoculated in London. She was the first person known to be professionally inoculated in England. The inoculation was done by Maitland. He also inoculated Dr Keith's only surviving son on 11 May 1721. It is difficult to estimate how much publicity these two inoculations received. They were not reported directly to the Royal Society, as Maitland, as a mere surgeon, was not a Fellow, but Lady Mary, who was a most forceful personality, invited "three learned physicians of the College one after another to visit the young lady". One was Sir Hans Sloane, who had attended Lady Mary when she was suffering from smallpox. There is an element of vindictiveness in this invitation, and it is very unlikely that she would not have made this known to all her acquaintances. Other persons, friends, were invited to see the child and spread the news (and probably also the smallpox). Many interested in the proceedings would be amongst the élite of the land,

and undoubtedly included Princess Caroline, who figures so largely in the further investigation on inoculation.

Unfortunately, the records of the time tell us nothing. For reasons which we can well understand, Hans Sloane's account written in 1736, but not published until 1756, did not even mention the inoculation of Lady Mary junior—let alone any reference to Lady Mary's influence on the nobility or the Court. But a great deal of information can be disseminated by word of mouth, particularly by women, about a disease affecting their looks.

Probably many people played a part in bringing inoculation to the attention of the Royal House, which gave it a send-off lacking in other countries. In spite of de Castro's claim that in 1721 inoculation was already being done secretly in London, his statement on another matter—"*There are few or none*"—suggests that his capacity for strict accuracy was somewhat limited, and although it is wrong to credit Lady Mary with bringing a highly original technique to England, she did cause the first professionally performed inoculation to be done in England, and had the courage of her convictions to have it done on her own daughter.

The inoculation story is by no means limited to England. In 1716, Cotton Mather, a pastor in Boston, Massachusetts, had learnt from Onisemus, his negro slave, who had originally come from the Fezzan in North Africa, that the inoculation of smallpox was a relatively common practice in many parts of Africa. On 12 July 1716, Mather wrote to the Royal Society asking why this practice had not been tried out in England, and pointed out that when smallpox next came to Boston (it had been absent since 1702) he would put it to the test. Miller (1957) goes to some lengths to show that Cotton Mather put this idea to the Royal Society in London before he could have read Timoni's account of inoculation and thereby credits him with great insight, but although he undoubtedly had courage, shown subsequently, he presumably would have read the earliest account of inoculation by the Chinese method which had been reported in 1700, as well as the *Proceedings of the Royal Society* for 1713 and 1714, and may well have heard of the practice in Asia Minor from travellers, just as others had prior to the publication of proper accounts in the *Proceedings of the Royal Society*.

In Europe information about inoculation had also spread, presumably by Timoni's book, which was published in 1715 in Breslau, and also by Pylarini's book, which probably had a fairly wide circulation. Writing many years afterwards, Eller (1762) claimed to have inoculated a child during the 1719 outbreak of smallpox in Paris stimulated to do so by a Greek named Carazza who possibly knew of the practice from his own country. According to Woodville the inoculation was done by the latter and not by Eller. However, Dr. Eller apparently performed an inoculation two years later at Bernberg at the request of the Prince of Anhalt-Bernberg. This illustrates the interest of the non-medical intellectuals in preventing a disease which, unlike the other plagues of the day, struck particularly hard at the wealthy and aristocratic classes.

On 14 June 1721, points of law were examined as to the practicability of experimenting on condemned prisoners in Newgate Prison in exchange for granting them pardons. By July 1721, the newspapers were reporting that experiments were to be undertaken. A Dr. J. de Castro Sarmento, a visiting physician, wrote the first English treatise on inoculation, which was originally claimed to have been published in March 1721, and, if so, might well have influenced Lady Mary to proceed with inoculating her daughter. On the other hand, Miller (1957) claims it was not published until July 1721, which tends to increase the credit due to Lady Mary for the start of inoculation on English soil. If the book appeared in March, this might have been

partly instrumental in initiating the experiments on the Newgate prisoners, whereas if the book appeared in July 1721, after most of the preliminary work had been done, it is only fair to assume that the inoculation of Lady Mary's daughter and Dr. Keith's son must have been the incident which started active interest. It seems unlikely that Lady Mary would have remained silent in the court circles of conversation in view of the fact that in May 1721, virtually at the same time as her daughter and Dr. Keith's son had been successfully inoculated, Caroline, the youngest daughter of Princess Caroline, was thought to have smallpox. This must have caused a stir in royal circles, although the diagnosis was ultimately changed to scarlet fever. In July, Amelia, the second daughter, had a quinsy, which tends to suggest that the diagnosis of scarlet fever might well have been correct, and between July and August all three had measles. There is no real evidence that any member of the orthodox medical profession or the principals in the Royal Society were instrumental in arranging the celebrated trials, and it was not until August 1721 that Dr. Walter Harris, physician to Queen Anne, gave a lecture to the Royal College of Physicians on inoculation. At this time the theoretical knowledge of a most hesitant medical profession was of scanty substance compared with the practical experience of a very astute woman—Lady Mary—who, as stated before, appeared to know more about some aspects of the practice than Maitland. As I shall attempt to show later, the greatest stumbling-block to the acceptance of the practice by the orthodox profession, particularly the London physician, was the impossibility of explaining the practice on the then current but quite erroneous theories of the pathogenesis of disease.

Insufficient attention has, I think, been given to the part played by Caroline of Anspach, the Princess of Wales, in furthering the experiments on inoculation. Sloane in his account stated that they were wholly on her initiative, although this does not prove the fact. During this period of history when the Royal Society was discussing inoculation, the Prince of Wales and George the First, his father, were in complete opposition, and at one stage he and Caroline were virtually imprisoned in the Palace of St. James. In 1720, it was Caroline, along with Walpole, with whom she was very friendly, who arranged a reconciliation. Caroline and her husband both took an interest in the arts and the sciences of the day, and had demonstrations of scientific experiments given to them at Hampton Court. They were also friendly, particularly Caroline, with the intelligentzia of the day who were also the friends of Lady Mary. Even when her husband became George the Second, Caroline undoubtedly had very great power. The King trusted and depended on her judgement and there is nothing in her character against, and very much to be said in favour of, the possibility that Sloane was correct and that Caroline was largely instrumental in pressing for the trials on the Newgate prisoners. She herself had had smallpox at the age of three years, and was motherly enough to be anxious to protect her daughters—although, for other reasons, not her son. What part Lady Mary played in this we shall never know, but Maitland was her protégé and we have evidence that he asked the Princess for the opportunity.

Princess Caroline, Lady Mary, Cotton Mather, Benjamin Colman and many other lay people appear to have been largely responsible for initiating inoculation in the western world. These lay people rushed in where the medical profession, particularly the physicians of London, feared to tread.

The person who now appears on the scene, although by no means a newcomer, is Sir Hans Sloane, who had been called in to see Lady Mary when she had smallpox in 1715. He is now President of the Royal Society and a most influential physician to the King. Having previously

been Vice-President and Secretary, he was obviously completely *au fait* with all the activities of the Royal Society in its search for information about the practice of inoculation. Although Sir Hans Sloane was involved in the arrangements for the Newgate experiments, particularly in obtaining the consent of the King (George I), he was still unconvinced about many aspects

FIG. 203. Princess Caroline of Anspach. (*Reproduced by gracious permission of Her Majesty the Queen.*)

of inoculation, as he wrote to Tarry, who at that time was in practice at Enfield, on 29 July 1721 to get further information. Miller (1957) claims that Sloane was the principal person behind the Newgate experiment and the person who indirectly stimulated interest and deserved most of the credit for introducing inoculation into England. It is surprising, however, that he should be so unsure of himself to write to Tarry in July 1721, in view of the previous well-documented reports of Timoni and Pylarini and observations he could have made, if he had so wished, on the success of the inoculation of Mary Montagu junior and Dr. Keith's son. Miller lays

emphasis on the fact that Maitland was reluctant to take part in the experiment and do the inoculations. The only evidence that he was reluctant is Sloane's own statement made some fifteen years later in the latter's account of inoculation which, whatever the reason, might well have been inaccurate in this, as acknowledged to be in other details. Sloane's account claims that because of the attack of smallpox in Princess Anne, the Princess of Wales wished to have the other children inoculated. There seems no evidence that Anne ever had smallpox—if she had, the other sisters would most likely have contracted it from her. All the evidence suggests it was scarlet fever. The only account by someone without a vested interest or a hurt pride was that of Dr. Boretius, a visiting German physician. According to him, Maitland appeared before the Princess of Wales and asked to be allowed to experiment on some criminals. Was Lady Mary really behind this? It is obvious that Lady Mary would have had little time for Sir Hans Sloane as he represented the very type of physician she loathed, one who was so cautious as not to try inoculation earlier which he knew about and which might have resulted in her not being scarred. Maitland was a mere surgeon, an inferior being to both Lady Mary and Sir Hans Sloane, and he would largely have been in the position of a servant carrying out orders. Perhaps in front of Sir Hans Sloane he might have appeared reluctant as he was being pushed into it by a non-medical person in the form of Lady Mary. He was of a quiet, retiring disposition, but from his experience in Turkey he knew enough of the procedure to carry it out. Perhaps he also knew of the possibility of an unsatisfactory outcome! The final details were left to Maitland who sent Sloane a note on 7 August saying that he was doing the inoculations on the next day. The two royal physicians, Sir Hans Sloane and Dr. John George Steigherthal, were present, technically representing the King who was most unlikely to have been interested in the pursuits of Caroline or his son. Twenty-five physicians, surgeons and apothecaries, some of them members of the Royal Society or the College of Physicians, also attended.

Dr. Mead, a colleague of Sloane's, tried the Chinese method on another prisoner independently of the inoculation experiment which suggests that the orthodox physicians might not have been backing the experiment to any great extent and tried the Chinese method as a diversion in case Maitland's work failed. No one will ever know who was really the driving force behind these trials—in my opinion it was not Sloane but rather Princess Caroline and Lady Mary and other unknown lay people.

Although the newspapers of the day could hardly criticize an experiment under royal patronage, they were hostile to Dr. Mead, representing the orthodox physician, alleging that the young woman had been taken advantage of by placing the smallpox material in her nostrils whilst she was asleep (quoted by Miller, 1957). However, the comments of the newspapers were more against the "trials" giving an opportunity for felons to escape their punishment than any criticism of the practice itself.

Senior physicians such as Sloane and Steigherthal were still very doubtful of the protective value of inoculation, which hardly supports Miller's contention that Sloane was the principal mover behind the Newgate trials.

Sloane and Steigherthal, moreover, paid for Maitland, who had then returned to practice at Hertford, to employ the nineteen-year-old woman from the Newgate trials as a nurse to a person ill with smallpox at Christ's Hospital, and later as a test she slept with a ten-year-old child suffering from smallpox without catching the disease.

Although this experiment convinced many, as we shall see later, it did not convince Sloane.

The critics could point to the fact that with smallpox, such a common disease, the young woman might have had it herself without knowing it when she was younger, and in the Newgate experiment the very slight rash which she suffered might not have been variolous. Some contended that the inoculations gave rise to chickenpox, not smallpox, and would therefore not protect. It is difficult today to appreciate that our modern views on infection and immunity were quite unthought of. Some physicians of the time regarded severe and mild attacks of the same disease as being inherently different from one another. Others classed smallpox, chickenpox and other diseases all together, and although by 1767 Heberden described with some accuracy the characteristics of both chickenpox and smallpox, and Maitland in 1722 showed some knowledge of both, in 1866 Hebra, the celebrated Viennese dermatologist, still believed that chickenpox and smallpox were one and the same disease and this view was revived as late as 1925 (Sahli).

In the middle of November 1721, the next experiment was planned, again, according to the newspapers (quoted by Miller, 1957), at the instigation and expense of Caroline, the Princess of Wales. Orphan children of St. James's Parish in Westminster who had not already had smallpox were to be inoculated. It is of interest that those who had had smallpox were to be excluded. Negative results on these would have been quite an interesting experiment and supported the theory of the identity of the two diseases, natural smallpox and inoculated smallpox, which was still in doubt. There is always the possibility that there were some who recognized that a history of having had the smallpox might not always be correct and that some positive results in these individuals would have been difficult to explain.

There was some delay, however, and meanwhile, in February 1722, Maitland inoculated six persons in London, again under the Princess's patronage. About this time he also inoculated the first person with material taken from an inoculated case of smallpox and not direct from a natural case of smallpox (Maitland, 1722). This practice also appeared almost simultaneously amongst inoculators in Boston (Newman, 1722). All Maitland's work had the official backing of Princess Caroline and her husband. Doubtless the whole Court was interested, as this was the scientific marvel of the day. It is difficult to imagine that Lady Mary was far in the background if she could help it, but it would not have been polite to have recorded this in writing and belittle the patronage of the Royal Family.

In April 1721, smallpox had been brought to Boston in the English American colonies and by June was epidemic. Cotton Mather tried to carry out his earlier resolve to try inoculation, and his suggestion that this procedure should be adopted during an epidemic. He persuaded Dr. Zabdiel Boylston to inoculate the latter's six-year-old son and two negro slaves on 26 June 1721. By 17 July Boylston had done ten, although forbidden to do so by the local justices. The clergy, doubtless led by Cotton Mather, supported him. There was considerable opposition from the local justices backed up by the medical profession, and the usual war of words followed in the local press. Minor violence occurred, and on one occasion a hand-grenade was thrown into Cotton Mather's house.

Nearly 6,000 cases of smallpox were reported, with 855 deaths. Boylston inoculated 242 persons during this outbreak, and it is related that of the 855 deaths only six were among inoculated patients. These were the first of many figures which have been produced on variolation and vaccination to try and prove or disprove the value of the practice and which we now know to be so difficult to interpret due to the many inaccuracies of reporting which can occur. Apart from the possible concealment of the cause of death of some of the inoculated

patients, we now know of the frequency of missed cases of fulminating smallpox as well as of the very mild cases. It is not stated whether the inoculated persons who died were inoculated before they came in contact with the disease, or, as often occurred, whether they were inoculated during the incubation period of a natural attack. We see the use of the term "inoculated" to indicate a definite state of the individual, just as later we have to contend with the term "vaccinated," both without any qualification as to whether the inoculation was successful, whether infection had occurred and immunity resulted. The interval between successful inoculation and subsequent challenge by natural smallpox is also never mentioned, although not until later would this be of any practical importance.

There was opposition to such a practice right from the start, but not so much on technical grounds. "It appears in the world without the least recommendation from any of the learned, and not with very considerable opposition from the rich" (de Castro Sarmento, 1721).

To the high society of fashionable London, with rapidly increasing scientific knowledge, it was indeed humiliating to admit that such inferior beings as Turks or others in Middle East countries *could* possibly contribute knowledge to the superior West—not only this, but it was even a practice of the common people rather than the aristocracy of those parts.

As Wagstaffe (1722) says, the practice of a "few ignorant women . . . so far obtains in one of the politest nations in the world, as to be received into the Royal Palace".

On 16 November 1721, at a meeting of the Royal Society in London, Dr. William Douglass of Boston spoke against inoculation, quoting, "that of about 1,000 cases of smallpox, 60 had occurred in those that had been inoculated, some had had severe attacks and some had died". Although no information appears to have been available on the lines indicated to determine whether the individuals died because of, or in spite of, inoculation, this experience was vastly greater than that of Maitland in England, where at this time barely twenty had been inoculated, all "successful". It should be pointed out that these inoculations had been done on selected persons and when the risk of smallpox was very much less than in Boston.

Cotton Mather prepared an account of the success of inoculation in New England, and on 7 September sent it to England to be printed. It was published by Jeremiah Dummer, being dated 23 February 1722, and was given the title "An Account of the Method and Success of inoculating Smallpox in Boston in New England, in a Letter from a Gentleman there to his Friend in London", the writer remaining anonymous. Further tracts on inoculation were written, also by clergymen, Benjamin Colman, Daniel Neal and William Cooper, all from Boston. The continued interest of Princess Caroline resulted in Neal being called in audience when he visited London.

In 1722 Charles Maitland also published his account of inoculating the smallpox in which he described the inoculations on Lady Mary's children and the Newgate Prison experiments. As the first planned scientific experiment in immunology, it is worth showing as recorded in the original.

IN Obedience to their Royal Highneſſes Commands, I performed the Operation of Inoculating the Small Pox, on Six condemned Criminals at *Newgate*; in Preſence of ſeveral eminent Phyſicians, Surgeons, and others. *The*

(21)

The Names of the Criminals are,

1. *Mary North* ——	Aged	36	Years,
2. *Anne Tompion* ——		25	
3. *Elizabeth Harriſon*		19	
4. *John Cawthery* ——		25	
5. *John Alcock* ——		20	
6. *Richard Evans* ——		19	

Auguſt 9. 1721. Being *Wedneſday*, betwixt the Hours of 9 and 10 in the Morning, I made Inciſions in both Arms and the right Leg of all the Six.

10 *and* 11. *Thurſday* and *Friday*, I find little or no Alteration in any of them, except *Mary North*, who ſometimes was troubled with Vapours, as uſual to her: They all ſleep well, dreſs, and walk about all day, and are hungry for their Food: Their Pulſe a little rais'd, but without any ſenſible Diſorder.

12. *Saturday*, In the Morning obſerving the Inciſions not ſo much inflamed, and tending to Suppuration as uſual; and thence ſuſpecting the Matter ingrafted to have been defective and languid, having been kept at leaſt 15 or 16 Hours, for a very good, but unavoidable Reaſon; I ſearch'd for freſh Matter, and having found it in *Chriſt's Hoſpital*, about 6 a Clock at Night I made new Inciſions in each Arm of five

of

(22)

of them, and ingrafted it as before. I had no Matter left for the ſixth, *Evans*.

13. *Sunday* Morning, theſe five complain all of Pain in both Arms: Having taken off the Dreſſings, I find all the firſt Inciſions inflamed and feſter'd, but without any Sickneſs in the Patients; their Pulſe ſenſibly higher, and their Water turbid.

14. *Monday* Morning, red Spots and Fluſhings appear on all the five; but moſt of all on *Mary North*, eſpecially about her Face, Neck, and Breaſt: And ſo likewiſe on *Ann Tompion*: But without any Sickneſs, Head-ach, or Thirſt; except a little they complained of in the Night; and a higher Pulſe.

15. *Tueſday*, The ſame Spots and Fluſhings appear freſh in the Morning; but turn paler and darker towards Night, yet without any Diſorder.

It is here to be obſerved, That the ſixth, *viz. Richard Evans*, who had had the Small Pox in Priſon laſt *September*, has had no manner of Pain, Heat, or Inflammation in any of his Inciſions, nor any manner of Alteration otherwiſe: But all continuing pale from the Beginning, yeſterday dry'd up entirely.

16. *Wedneſday*, They all continue much as before, only their Inciſions begin to diſcharge a thick, purulent Matter. *Anne Tompion* has a large yellow Puſtule on the bending of her Thigh, and another on the outſide

(23)

outſide of her right Arm, like Small Pox: And *John Alcock* has more freſh Puſtules appearing on his Face and Arms; having had a ſlight *Febricula* in the Night, with diſturb'd Water. And *John Cawthery* has a large yellow Puſtule on his left Cheek, and ſeveral ſmall ones on his Face.

17. *Thurſday*, The ſaid *Alcock* has theſe Puſtules appearing now fairly, with a yellow digeſted Matter, and red Bottoms, and a great many of them, but without Sickneſs. *Ann Tompion* has the ſame yellow Puſtules on her right Arm and Thigh, with other freſh ones ſtruck out about her Chin and Mouth.

18. *Friday*, *Alcock's* Small Pox appear ſtill fair and yellow, but fuller and larger, with a bright red round them. All the others much the ſame, with their Inciſions running.

19. *Saturday*, Laſt Night, this *Alcock* unaccountably pricks and opens all the Puſtules he could come at with a Pin; which occaſions them to fall and cruſt ſooner: But they continue red at Bottom; and the Inciſions in him abate of their Running.

It is here to be noted, that tho' he has had by much the greateſt Number of Puſtules or Small Pox upon him, yet the ſecond Time he was touch'd in one Arm only, there not being Matter enough for the other Arm; whereas the other four had both Arms ingrafted, and Matter in Abundance.

(24)

20 *and* 21. *Sunday* and *Monday*, All of them continue as before: The Inciſions on the other four, run ſtill a thick, digeſted, yellow *Pus*.

Here I muſt obſerve, that the ſecond Inciſions in both Arms, by which a vaſt Diſcharge has been made, ſeem to me, in the Iſſue, to have been rather a Prejudice and Impediment to the *Eruption*, than to have, in any Sort, contributed towards it: But however, I believe them to be, in all Reſpects, as ſafe from any future Infection as *Alcock*, who had 60 Small Pox, at leaſt upon him.

22 *and* 23. *Tueſday* and *Wedneſday*, All of them continue well; and their Inciſions ceaſe running, and dry up apace.

24. *Thurſday*, I purg'd *Alcock* and *Cawthery* for the firſt Time; and did deſign alſo to purge the three Women; but was prevented by their *Monthly Purgations*, which, I was not a little ſurpriz'd to hear, ſeiz'd them all about the ſame Time; tho' ſome of them had been obſtructed ſeveral Months before.

28. *Monday*, *Mary North*, before ſhe was quite free, unaccountably waſh'd in cold Water, and thence caught a violent Colic, which laſted near two Days.

30. *Wedneſday*, They all three take a purging Potion, which anſwers the Intention, and perfectly carries off *Mary North*'s Colic Pains.

31.

(25)

31. The two Men are again purg'd, in Order to their being diſcharg'd: And ſo likewiſe, next Day, are the Women.

And on the Sixth of *September*, they were all diſmiſs'd to their ſeveral Counties and Habitations.

On 17 April 1722, after consultation with Sir Hans Sloane and in the presence of Steigherthal and Maitland, Claude Amyand, the King's surgeon, inoculated Princess Amelia, aged eleven, and Princess Caroline, aged nine. Sloane, far from being the advocate of inoculation, was still very hesitant when asked to give his opinion for the benefit of Princess Caroline (Princess of Wales). He was the emissary sent to ask the King's permission, where his opinion was equally lukewarm. As at this time the King disliked the Prince of Wales intensely and they were not on speaking terms, it seems doubtful, particularly in view of Caroline's powers, whether he would have acted otherwise whatever Sloane had said. Four days later the two-year-old son of the Earl of Sunderland died, reputedly from the effects of inoculation. This would have been the eighteenth day after the inoculation, so that the death, assuming it had any real connection with inoculation, would most likely have been from broncho-pneumonia. There is no proof, of course, that death was not from some intercurrent disease quite unconnected with inoculation. The report on the post-mortem examination gives little help to establish the cause.

Amyand, besides inoculating his own children, had, the day after the royal inoculations (18 April), performed it on the six children of Lord Bathurst, a friend of Lady Mary's. On 30 April a nineteen-year-old footman of Lord Bathurst's was inoculated, "a strong hale young man", but he died from smallpox on 19 May, "following exposure to the Bathurst children" (*The Post Boy*, 1722, quoted by Miller).

One can see here the first of the many mistakes in interpretation of the course of simultaneous natural and cutaneous infection. Lord Bathurst's nameless servant was exposed to natural smallpox, that is respiratory infection from the six Bathurst children, on about the 25 or 26 April, the seventh or eighth day of their inoculated smallpox. He was, however, inoculated four or five days after contact with their infectious stage, and in my opinion contracted natural smallpox and died from the effects of the natural and not the inoculated disease.

The trouble, however was caused. Considerable publicity was given to these cases, and Maitland only performed twelve more inoculations that spring, and by early summer the practice in London had temporarily stopped. In spite of the warnings in the earlier writings (Timoni, 1714; and Lady Mary, 1718: letter to her husband) of the desirability of sending someone else to collect the smallpox matter so as to avoid infecting the inoculated person simultaneously with the natural disease (from respiratory virus on clothing, or in other ways from an infectious patient), it seems clear that Amyand as well as Maitland did not realize the effect of inoculating simultaneously with, or after contact with, natural smallpox in confusing the statistics of inoculation. The same problem was to come in the vaccination controversy in the next century.

It might be regarded as natural for the public to be critical of two reported "deaths from inoculation" in so few cases, an experience quite at variance with the writings of Timoni, Pylarini, or even Lady Mary. However, even more powerful factors affect public opinion—ignorance and prejudice dominate the whole story. The picture is painted so vividly by Cotton Mather (1722) in his account of public reaction, a situation encountered by medical officers of health since, when endeavouring to introduce control measures amongst an ignorant population.

> "I must say it, I never saw the Devil so let loose upon any Occasion. A lying Spirit was gone forth at such a Rate, that there was no believing any Thing one heard. If the inoculated Patients were a little sickish, or had a Vomit given them, it was immediately reported, That they were at the point of Death, or actually dead. While the Patients lay blessing and praising Almighty God, for shewing them this easy Way to escape a formidable Enemy, it was confidently reported, That they bitterly repented of what had been done upon them, and would not, upon any Terms, be brought into it, if it were to do again. When the Patients had their incisious Places, either actually and perfectly heal'd in some, or within a Day or two of it in others, it was confidently reported, That they were perishing under terrible Ulcers, and had their Arms or Legs rotting off.
>
> These, and the like Things, were asserted with such impudent Confidence, even by such as liv'd in the nearest Neighbourhood, that one was almost ready to fear a Beating, if they durst offer to question them. Then the People would assert, that here were Persons on the very Spot, who underwent the Inoculation in England a great many Years ago; but afterwards had the Small-Pox in the common Way, and, they said, they would bring these Persons to us. A few minutes after, they would assert, that it was never practis'd in England; but there was an Act of Parliament which made it Felony; and, they said, they would produce the Act to us. But never any Patient had so many Pustules of the Small-Pox, as there were Lies now daily told, and spread among our deluded People.
>
> That which much added to the Misery, was, that the People who made the loudest Cry, (who most commonly were what we may not improperly call of the confluent Sort, and such also as were past the Dangers of the Small-Pox themselves) had a very Satanic Fury acting them.
>
> They were like the posses'd People in the Gospel, exceeding fierce; insomuch, that one could scarce pass by the Way where they were to be met withal. Their common Way was to rail and rave, and with Death, or other Mischiefs, to them that practis'd, or favour'd this devilish Invention. To inflame them in their Transports, and harden them in their Violences and Exclamations, they pretended Religion on their Side; and charg'd all that were not so, with denying and renouncing the divine Providence, and I know not how many more Abominations; yea, with going to the Devil, and the God of Ekron. And how strangely they treated the most meritorious Ministers of the Gospel, who did not come into their Frenzies, I leave unmention'd. Father forgive them."

The panic in Boston was, of course, largely due to the fear induced by a large-scale epidemic of a disease with a high mortality, and the deaths in persons who had been inoculated, whether due to the inoculation or not, could not be explained to a frightened public. In London smallpox was endemic with sporadic epidemics. In Boston it was wholly absent except at intervals of a number of years when large epidemics occurred (1689, 1702, 1721, 1730, 1738).

In England, professional opposition to inoculation commenced in the early summer of 1722 with a pamphlet by the surgeon Legard Sparham (1722), who did not believe that it gave rise to smallpox.

On 8 July, the Reverend Edmund Massey preached his celebrated sermon in St. Andrew's Holborn, on the evils of inoculation. His plea was not only that the practice was dangerous, but that disease was an act of God, a punishment for our sins and we had no right to interfere with divine providence. A theme repeated many times in the nineteenth-century vaccination controversy and not entirely dead today.

Nettleton of Halifax inoculated the largest series in England in 1722; he did sixty-one, but he soon ran into local opposition. However, he sent his results and his views on the necessity for an adequate trial to Jurin, the Secretary of the Royal Society. Jurin, to whom greater credit is really due as an enlightened scientific investigator, carried out one of the earliest real assessments of an agent of this kind. His attempt at accuracy is most commendable, as the advertisement asking for information given below shows.

ADVERTISEMENT

"All Persons concern'd in the Practice of inoculating the Small Pox, are desir'd to keep a Register of the Names and Ages of every Person inoculated, the Place where it is done, the Manner of the Operation, the Days of sickening and of the Eruption, the Sort of Small Pox that is produc'd, and the Event.

"Where the true Small Pox is not produc'd by Inoculation, it will be of Use to take particular Notice, whether the Patient had any other Kind of Eruption, what Symptoms preceded or attended it, whether the Incisions inflam'd and run, and for what Time their Running continu'd.

"In Case any Person shall happen to die after Inoculation, either in the Course of the Small Pox, or after they are gone off, it is desir'd that a particular Relation of the Case may be made, and attested, if it be judg'd necessary, by the nearest Relations of the Party deceas'd, or by other credible Persons, that were Witnesses to the Fact.

"They are intreated to send these Accounts, or an Extract from them, comprehending all Persons inoculated from the Beginning, to the End of the present Year, to Dr. Jurin, Secretary to the Royal Society, some Time in January, or at farthest in February next, that so the Result of them may be publish'd early in the Spring."

He was backed up by Arbuthnot (1722), who had already replied anonymously to some of the earlier critics. Jurin set about compiling statistics of inoculations to assess the real mortality from this practice. He assumed without any trial that it would protect against subsequent smallpox, a view challenged by many. It is well to remind the reader that with the confusion between chickenpox and smallpox and with other eruptions as well, the idea that second attacks of the disease were extremely rare, or even impossible, the basis of inoculation, was by no means accepted by all. Jurin lumped together all the statistical evidence from various sources in England as well as the figures from Boston. He was, of course, in a hurry to get as much evidence as possible, but it seems doubtful whether all the deaths from inoculation would be recorded, particularly by some of the more amateur inoculators, and there can be little doubt that some of the deaths ascribed to inoculation were not due to this at all. The Bills of Mortality gave figures of recorded deaths from smallpox in London only. The incidence of

smallpox elsewhere was quite unknown, although it was usually deduced from crude mortality figures and from case fatality rates based on figures in small country towns where a local practitioner might be able to produce figures of both cases and deaths. However, the total population of London was not known at the time and the risk of smallpox to any person in any one year was impossible to assess.

From the Bills of Mortality for London, Jurin concluded that 2 out of 17 deaths from all causes were due to smallpox, whereas the case mortality from inoculation varied from about 1 in 60 in Boston to 1 in 91 in England. It is of some interest to compare these figures with Rosenwald's (1951) observations on inoculation of smallpox in Tanganyika, where to his surprise he found "only one person who died after variolation (this patient was infected naturally) though I have heard of others. On the other hand, the vast majority of cases which I have seen, following variolation, have been very mild. At three villages I found all the children and young persons to have been variolated, not one having had a severe attack".

Nettleton of Halifax was able to give case mortality figures for smallpox in Yorkshire of 43 out of 276 (15 per cent), 59 out of 297 (19 per cent), and 28 out of 268 (10 per cent). These figures only afforded a comparison of the risk of anyone dying of smallpox, assuming that they caught it at some time of life with the inescapable risk of inoculation.

Besides the inclusion of deaths from natural smallpox amongst those inoculated during the incubation period, Jurin's early accounts show some died from pyaemia, probably from the treatment of the inoculation site rather than from the primary effect, and at least one would appear to have subsequently died some months later from pulmonary tuberculosis. It seems clear that in the search for a "favourable kind" of smallpox eruption for inoculation purposes, the operator, particularly the apothecary or layman, might use smallpox material contaminated with virulent secondary organisms, particularly as it was the English and Boston practice to take the "ripe" pustules. On occasion streptococci or staphylococci without any variolous material were probably taken from some types of pustular dermatitis and with the deep incisions commonly used were quite likely to give rise to cellulitis, erysipelas or septicaemia and no immunity. Some types of chickenpox lesions could also be used without producing immunity against smallpox. The difference in effects between the English and Boston inoculations and the original Graeco-Turkish ones might, to some extent, be accounted for by the more vigorous methods of the Western inoculations which were the basis of some of Lady Mary's criticisms. Deep incisions with the lancet right through the "dermis" and massive doses of infectious material, the incisions being kept open by plugging with linen thread or some such material, might well have produced a larger number of more generalized rashes. Presumably, some, as in one of Jurin's fatal cases, were done on children with infantile eczema.

Although the controversy became much more complicated in the middle of the century, by 1725 organized opposition saw to it that notices of deaths were published in the press in a manner calculated to deter any save the most adventurous.

> "March 16, died Mrs. Eyles, niece of Sir John Eyles, alderman of London, of the smallpox contracted by inoculation. June 17 died of the smallpox contracted by inoculation Arthur Hill, esquire eldest son of Viscount Hilsborough. August 12, died of the smallpox by inoculation——Hurst, of Salisbury, Esquire" (Miller, 1957).

The final reported figures for 1721–8 for the British Isles, American Colonies and Hanover, compiled by Jurin and his successor Scheuchzer, were 897 inoculated; 845 had "true smallpox",

13 imperfect smallpox, and in 39 there was no effect. Seventeen died reputedly from the effects of inoculation, about 1 in 50. A very balanced view was put earlier by the Reverend Colman of Boston (1722):

> "Only one gentlewoman has yet died out of 100 who have now passed through the operation, but as you must needs suppose, in a town so full of infection as this has been, some ten or twelve of this number appeared to have taken the infection in the common way (among whom the person deceased was evidently one) and accordingly they had it of the confluent kind, or in a fulness of the distinct sort not known among the inoculated in the Levant. This will be so far from seeming strange to you, that indeed it would be next to a miracle had it been otherwise. At the same time it must be allowed that a good number of those that passed so favourably through the inoculation, would probably have had it very favourably in the common way; but that so many should pass so favourably and easily as well as safely through the inoculation; while their neighbours had so many in every hundred that suffered so much, as well as died; is a sufficient distinction put by providence on the method."

In the eyes of the supporters of inoculation the most important figure was the take rate of 845 out of 897; 94 per cent had "true smallpox". The accidental infection and even death of contacts of the inoculated was publicized to prove the true nature of the inoculated disease. (Fig. 204). Maitland in 1722 wrote thus:

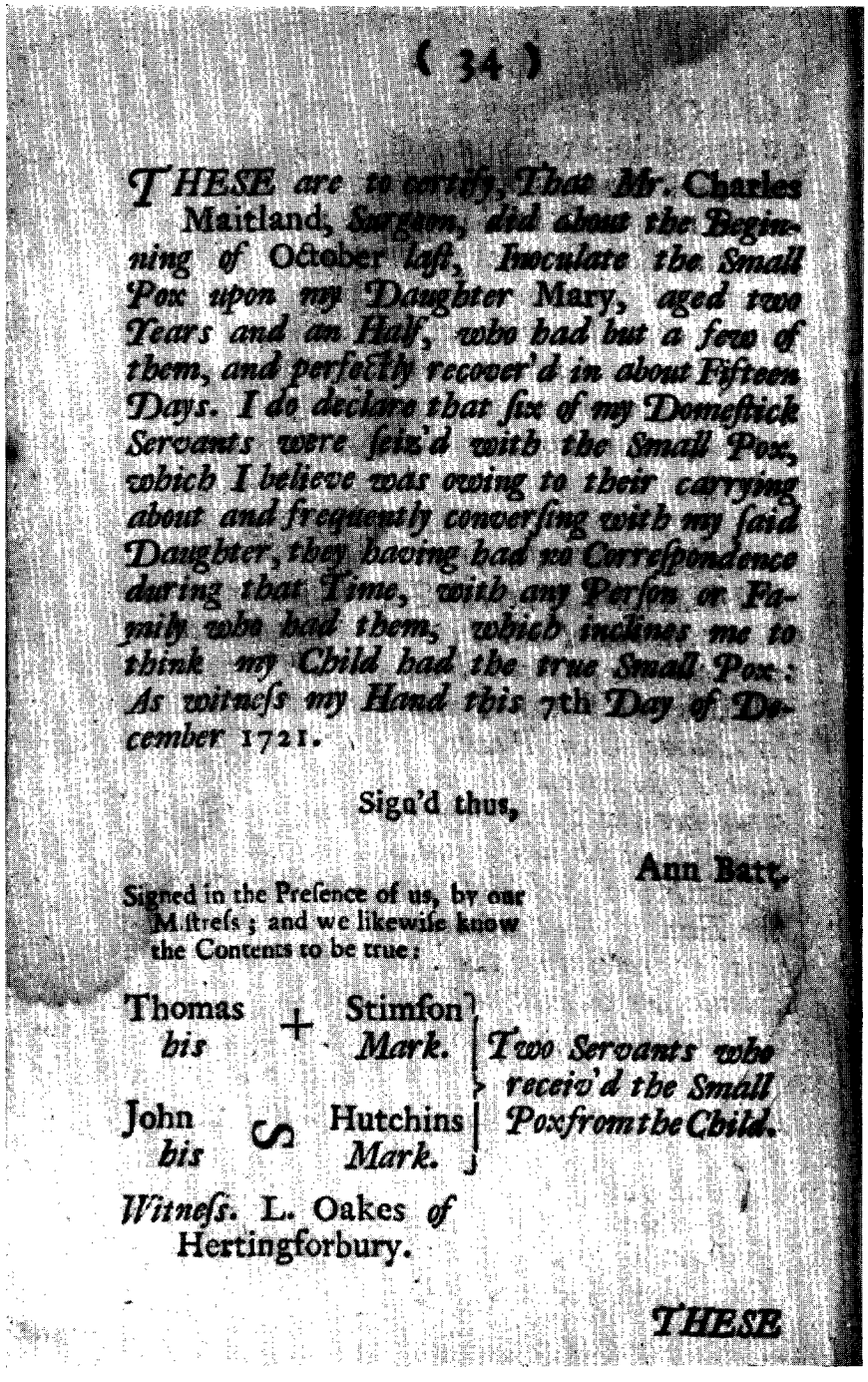
> "What happened afterwards was, I must own, not a little surprizing to me, not having seen or observed anything like it before. Six of Mr. Batt's domestick servants were all seiz'd at once with the right natural Small Pox, of several and very different kinds; for some had the round distinct Sort, some the small continued, and others the confluent; all of 'em had a great many, but especially the last, with the usual bad Symptoms, and very narrowly escap'd: But they all (God be thanked) did well, (except one Maid, that would not be govern'd under the Distemper, who dy'd of it) and now enjoy a perfect State of Health."

Assuming that the risk of contracting smallpox was very high, for example in London or in Boston during actual epidemics, the case mortality of inoculation of 1–2 per cent compares very favourably with the overall mortality of natural smallpox of the time between 10 and 30 per cent. In a non-epidemic period, and particularly in the remoter parts of the country away from London, a certain risk of 1 per cent mortality against an extremely speculative risk of smallpox was quite another story. It is not always appreciated that with a short expectation of life, men realized that natural smallpox was a risk, but only one of very many.

In Jurin's report in 1724 he put the problem neatly. "People do not easily come into a practice, in which they appreciate any hazard, unless they are frightened into it by a greater danger." The aristocracy were particularly conscious of the disease, not because of any inherent greater susceptibility, although this is sometimes claimed, but due to their more secluded upbringing they had a greater liability not only to death at an important age, but to disfiguring scarring, particularly tragic in an otherwise unblemished young adult.

In the New World, inoculation of quite large groups occurred (for example, Amazon Indians) by Carmelite missionaries (Crookshank, 1889). A sugar-plantation owner also inoculated a large number of slaves, doubtless for less altruistic reasons (Crookshank, 1889).

Creighton, Klebs and others believed that inoculation died out completely in England



(34)

THESE are to certify, That Mr. Charles Maitland, *Surgeon, did about the Beginning of* October *laſt, Inoculate the Small Pox upon my Daughter* Mary, *aged two Years and an Half, who had but a few of them, and perfectly recover'd in about Fifteen Days. I do declare that ſix of my Domeſtick Servants were ſeiz'd with the Small Pox, which I believe was owing to their carrying about and frequently converſing with my ſaid Daughter, they having had no Correſpondence during that Time, with any Perſon or Family who had them, which inclines me to think my Child had the true Small Pox: As witneſs my Hand this 7th Day of December* 1721.

Sign'd thus,

Ann Baty.

Signed in the Preſence of us, by our Miſtreſs; and we likewiſe know the Contents to be true:

Thomas *his* + Stimſon *Mark.*
John *his* S Hutchins *Mark.*
} *Two Servants who receiv'd the Small Pox from the Child.*

Witneſs. L. Oakes *of* Hertingforbury.

THESE

FIG. 204. Certificate to verify that inoculation produced genuine smallpox.

between 1728 and 1740. Miller (1957) shows that this was not true, though this view was advanced earlier by Guy in 1882. Although the College of Physicians in London was silent, the Royal Society, the original instigators of research into the subject, continued to listen to many papers, the majority being in favour of the practice. A number of inoculation exponents were elected Fellows for their work in this subject, so there can be little doubt that the majority of Fellows firmly believed that inoculation would prevent smallpox, but it is much less clear that there was an opinion, let alone uniformity of opinion, that large-scale inoculation should be done. The Society, however, seems to have gone to some considerable length to reply in the lay press to horrific and inaccurate accounts therein.

The strongest opposition came from the Church. Miller (1957) quotes this letter of Beeston's from Ipswich:

> "The practice of Inocculation in this town, has so inflamed the angry passions, & stirred up the bitter Zeale of the biggotted high churchmen, and dissenters, to such a degree: that they sentence to damnation, all that are any way concerned in it. They say the practice is heathenish, and diabolicall; it is distrusting providence, and taking the power out of Gods hand; it will draw down divine Judgmente, and for the proof of this point, they are so stupid as to urge, that God has begun to show his displeasure against it & us by that great mortality that is amongst us, tho not one that has been in ye practice, has fallen by it. This and a great deal more they say, but reason they do not, upon the Subject." (W. Beeston, 1724.)

Miller also quotes this letter of the Rev. John Hough (1737) which reflects the view of many common people:

> "Notwithstanding this [he continued], the method loses ground, even in this country; for parents are tender and fearful, not without hope their children may escape this disease, or have it favourably; whereas, in the way of art, should it prove fatal, they could never forgive themselves; for this reason, nobody dares to advise in the case."

In the Royal Society, papers were read on this subject in 1729 (2), 1730 (2), and 1731–4, and there are the records of inoculations in Pembrokeshire and elsewhere (Evan Davis, 1733). It is assumed that inoculation declined in England in the 1730's, because of a low incidence of smallpox in London. On the other hand, in spite of the attempts at accuracy of Jurin's "reported cases", we have no idea, or perhaps a false idea, of what was going on in the country as a whole. Jurin's quest for exactness probably frightened off many of the amateurs from recording their results. In the peak year 1725, Jurin only recorded 152 inoculations for the whole country, and it seems highly improbable that this was the actual number done, particularly as the practice was not restricted to persons with any sort of medical qualification. In any case, we only have figures for smallpox deaths for London (in the Bills of Mortality) and have very little knowledge of what was happening elsewhere. London certainly had no spectacular epidemics in these years, the recorded incidence being "average".

It seems probable that it was not the number, but the quality of those who died from the disease that would most affect the limited public opinion of the day. In writing of the severity of smallpox in the community there is often confusion between frequency of the disease in the population, that is incidence, and case mortality. The latter can be greatly affected by errors in diagnosis, particularly by confusion with chickenpox, and there is always the possibility that variola minor was also introduced from time to time.

In 1731 Lobb, whose treatise on the clinical aspects of smallpox is very sound, thought that inoculation should be limited to times of epidemic because of the very real danger of introducing the disease in an area where it *did not already exist*. Too much has been written to create the idea that in this period smallpox was present everywhere. With the poor communications of the early eighteenth century, there is little doubt that many places could be completely free of the disease for many years. It is perhaps significant that it was possible to find felons to inoculate in Newgate Prison, all over nineteen years of age, who almost certainly came from the lowest stratum of society and who had not previously had smallpox. London, in contrast to much of the remainder of the country, was never free from the disease and therefore the physicians and the public looked at the problem in a totally different way.

Miller (1957) points out that, in 1738, *Chambers's Cyclopaedia*, a work for the general public, mentioned the practice of inoculation without any special comment, and in the American colonies in a further epidemic in Boston in 1738, over 400 persons were inoculated.

Inoculation in England was stimulated by the arrival of John Kirkpatrick, a physician from Charleston in the Carolinas, who had been persuaded to carry out inoculation in the 1738 outbreak by a Mr. Mowbray, a surgeon from a British man-of-war in harbour. The measure was done only in the face of a severe epidemic.

Kirkpatrick, whose original name was Killpatrick, not particularly apt for an inoculator, was given to considerable self-advertisement and, as Miller (1957) points out, was chiefly instrumental in creating the myth that he reintroduced inoculation into England. This was strengthened by his part in the founding of the Smallpox and Inoculation Hospital in London in 1746.

However, by 1743 the governors of the Foundling Hospital had decided that all children in the hospital and those admitted over the age of three, who had not had the disease, would be inoculated. Apart from the inoculation of American slaves, this would appear to be the first example of compulsory inoculation of a group and maintaining immunity of the herd by this method. This would be wholly successful as the children would not be retained after the age of ten or twelve. This practice continued without a break until superseded by vaccination. This Institution carried out valuable experiments on the clinical aspects and technique of inoculation.

The return of a higher incidence of smallpox in London in 1746, the highest since 1736, stimulated public opinion that something should be done about the disease amongst the poor. Although Miller states that "the upper classes were already preserving their children by inoculation, it was done quietly with little publicity", we really have no knowledge of how many, probably far fewer than usually supposed; even members of the Royal Family were neglected. Smallpox still occurred in the upper classes and a past history of the disease was virtually an essential qualification for employment in the noble's household to obviate the risk of bringing infection by this means. What reliance was placed on scars or on a history of the disease was not known; either could be wrong.

Woodville in 1796 gave an interesting account of the history and development of the Smallpox and Inoculation Hospital founded in London in 1746. Although some cases were already admitted to infectious-disease wards in a number of hospitals and infirmaries in the country, this scheme proposed a hospital for persons naturally infected with smallpox, with an additional building for inoculating the poor. It was backed by important people like the Duke of Marlborough and the Bishop of Worcester. A small house was taken in Windmill Street, Tottenham

Court Road, and first opened in July 1746 under the title of Middlesex County Hospital for Smallpox. A second house was provided in Bethnal Green and a third house in Old Street. By 1747 the subscriptions had amounted to over £1,000. The house in Windmill Street only had thirteen beds and therefore a move was made to Mortimer Street, Cavendish Square. The local inhabitants, however, complained of its presence and, the charity having been compensated, it moved from Mortimer Street to Lower Street, Islington. By 1750, three houses were in use, one in Old Street for preparing the patients, another in Frog Lane, Islington, for receiving them "when the disease appeared", necessitating the transfer of patients from one to the other, and a third in Lower Street, Islington, as a normal smallpox hospital. Although for the "poor", all patients for inoculation were admitted only on the recommendation of a subscriber.

From 1748 Dr. Archer was the physician but, although anxious to promote inoculation and supported by a strong committee, very little progress was made. In 1750, although six hundred cases of smallpox had been cared for, only thirty-four persons had been inoculated. It would appear that not until 1751 was the practice regularly carried out. From 1752 until 1768, the numbers rose fairly steadily from 100 per year to just over 1,000. It is of interest that of the individuals who came for inoculation, presumably with no history of smallpox, about 1 in 250 appeared to be already immune. The procedure was greatly hampered by the insistence on preparatory courses of medicine and diet for a month before inoculation, so that each patient was confined for practically two months before the process was complete. Each house was given over to the reception of patients of one sex at a time, but it would seem very unlikely that patients were retained without some contact with the public during their stay. In 1752, a building in Cold Bath Fields was opened both as a smallpox hospital and as a house of preparation for the inoculated, and in all it had 130 beds. The new hospital, like all the former, was opposed by the local people and an application was made to the Court of Chancery for an injunction against the use of the buildings as a smallpox hospital. The Lord Chancellor gave a ruling that no nuisance had been proved. However, local opposition was so great that patients leaving hospital were abused and insulted and all the discharges were therefore made at night. The site of this hospital is at present occupied by King's Cross Railway Station.

The hospital authorities made a real attempt, with scientific advice of the time from the Rev. Dr. Hale, a vice-president, to control the risks of infection by the design of the buildings, and their ventilation, and by separate preparation, inoculation and smallpox wards. In the face of smallpox outbreaks much inoculation was done in persons' homes by individual surgeons, ministers and other interested persons. In some instances the former were paid by wealthy landowners to do the work, and even the General Dispensary in London undertook to "inoculate the poor in their own homes". Although much of the pressure occurred in times of epidemic when in small communities the remainder of the non-immunes were inoculated, the action of many individual surgeons and others and of the Public Dispensary must have contributed enormously to the spread of the disease, whereas the proportion of the total susceptible population inoculated even during the epidemics must have been too small or too late to really affect the spread of the disease by interposing a barrier of immunes. It seems possible that the major outbreak of 1752 was largely due to the spread of infection by inoculation. It gave rise to more inoculation, as by this time there was no doubt in the minds of most that, compared with natural smallpox, it was the lesser of two evils. From 1752 to the turn of the century was the inoculation age in England.

It is rather refreshing to get evidence of the experience of ordinary people as distinct from the not unbiased views of the medical profession or other participants.

On the top of an isolated hill, Bow Hill, in Sussex, there lies a small cottage. Even today it is surrounded by trees, and doubtless two hundred years ago it was even more isolated. On two of the doors in the living-room are carved the names of nineteen persons inoculated between 1753 and 1788 (Figs. 205 and 206). The first case thus appears to have been done soon after the increased incidence in London in 1752. Steer (1956), who first reported this interesting find, thought that this was an early example of an isolation hospital. It would appear, however, that this was an inoculation house probably privately maintained on the West Dean estate of

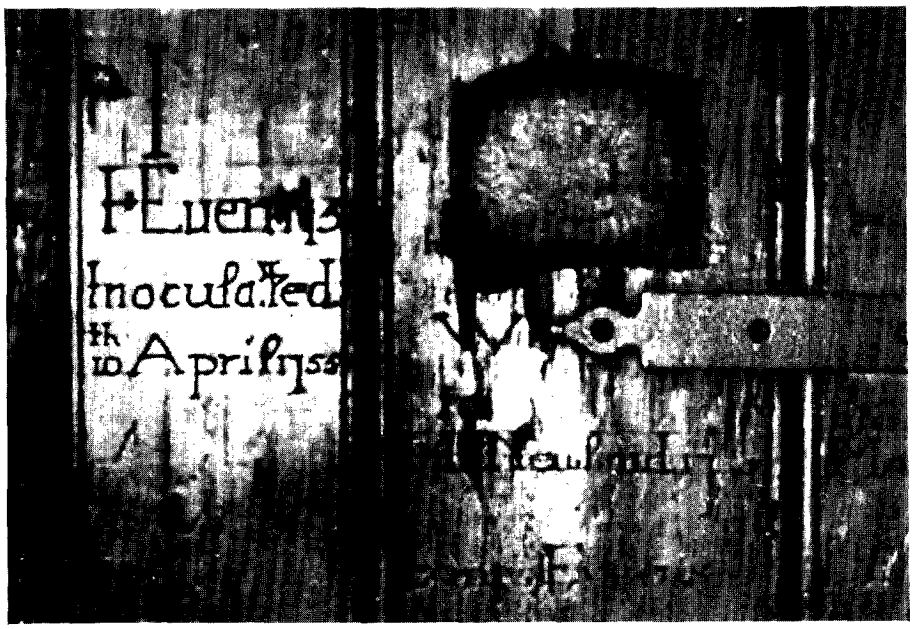


FIG. 205. One of the names carved in 1755 on a door in Blackbush Cottage, Bow Hill, Sussex, used as an inoculation house.

Sir John or James Peachey, a prominent merchant in the City of London, who was subsequently given the title of Lord Selsey. Who the individuals were whose names appear on the doors we shall never know. Steer has checked from registers that some were local people. From these records it would seem that one, Jane Peachey, was seventeen years of age; Richard Cablin could have been twelve, but it is possible that the carving relates to his father, also Richard, who possibly would have been thirty-five years or more. I think that these individuals were relatives or recruits to the house staff of the lord of the manor and were probably inoculated prior to being taken into employment which would bring them in close contact with the family. The fact that inoculations were carried on at intervals over some twenty years suggests that it was a private inoculation house rather than one which was being maintained by some practitioner from the nearby town of Chichester. This episode also illustrates that safe inoculation with adequate isolation of the patients was only possible for the

wealthy in such private houses or in the establishments later set up by Daniel Sutton, Dimsdale and others. The use of the very isolated Blackbush Cottage, rather than a house near to the manor, suggests that the fear of introducing the disease into an area already uninfected was very real and appreciated by some of the more responsible lay people in contrast to the well-meaning but unwise policy of the Inoculation Dispensary backed by otherwise very sound physicians such as Lettsom.

The increasing use of inoculation, however, had little effect on reducing the mortality rates.

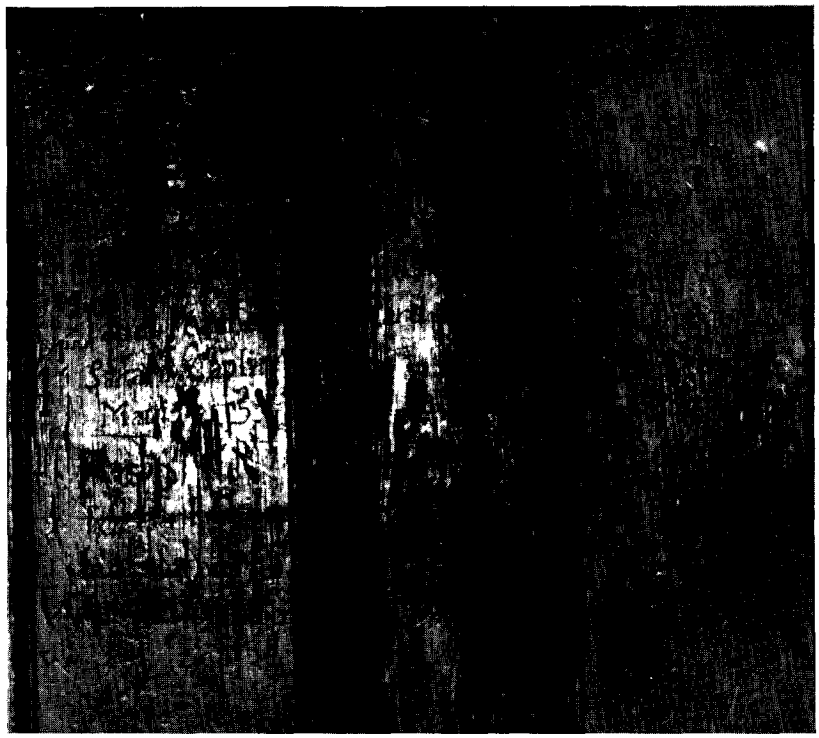


FIG. 206. Names of persons inoculated and carved on the doors in Blackbush Cottage, Bow Hill, Sussex. The dates run from 1750–77.

In the London Bills of Mortality, 1796, an auspicious year, that of Jenner's experiment, had the highest ratio of smallpox deaths of the century (Guy, 1882).

In any case, the recurrence of high ratios every two or three years showed that the often-repeated assertion, that when an epidemic occurred nearly everybody was attacked was quite untrue, even allowing for the relatively less stable population of London. It also shows that the amount of inoculation in itself had an insignificant effect on the ratio of immunes to susceptibles at any one time and played a much more important part in spreading the disease.

As we have already seen, inoculation in the hands of the orthodox physicians and surgeons of the time had an appreciable mortality, and yet others, for reasons that we will discuss later, appeared to be able to inoculate a large series of patients without any deaths (Woodville, 1796).

In 1757 Robert Sutton, an apothecary of Framlingham and afterwards of Ipswich, claimed to have discovered an infallible method and in the subsequent eleven years is said to have inoculated 2,500 people without a death. His son Daniel, however, was the man who made a personal system of inoculation famous, so that by 1767 the Sutton technique was known throughout Europe, and when the subject came before Parliament in 1808 in connection with Jenner's vaccination claims, the method of inoculation was referred to as the Suttonian system (Creighton, 1894).

As a result of disagreement with his father over the reduction in the preparation regime, Daniel Sutton decided to practise on his own as a specialist in inoculation and settled at Ingatestone in Essex astride the road between the East Anglian continental ports and London, a convenient place for travellers to stop and receive his attention. It was sufficiently near London to also tap a wealthy clientele from the metropolis, and yet it was outside the boundary of jurisdiction of the Corporation of Surgeons or the College of Physicians, Sutton being an irregular practitioner of medicine. He set up his house in 1763 when he was twenty-eight, and in his first year made 2,000 guineas, reaching the large sum of 6,000 guineas by the third year. He had two classes of patient, those who paid him moderate fees and the poor whom he treated for nothing. The paying patients were lodged in special houses for the purpose for two weeks before the inoculation was performed; they remained while the rash was present and then when no longer infectious returned to their homes; a total of about five weeks. He is reputed to have treated over 100 poor patients in one day, and these would return home carrying infection to wherever they normally lived. Small wonder that the village was often crowded with a motley collection of people and the ordinary inhabitants were alarmed at the effect of this on trade. In 1765 Sutton was put upon trial at Chelmsford Assizes accused of spreading smallpox in the community. The Grand Jury threw out the bill, largely on the grounds that the type of infection he produced was so light, judging of course only on the extent of the rash, that his patients could not infect anyone. It is obvious that Sutton used the argument that the patient was infectious in proportion to the rash, although in the light of his experience of the infection he may well have known otherwise. He did, however, in his private patients restrict them to the grounds of the house and provided them with additional amenities. He hired the services of a resident chaplain and provided a house in the grounds which could be used as a chapel so that regular services could be attended. This was a cunning piece of propaganda in putting himself on the right side of the Church, and the chaplain lost no time in acting as a publicity agent in boosting the merits of the Suttonian system.

Sutton's fame, however, was short-lived as he died in obscurity in 1819. But for Jenner's discovery he would have been regarded as one of the most famous medical men of his time. As pointed out by Abraham (1933), his name does not even appear in the *Dictionary of National Biography*.

Dimsdale, who came from an old medical family, and was more suave than the rather rough Daniel Sutton, copied the principles of the latter's method and, although at first advertised as his own, he later acknowledged it to be the Suttonian system. He described the method in detail in 1767, whereas Sutton did not produce his account until 1796 when he had to a considerable extent been supplanted.

Dimsdale's method was very sound. He placed great emphasis on taking the virus from the primary inoculation site of the donor, usually on the day that the fever commenced, but often as early as the fourth day after inoculation. He avoided frankly pustular lesions. He did not

normally take virus from the secondary eruption, and his method, as with Sutton, was an arm-to-arm technique similar to the method subsequently used in vaccination. There is little doubt that this method gave rise to very mild general attacks in the vast majority and inoculation lesions only in some. On the other hand, although Sutton had claimed that his patients were not infectious, Dimsdale fought a pamphlet battle with Lettsom, who was supporting the establishment of domiciliary inoculation of the poor, on the quite correct grounds that it would spread infection. Whether he fought this battle primarily for the public good, or the protection of his own practice, is not known. In 1767, Dimsdale wrote, "perhaps we should be found to have improved but little upon the judicious Sydenham's cool method of treating the disease, and the old Greek woman's method of inoculating with fluid matter carried warm in her servant's bosom". Perhaps Dimsdale would have agreed that Lady Mary was right to criticize the medical profession in her letter of 1722.

Made affluent by his second marriage in 1746 Dimsdale gave up medical practice for a time, but his family liabilities forced him back again, he acquired an M.D. Aberdeen in 1761 and took up inoculation practice with some success at Hertford. In 1767 he published his account of the practice of inoculation, but his real chance came in 1768 when Fothergill recommended him to the Russian Ambassador as a suitable person to go to Russia to inoculate the Empress. It seems possible that Sutton was asked first as he was famous and Dimsdale was not, but he declined, although we do not know the reason. Failure in the task might have had dire consequences. Even Dimsdale had his anxious moments as the first experiments on some "volunteers" gave a negative response, suggesting that they were already immune. Unable to get virus for the arm-to-arm technique, the Empress Catherine II was inoculated direct from a child in whom the smallpox had "just commenced to appear". This suggests that Dimsdale did not feel that it was the innate quality of the virus so much as the technique that really mattered. The Empress and the Grand Duke, however, allowed persons to be inoculated from them, which suggests he preferred this source. This gracious act to some extent overcame the natural reluctance of the "inferior ranks of people". Dimsdale was made a Baron of the Russian Empire, a Councillor of State, Physician to Her Imperial Majesty, awarded a sum of £10,000 and an annuity of £500.

One wonders whether these were some of the glories which Jenner had at the back of his mind when he felt his country had treated him rather shabbily. Dimsdale returned to England in triumph and continued to practise as an inoculator and a physician in Hertford until his death in 1800.

What was the cause of the apparent success of the Suttonian technique whereby operators had inoculated many thousands without losing a single patient? Even if one doubts the absolute truth of this statement there can be little doubt that the deaths from inoculation were infinitely less frequent than the 1 in 50 to 1 in 90 of the earlier inoculators, and in view of the recent observations of Rosenwald (1951), it seems quite probable that the mortality was extremely low. Unfortunately we will never know the real rate because records were not kept. As we are well aware from the controversy over all forms of inoculation, it is exceedingly difficult to be certain that a person dies as a direct result of the inoculation and not from some other disease. The most important features of the Suttonian system appear to have been the isolation of the patient for a fortnight with some simple rules restricting diet, the taking of fresh air and the avoidance of excesses of various kinds. Doubtless a relief from gross overeating would benefit many of his well-to-do patients and the time would act as a quarantine

period to exclude the inoculation of individuals who had already been infected naturally. This would be a prudent move in avoiding blame for unexpected deaths.

The other important point was that lymph was obtained from the early vesicle on about the fourth day rather than from the mature pustule which was likely to be contaminated with a wide variety of organisms, particularly if treated with the traditional cabbage-leaf or similar type of application. Another feature of the Suttonian technique was the very light inoculation, superficial scarification instead of cutting into the dermis as done by Boylston (1726). "The Turkey way of scarifying and applying the nut-shell etc. I soon left off and made an incision through the true skin, and applied a plaister over it; which I found since to be the better way." The earlier inoculators were bedevilled by the fact that unless the patient had a fairly definite discrete smallpox attack, the critics would not believe that the individual had been "small poxed" and get any subsequent protection. It is not without interest that Patrick Russell, writing from Aleppo in 1767, pointed out that in his investigations on the origin of inoculation, the Bedouins, who appeared to have practised it in many parts of the Middle East for a long time, asserted that the operation should be "performed with a needle and not with a lancet", emphasizing the need for a superficial inoculation rather than a deep one.

Maitland, Bolyston and Nettleton seem to have used the lancet, making deep cuts right from the beginning. They were also obsessed with the virtues of "laudable pus" and opened mature vesicles. In the prevailing theories of pathogenesis of infection, good prognosis was dependent on gross suppuration. To obtain "free running" sores, to get rid of the smallpox "poison", every effort was made by trauma and by the insertion of foreign material to produce large freely suppurating primary lesions. This technique differs from all the genuine accounts of the Graeco-Turkish method of light scratching with a needle and a small quantity of matter—"as much as would settle on the needle—covered with half a walnut shell for a few hours and then left alone" (Timoni, 1714).

Most of the difficulties of the early inoculators both in England and Boston were due to over-treatment of the local lesions. They also could not, or would not, carry out the simple measures described without amplifying them with the so-called preparation of the patient. Sutton's success was almost entirely due to the fact that he followed the original method lost sight of for some forty years, and Lady Mary's criticisms of the technique of her contemporaries seems amply justified.

The continent of Europe was relatively late in adopting inoculation; Woodville (1796) and Miller (1957) outline the history. In 1749 inoculations were first done in Holland, and in 1750 in Germany, but not until 1755 was inoculation taken up in France, and then only after the forceful argument of de La Condamine in his address to the French Academy. Miller discusses the reasons for the latter in great detail and concludes that "the early rejection in France was the political struggle between the Royal Physicians and the Paris Faculté de Médecin for control of medical affairs in France". Inoculation was never practised in Europe to the extent it was in England, which perhaps accounts to some extent for the earlier acceptance of vaccination, particularly its compulsory use.

At the end of the century, in 1796, Edward Jenner performed his celebrated vaccination experiment. Perhaps, to be fair to him, it is worth reviewing the knowledge of smallpox and inoculation at this period.

Although at this time smallpox was regarded as a contagious disease and many thought touching the sick was a method of spread, the more enlightened recognized that it was "spread

by the breath" (Colman, 1722), that is, infectious. However, Sydenham's concept of constitution as being all-important in the cause of disease was accepted as the reason why two people exposed similarly to smallpox might react by one getting the disease and not the other. The seed of smallpox was in all and only required to be awakened by some imprudent act of diet or adverse environment. The strict regimen before inoculation was partly to avoid tempting fate.

Failures of inoculation were also "proved" by the history of undoubted successful inoculation followed by definite smallpox—often after an interval of twenty or thirty years (de La Condamine, 1768). It is not without interest that the failure of one of Timoni's inoculations after twenty-six years was excused by the statement that it was not done by his own hand—the same as Jenner's excuse for the failure of some early vaccinations to give lifelong protection. The concept of a declining immunity in individuals not exposed to a suitable stimulus was quite unknown at this period.

In general, inoculators preached that second attacks of "natural" smallpox were exceedingly rare or never occurred. The anti-inoculators claimed that second attacks were common and that smallpox, chickenpox and other conditions of the skin were a variation of one disease process, the particular form related to diathesis, climatic and other environmental factors, rather than different specific infections. In their view inoculation would not protect against this "group disease", and, of course, it would not.

Some claimed that "genuine" smallpox by inoculation, with a fairly large number of secondary lesions closely resembling discrete natural smallpox, would protect, whereas the very mild inoculations, particularly with a modified secondary rash superficially resembling chickenpox, would not. All inoculations without any secondary rash, the most artistic kind from the inoculator's point of view, were held by many to afford no protection. Dimsdale and Sutton were both adamant that the solitary local inoculation lesion gave protection. "Yet, where infection appeared to have succeeded satisfactorily on a punctured part of the arm, although no eruption should be discovered in consequence of it, the party will never receive the disease in future. I am emboldened to speak in this positive manner from having made repeated trials to infect such patients again, and in every instance ineffectively" (Dimsdale, 1767). Undoubtedly many inoculations failed because the primary inoculation was only traumatic or only contained secondary organisms and no variola virus, particularly if this had been dried on threads or preserved in other ways. Plenty of evidence of the failure of this type could obviously be produced by the anti-inoculators and there can be little doubt that in the search for very mild "favourable" cases, individuals may have been inoculated with anything.

It seems highly probable that the duration of immunity following some of these continuously skin-passaged strains was of relatively short duration, certainly not lifelong. However, by 1796, the inoculator, if he suspected this, or even found it out by experience, would not admit it. It was only later in the era of the vaccination controversy that accounts of the failure of some thousands of inoculations were used to explain away the failure of some vaccinations. The comparisons with horticulture were carried too far, the "ingrafted", the earlier word for inoculated, were thought to have acquired permanent characteristics like the ingrafted tree. It did not fit the contemporary ideas on pathogenesis of disease, and one admission that duration of immunity was not lifelong would have given rise to a flow of anti-inoculation propaganda which could not have been stemmed. The return to more vigorous methods, with possibly greater immunity, would doubtless have given rise to more deaths and public grumbles on that account.

Many of the early groups inoculated were young adolescents or adults who might see their relatively short lives through without an obvious attack of natural smallpox. The increase in the practice of inoculating young children between three and six years meant that for many the number of subsequent years at risk was substantially greater and, all other things being equal, declining immunity was likely to show up by attacks of smallpox. The majority, however, would be mild and many would be misdiagnosed by the doctors of the day. Those most likely to show declining immunity due to missing natural boost would be the nobility, the more protected class, who would, moreover, be the principal source of publicity failures.

Inoculation was undoubtedly infectious; even as late as 1796, Willan (1801) related how one inoculated child infected seventeen other persons of whom eight died. Infection was judged erroneously by the extent of a rash, and Sutton was able to convince a grand jury that none of his patients spread the disease as the secondary eruption was too light. Dimsdale thought otherwise. However, the reluctance of the inoculators to introduce the practice in communities without smallpox showed that the more responsible ones at least knew that even the lightest attack might be infectious. We now know that the route of infection is respiratory and that the period of infectivity in many of these cases is likely to be very short, possibly only a few hours. Depending on local circumstances, inoculated persons might only occasionally infect others. Done at random in overcrowded cities like London, it would most likely spatter the community with infection.

Inoculation was to many the logical improvement on the widespread practice of exposing young children between the ages of about three and six years of age to mild cases of smallpox. "It will be found that the conveying the infection by the insensible particles is neither so certain, safe or convenient as that of inoculation" (Maitland, 1722).

Inoculation did not master smallpox as some historians suggest. Although the wealthy practised it to some extent, it was not invariably done even on those who could afford it, or even in the Royal Family. The artisans and the poor, in spite of well-meaning attempts to give them the benefit of inoculation, could not afford the time or the money to have their children done and consequently throughout the century were exposed to the risk of this disease.

The value of inoculation in protecting an army is perhaps best illustrated from American history. According to Bernstein (1951), the Colonial troops were unable to capture Quebec as although smallpox was prevalent there was considerable opposition to the practice of inoculation. The British troops were, however, inoculated, as had been the practice for many years, and many of them had also had natural smallpox. In June 1766, of Washington's army of 10,000 men, 5,500 were unfit, principally as a result of smallpox, and British reinforcements had time to arrive. Bernstein states: "It can hardly be an exaggeration to say that smallpox was the main cause for the preservation of Canada for the British Empire."

The risk at the end of the century, to some extent due to the continuous inoculation of a minority, was probably greater than at the beginning, but this was also partly due to improved communications by roads and canals and increasing commercial activity. Throughout the whole century much of the public, rich and poor, were content with a life of cruelty, the love of blood-sports and gambling. In 1748, a girl of seventeen was burnt at the stake for poisoning her mistress, and adolescents were hanged for quite minor offences. It cannot be really believed that men were particularly upset by the ravages of smallpox amongst the many risks that life held. The aristocratic women were probably more interested than most because of its effects

on their looks. The only relatively stable section of the community were the inhabitants of the villages, who, still living in a rather fatalistic past, as yet unaffected by the rising commercial prosperity of the towns, were even less likely to seize upon a new invention which even their own clergy regarded as interfering with divine providence.

The incorrect theoretical knowledge and limited practical experience of the London physicians was in contrast to the relatively wide experience of apothecaries and surgeons whose absence of scientific knowledge made them quick to adopt what appeared to be a lucrative practice, but slow to appreciate or understand its possible imperfections.

Jenner, therefore, as an orthodox physician, was brought up to regard inoculation by the Suttonian technique as a proved valuable measure. The risk of permanent scarring or death was much less than in those attacked by natural smallpox. Immunity was lifelong because to him a good inoculation was genuine smallpox and, as with the ingrafted tree, the person's constitution was permanently altered. How these contemporary views on inoculation were to influence his teaching on vaccination we shall see later.

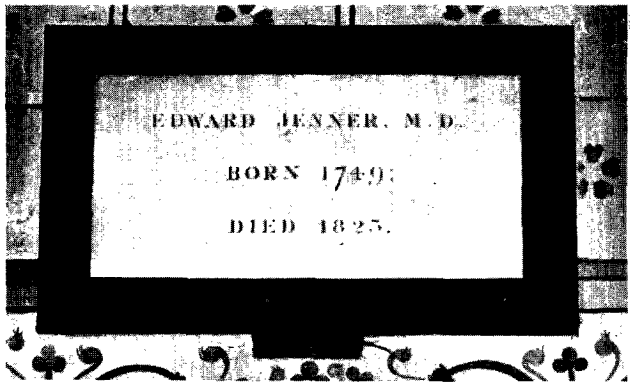


FIG. 207. Memorial Tablet in Berkeley Church

CHAPTER 12 | *The History of Vaccination*

"My opinion of vaccination is precisely as it was when I first promulgated the discovery. It is not in the least strengthened by any event that has happened, for it could gain no strength; it is not in the least weakened, for if the failures you speak of had not happened, the truth of my assertions respecting those coincidences which occasioned them would not have been made out."

EDWARD JENNER, *24 January, 1823.*

As mentioned in the introduction to the chapter on inoculation, a new practice, particularly if it brings fame and glory to the "inventor", arouses the cry that prior claims exist.

There has been more controversy about Edward Jenner and vaccination than most other medical discoveries, but I don't think anyone today can seriously deny that Edward Jenner carried out the first professional vaccination as a scientific experiment, subsequently testing its effect by variolation, a term which can be used to differentiate inoculation with smallpox virus from the many other forms of inoculation which now exist. The word variolation was not used before 1798 as inoculation had only one meaning. The first description by Jenner spoke of inoculating the cow-pox, and the word cowpoxing was also used. The relationship of cowpox to the modern vaccinia is discussed in Chapter 8.

No one did a vaccination before Jenner's time as the term *variolae vaccinae* (smallpox of the cow) was coined by him and from this was derived the term vaccination. Before considering Jenner and his claim to fame, it is necessary to examine briefly the history of cowpox.

In many parts of Europe, particularly in dairying areas, cows suffered from time to time from a local infection of the udder called cowpox. Although one of a number of local infections of the udder, it was a fairly distinct clinical entity which gave rise to similar infections on the hands of those who milked the cows. These vesicular lesions, which heal leaving a scar, an important point in corroborating the history, occurred frequently enough in those who

milked cows, for it to be included in the folk-lore of such places. It is claimed by some that the beauty of the dairymaids extolled by the poets of the time was not unconnected with their un-pockmarked faces, due to protection derived from cowpox. It is doubtful, however, whether this fact was known during most of the eighteenth century, as no reference is made to it. It should be noted that in the voluminous professional literature on variolation, insusceptibility, occurring in about 1 to 250 persons (Woodville, 1796), was not ascribed to a previous attack of cowpox.

Although it has been asserted by more than one writer that the knowledge that an attack of cowpox prevented a subsequent attack of smallpox in many individuals was a very general belief in Gloucestershire and other areas of England where dairying was an important aspect of farming, it appears to have been unknown in other areas, some perhaps more given to arable farming, although at the time milch cows must have been kept for local supplies. Cows were kept in cowsheds in large towns, and although the disease occurred, Woodville obtaining his supply of lymph from a dairy in the Gray's Inn Road, the town dairyman was apparently unaware of this belief. It is sometimes thought that the disease was more frequent in cattle than admitted by the dairymen, due to the fear that such a reputation might injure business. It is hard to believe that eighteenth-century customers would have had qualms on this account. There is no satisfactory explanation of the very real difference in the apparent knowledge of the connection between cowpox and smallpox in different parts of the country.

Whereas a person's escape from natural smallpox might easily be ascribed to their not having been infected, to their "strength" of constitution, to the weather, or to some other vague reason, one of the mysteries of variolation during the eighteenth century was the extraordinary and *unexpected* regularity with which the disease occurred following the introduction of the virus. Under these circumstances, the inoculator was more likely to look round for reasons to explain insusceptibility, and it seems probable that it was failure to get a reaction to variolation, rather than insusceptibility to natural smallpox, which caused the story about the milkmaids and cowpox. Jenner himself in his evidence to the House of Commons stated that the "vague opinion" of its protective value was quite recent amongst farmers and probably due to the increase in variolation following the introduction of Sutton's improved method. Presumably it was then observed that people who were insusceptible to inoculated smallpox because of previous cowpox were also able to nurse natural smallpox with impunity.

It would seem that this fact became increasingly known from about 1760 onwards. In 1765 Fewster wrote a paper on "Cow Pox and its Ability to Prevent Smallpox" and presented it to the Medical Society of London, but it was not published and the matter not followed any further. In 1769 Jobst Böse in Germany called attention to the protection enjoyed by milkmaids. A Mr. Nash in 1781 described fairly accurately the natural history of cowpox and its mode of spread in the herd by the milkers' hands, and suggested that it should be recommended as a method of inoculation which would be superior to that of inoculation with smallpox virus as it was not infectious. He also recorded that cows appeared to only have cowpox once, which suggested a similarity with natural smallpox, and he also noticed that those persons who had cowpox and were subsequently inoculated for smallpox responded with an allergic reaction on the arm but without vesiculation. This information was not published until 1799, and although Crookshank (1889) unkindly says that it was rumoured that Jenner was acquainted with Nash, there is absolutely no evidence to support this.

During this period, from 1770 to 1790, it does not seem to have been a common practice

to variolate systematically in the country areas, but to use a small outbreak of smallpox in a village or a family as an opportunity to variolate a few people around who had not previously had the disease. That the results were not always as good as those claimed by Sutton, Dimsdale or Woodville is admitted by Jenner himself. Outbreaks of smallpox in country districts were relatively rare, which meant that virus for inoculation was not likely to be available. The Rev. Dr. Bell, writing in 1802, remarked that smallpox had been absent from Purbeck in South Dorset for fifty years, except on two occasions, one when it was introduced by a natural attack, and one by a variolated person.

It seems therefore that in areas where cowpox outbreaks occurred amongst cattle and milkers this knowledge would be common to laymen and to the medical profession alike. Although man accepted such blessings as an act of God, he would be reluctant to interfere with and imitate the process itself. The disease on the hands is also by no means trifling, but it could have been done for two reasons: to have cowpox at one's convenience and so prevent a natural attack on the hands, or to get cowpox to protect against smallpox. Although *after* Jenner's account all the stories suggest the "pioneers" inoculated themselves for the latter reason, we shall never know whether most were not self-inflicted, if they really were self-inflicted, for quite other reasons.

Crookshank quotes from a number of letters *written after 1798* in which writers have stirred up their memories to prove "that numerous people had inoculated cowpox intentionally by handling the cows or by inoculating with a needle", in the latter case surprisingly on the hand instead of on the arm, as in variolation. Even Crookshank, antivaccinator as he was, admits that these stories cannot be substantiated. In my opinion, those where inoculation was done on the hand are particularly likely to be attempts to claim intentional infection for what was really accidental. This also applies to the often-quoted account of cowpoxing by Platt of Holstein, a teacher in 1791, who chose (?) a site between the thumb and index finger. In 1791, Jensen, a farmer in Holstein, is also reputed to have inoculated cowpox material from the cow.

The most authentic account is that relating to Benjamin Jesty, although the information came to light after Jenner's paper was written.

In 1774 Jesty farmed Upbury, a large farm at Yetminster not far from Yeovil in the County of Dorset, with his wife Elizabeth and two sons, Robert and Benjamin, aged three and two years respectively. Smallpox had broken out in Dorset and variolation was being done in Yetminster. Benjamin himself had had cowpox as a young man and besides knowing of its traditional powers he had seen two servant girls of his own house who had caught cowpox from cows and were subsequently able to nurse relatives suffering from smallpox without harm. Jesty was not primarily a dairy farmer, but a breeder and dealer in cattle, and doubtless travelled more than most farmers in buying and selling and was probably aware of the presence of cowpox in cattle and its possible effects on the sale value of the animal. At the time he also knew that his neighbour, Farmer Elford, had cowpox in his herd and he therefore took his wife and two small sons to his neighbour's farm and with a "stocking needle" inoculated all three with material direct from the udder of the cow. The imitation of variolation is strengthened by the choice of the upper arm in the two boys and not the hand, the normal site of natural cowpox. His wife, doubtless because of her dress, was cowpoxed on the forearm. All gave rise to typical cowpox lesions and Mrs. Jesty's reaction was sufficiently alarming to cause Benjamin to call the local doctor. Whether this was Mr. Meech or Mr. Trowbridge of Cerne is not known with certainty. Accounts suggest that Jesty was reproached by the neighbours

for his actions, but as the whole episode was only written up many years later, Jesty's supporters doubtless gave suitable embellishments to the story to enhance his martyrdom to science.

Although Trowbridge inoculated the two sons with smallpox some fifteen years later (1789), there is no suggestion that this was done to test the previous cowpox or that the cowpoxing was thought to have spent its powers. It was probably done by chance with other persons in the same locality because of an outbreak of smallpox. It does not strengthen the claim that the protective power of cowpox was a universal conviction. The account of Jesty's cowpoxing was not brought to light until 1802 or 1803 when the Rev. Dr. Bell, Vicar of Swanage, an enthusiastic vaccinator, heard of it from Jesty, who by now lived at Downshay Farm, Worth Matravers, not far from Swanage. Much of the facts have, however, been gleaned from the

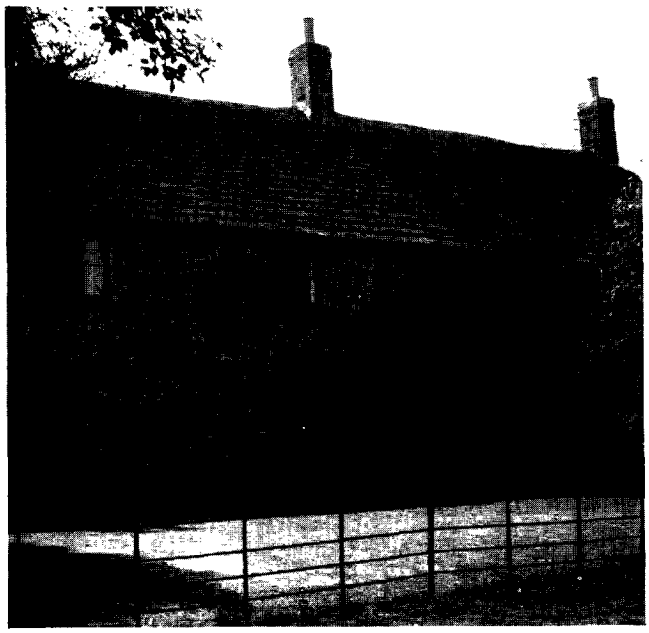


FIG. 208. Jesty's farm, Upbury, at Yetminster, near Yeovil, Dorset.

Life of Bell by C. and L. R. Southey, published in 1844, some forty years after the story was first brought to light, but according to O'Malley (1954) it is probably accurate.

The rest of the story is more sordid. Jesty's action was not believed by Jenner, chiefly because he felt Dr. Pearson, one of his enemies, was behind it, although it is obvious from a letter of Bell's written to the Royal Jennerian Society apologizing for not having acknowledged Pearson's reference to Jesty in a pamphlet of 1804, that he at least was oblivious of this controversy and in no way was suggesting that Jenner was not the "great benefactor of the human race". Unfortunately the disclosures only added to the feud between Jenner and Pearson, which culminated in Jesty and his son Robert being invited to London in 1805, not by the Royal Jennerian Society, but the Original Vaccine Pock Institution supported by the rival Pearson. Jesty's very old-fashioned clothes and appearance excited much interest and

suggest that he certainly did not go with any intention of representing himself as other than a quiet country farmer. His portrait was painted to be hung in the Institution and he was presented with a pair of gold-mounted lancets (an instrument he had never used), and a testimonial

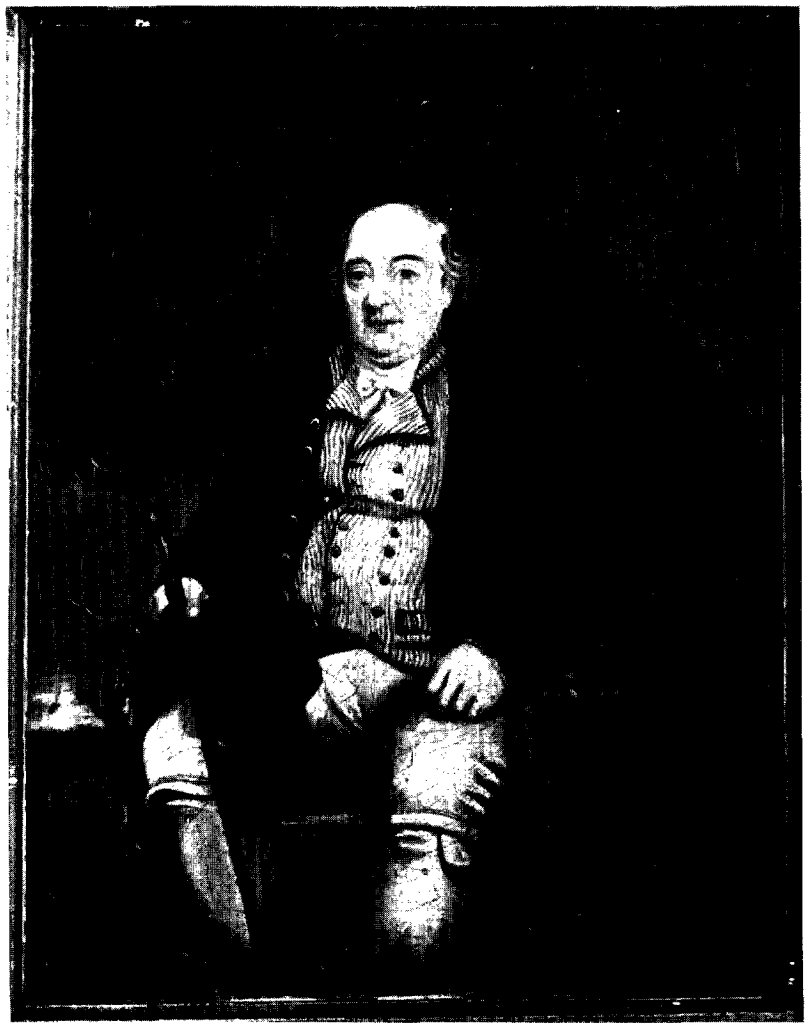


FIG. 209. Benjamin Jesty in 1805, a portrait commissioned by the Vaccine Pock Institution. This reproduction is made from a copy, in oils, of the original portrait. The owner of this copy, Mr. E. H. Jesty, is a descendant of the brother of Benjamin Jesty.

that he had "afforded decisive evidence of having vaccinated Mrs. Jesty and the two boys in 1774". This is not strictly true, as the term "vaccination" was not invented then and more correctly referred to human transfer. An examination of this evidence in the *Edinburgh Medical and Surgical Journal* of 1805 shows that there is no absolute proof that the cowpoxing was done

in 1774. The only examination possible was of the scar on Robert's arm, which would not have any characteristic appearance to prove that it had been done long before Jenner's publication of 1798. There is also nothing to prove that it could not have been a smallpox inoculation. While in London, the son Robert was "inoculated for smallpox" in a "vigorous" manner, without it taking. He had been variolated before and this procedure, therefore, did not test his cowpox immunity. Old Jesty was vaccinated, but this also did not take. It is doubtful if his natural cowpox, occurring well over fifty years before, determined this response, but rather his unknown but probably not infrequent contact with both viruses in the intervening years.

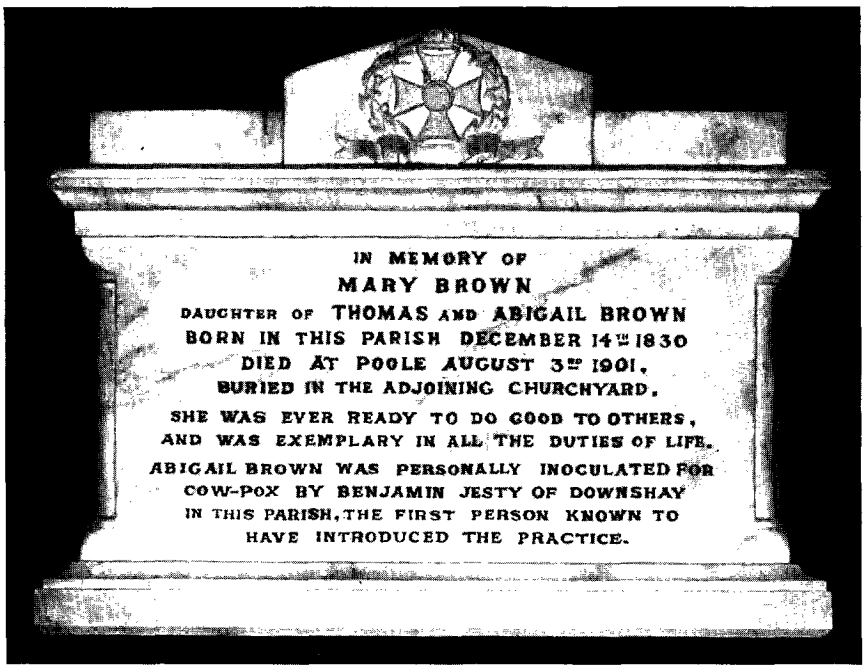


FIG. 210. Tablet in the church at Worth Matravers, where Jesty later lived, supporting his claim to have been the first vaccinator.

Jesty returned to his farm in Dorset and was much respected locally for this honour. In any case he and his relatives were quite wealthy farmers. However, from this date, the glorification of Jesty increased with each generation of the Jesty family. It is doubtful, although claimed (Figs. 210 and 211), that Benjamin ever did any vaccinations subsequently; he was sixty-eight when he died in 1816, but his second son, Benjamin, was a professional vaccinator from at least 1809 and some confusion might have arisen in the stories quoted many years later. His relatives were particularly keen on obtaining financial reward similar to Jenner's and some have suggested that Jesty only approached Bell after Jenner's first award in 1802. On the other hand, Bell's original letters to the Royal Jennerian Society do not suggest that financial reward was the motive at this time. The year after his visit to London Jesty approached the Original Vaccine Pock Institution asking for their support that he should get some reward, but they politely declined to support his claim, which they felt would get little recognition. Perhaps

Jesty's story was now spent ammunition in the battle with Jenner. The family, however, felt aggrieved and a petition was presented to Parliament but failed to obtain any response. Jesty pride continued, and in 1867 George, a grandson, still hoping to prove a claim of priority,

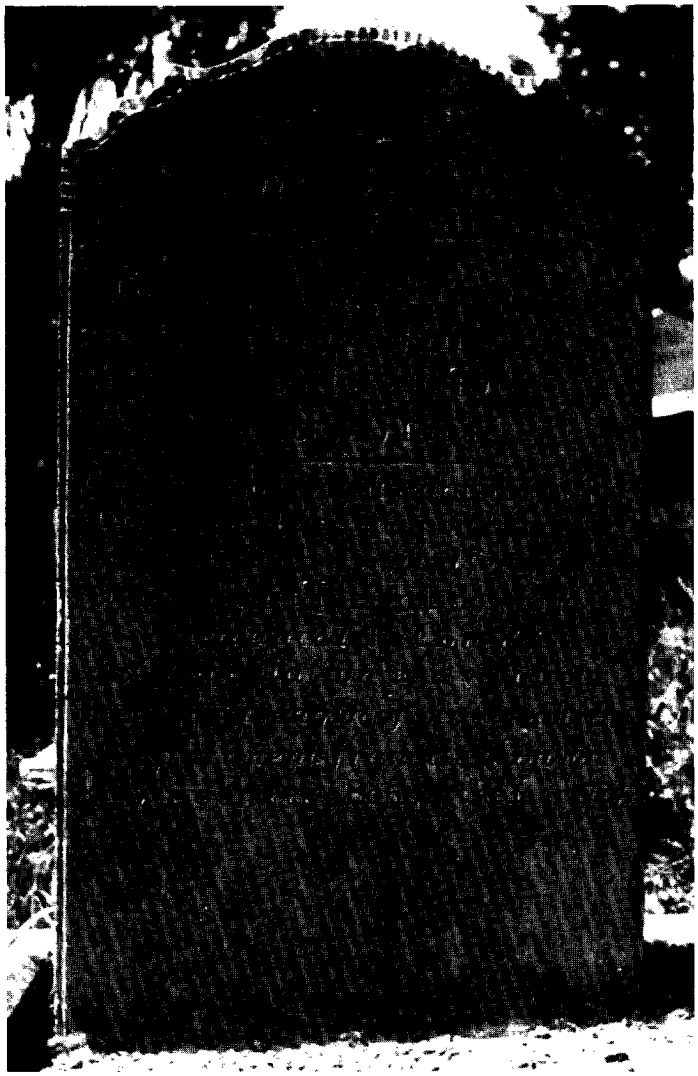


FIG. 211. Tombstone of Benjamin Jesty, Worth Matravers church, Dorset.

wrote that Jenner "visited [Benjamin Jesty] and ascertained how he discovered it and the way it was applied" (O'Malley, 1954). There is no evidence that there is a grain of truth in this statement—equally untrue is any claim that Jesty made known his "experiment" or "cow-poxed" anyone else. There seems little doubt, however, in the light of the evidence of other

physicians, writing before Jenner's work, that the basic facts of Jesty's story are true. Whether Jesty was really the first person to inoculate cowpox with the intention of producing an immunity similar to that given by natural cowpox seems less likely, in view of the intense interest in variolation over the previous thirty years, but we shall never know.

An account of Jenner and his work brings us into contact with the most tendentious literature on any disease. In the words of Greenwood (1935), "anybody who writes on this or indeed upon any other subject which has excited human passions and fancies himself to be impartial is a self-deceiver". Although fully recognizing this, I hope the reader will feel that I am trying to be impartial in condemning both the intolerance of critics like Creighton (1889), or Crookshank (1889), and the blind adulation of Baron (1838) or Simon (1857).

Edward Jenner was born on 17 May 1749. This date is generally given for his birth, although Greenwood (1935), an unusually accurate writer, gives 16 May. An enquiry to the Registrar in Berkeley reveals that no record exists in any parish register or in the church to decide which date is correct, but the former is the most likely. He was the third son of the Rev. Stephen Jenner, M.A., Vicar of Berkeley in Gloucestershire, who had been a tutor to a former Earl of Berkeley. This family connection was of considerable help to Jenner in later life. Jenner went to school at Wootton-under-Edge, but a notable event in his early life was his variolation when eight years of age (1757). After a very lengthy preparation during which he was bled, purged and dieted, he is reputed to have had quite a severe attack of the disease. The severity is claimed by Baron and others to have made a permanent impression on Jenner's mind so as to fix his attention on the prevention of this disease once he became a doctor, but there is no real evidence of this; all the portraits, at any rate, show him to be unpockmarked and the idea of a severe attack may well have crept into the story many years later. Jenner's severe attack of typhus in 1794 did not draw his attention to this disease.

When Jenner left school at the age of thirteen, he was apprenticed to a surgeon apothecary, Daniel Ludlow of Sodbury, near Bristol. As Greenwood (1935) pointed out, in due course he became a surgeon apothecary without examination, and in status was in no sense the physician of today. Where Jenner departed from the normal run of village apothecaries was that in 1770 he became for two years a resident house pupil with John Hunter. Although Hunter was not one of the university intellectuals trained at Oxford or Cambridge, he left his mark on science as the founder of experimental biology and pathology. His long friendship with Jenner showed beyond doubt that Jenner had intellectual qualities much above that of an ordinary apothecary.

In 1771 Jenner arranged the natural-history collection brought back from Cook's first voyage and he published several papers. He declined an invitation to go with Cook on his second voyage, an event which might well have changed medical history, and in 1772 he set up in practice at Berkeley.

He corresponded frequently with Hunter, who usually appeared to be pressing him to carry out natural-history investigations. In 1788 he wrote his celebrated paper on the "Natural History of the Cuckoo" which won him the Fellowship of the Royal Society, a considerable honour which perhaps was in part due to the powerful support of John Hunter. Creighton (1889) the academic scholar was a most scathing critic of this "tissue of inconsistencies and absurdities" and felt that the award of the F.R.S. to Jenner for this paper proved more than anything that Jenner was a charlatan trading on the support of others. Jenner's paper was received with great interest in many other European countries. His most important observation

was that the eggs or young of other birds were ejected by the young cuckoo and that the latter was provided with a peculiar depression between its scapulae which seemed formed for this specific purpose. After about twelve days, this disappeared. Over 100 years later the cine-camera recorded that Jenner was correct in his observations and his learned arm-chair critic Creighton was wrong.

On the other hand, Jenner's method of conducting research was certainly unorthodox by present-day standards, or even those of Creighton's time. Was he the methodical, diligent searcher after truth, working from morning till night, systematically investigating every single

FIG. 212. Edward Jenner. 1749–1823. Mezzotint in the possession of the Wellcome Historical Medical Museum.

point?—a picture painted by Baron (1838) and Simon (1857). In 1786 Jenner wrote his manuscript on the "Natural History of the Cuckoo", but it was not until 19 June 1787 that he actually saw the freshly hatched cuckoo performing so he cancelled his accepted manuscript and rewrote it for the Royal Society (Le Fanu 1951). Even Jenner's observations on the temperature of hedgehogs seems to have been done in a somewhat haphazard way, although he was continuously spurred on by John Hunter, who in spite of his great affection for Jenner, said that he "had damned clumsy fingers" and advised him "*to speculate less and experiment more*".

Soon after he became a Fellow in 1788, he married Catherine Kingscote and was assisted in his practice by his nephew Henry, whom he had taken on as an apprentice. Jenner then inherited some money and in 1792 obtained the M.D. degree of St. Andrew's, upon the recommendation of Dr. Hickes of Gloucester, and Dr. Parry of Bath. He settled in Chantry Cottage, Berkeley, where he was interested in gardening, and his summerhouse and the grape vine he planted are still in existence (Fig. 213). By now, he was to some extent a semi-consultant, being called in by other practitioners, and he had a further residence in Cheltenham, where he lived during the season. How much time he gave to medicine and how much to his general interest in biology and to the writing of poetry, we shall never know. According to Baron (1838) and others, Jenner spent thirty years in which "incessantly he thought and watched and experimented on the subject" (Simon, 1857). This myth arose from the often-repeated

FIG. 213. Jenner's house, the Chantry, Berkeley, Gloucestershire. Photograph taken in 1958. Jenner had his fatal seizure in the room with the French windows. The greenhouse contains a grapevine planted by Jenner.

statement, for which there is no real evidence, that Jenner thought of little but the prevention of smallpox from the time in 1770, when he was an apprentice at Sodbury, a young countrywoman who came for advice had observed, "I cannot take that disease (smallpox) for I have had cowpox". If, as is frequently claimed, cowpox was relatively common and the idea of protection was quite widespread in dairying areas, Jenner must have heard this sort of remark on many occasions. Baron, his biographer, whose sole object seems to be to make Jenner the most famous man in history, rather pathetically writes: "Newton had unfolded his doctrine of light and colours before he was twenty; Bacon wrote his 'Temporis Partus Maximus' before he attained that age; Montesquieu had sketched his 'Spirit of Laws' at an equally early period of life; and Jenner, *when he was still younger*, contemplated the possibility of removing from among the list of human diseases one of the most mortal that ever scourged our race." Baron's blind adulation greatly weakens his supporting evidence of conversations reputed to have taken place between Jenner and a number of other people prior to 1796. I think he even

convinced Jenner in later years of events which never happened. According to Baron, Jenner was thinking seriously about the subject of cowpox in 1780 when he discussed the relationship of cowpox to smallpox, but it is difficult to believe that he really said the following words: "Gardner I have entrusted a most important matter to you, which I firmly believe will prove of essential benefit to the human race. I know you, and should not wish what I have stated to be brought into conversation."

In 1787, *seven years later*, during which time apparently Jenner made no real attempt to prove or disprove any of his ideas, it is related by Baron (1838) that his nephew George Jenner accompanied him to a stable to look at a horse with diseased heels, and Jenner is reputed to have said, "There is the source of smallpox." However, in 1788 Jenner took to London a drawing of the hand of a milker suffering from cowpox and showed it to Sir Everard Home and other members of the medical profession. There can be little doubt that Jenner, dreamer that I think he was, freely conversed with other people on this subject, not because he was certain of his ideas, far from it, but rather to test others' reactions and obtain additional information. Apparently Haygarth, who was very interested in smallpox and its control, had also heard of Jenner's ideas at this time through a Dr. Worthington.

In 1789, a new disease appeared in Gloucestershire, which was given the name swinepox. It was brought to the notice of the Gloucestershire Medical Society, of which Jenner was an important member, by Dr. Hickes. Apparently the disease was not really new and was known to the people of Gloucestershire and surrounding parts by this name or also by the name of pig pox, and it was on occasion also called the cowpox, all names liable to give rise to a great deal of confusion later. It was noted that professional men could not make up their minds whether the disease was smallpox or not, and Dr. Hickes stated that "if it be not smallpox, it certainly is a disease which renders the person who has had it much less liable to receive the infection of the smallpox, or the febrile consequences of it". The nurse for Jenner's infant son, then ten months old, also contracted this mysterious disease, with the result that Jenner inoculated his son Edward from the pustules of the girl, with matter which could not be distinguished from "variolous matter". Two female servants in a neighbouring family who had never had smallpox or chickenpox were inoculated at the same time from the nurse. Jenner related the results and these were given in Dr. Hickes' paper to the Gloucestershire Medical Society. "Two young women who were inoculated with the swine pox matter sickened on the ninth day after its insertion into the arm. The symptoms were more severe than we generally find them in patients sickening with smallpox from inoculation. The headache was remarkably severe and the state of lassitude and general debility continued longer. I could not observe any material difference between the progress of the inflammation of the arm and its termination in this disease and the common smallpox. A few pustules, or rather little eminences, appeared which did not suppurate. They very much resembled the eruption in the case of Edward Jenner." On 12 January 1790, Jenner inoculated both his son and the nurse, who had both had swinepox, the one by inoculation and the other naturally, with true smallpox material. No inflammation appeared on their arms, nor was there any other sign of the disease. Creighton, in his blind criticism of everything Jenner did, assumes it was a disease of pigs, and says: "The true virtuoso [Jenner] however has no antecedent objection to experimenting with anything."

By 1795, cowpox was sufficiently well known to appear in Adams' book on morbid poisons, which contains an account, not completely correct, of the disease in cattle and in man and the

fact that it was already claimed that it produced immunity to smallpox. In 1796, it was also referred to in a footnote in Woodville's *The History of the Inoculation of the Smallpox in Great Britain*.

Jenner appears to have been far more interested in the almost philosophical relationship between human and animal disease than in the purely practical aspect of preventing smallpox. It must be appreciated that at this time prevention by variolation, using the Sutton and Dimsdale technique, was a very satisfactory process far removed from the type that Jenner himself had in 1757. Jenner's most important theory was that the domestication of many animals was the cause of numerous diseases in man, and this even appeared later in his writings. His most important belief was that smallpox originated from the disease "grease" in horses. He was also interested in a number of other diseases, and claimed that "scirrhus and tubercle originated in a hydatid". In 1814 in an interview with the Duchess of Oldenburg, sister of the Emperor of Russia, he was still propounding this origin of phthisis pulmonalis. In my opinion it was Jenner's firm belief that diseases of animals and man were closely related to one another that caused so much opposition from some sections of the profession and the public, who strongly resented the idea that the Almighty could possibly allow a disease of man, so closely related to Him, to be in any way derived from disease of brute animals. I think Jenner's real interest was in what might be called general biology, rather than medicine, in contrast to both Simon's and Baron's idea of Jenner's unremitting and sole interest for thirty years in smallpox prevention, a view to some extent supported by Underwood as recently as 1949. The latter believed that Jenner's claim to fame was because he "set out deliberately with the intention of showing that cowpox naturally acquired could be transmitted artificially from *person to person* so that there would result an increasing reservoir of persons who had been given the opportunity of becoming invunerable—or 'immune' as we would say, to smallpox. There is no doubt that this was what was in Jenner's mind." I don't think there is any doubt that by 1800 this idea was in Jenner's mind, but whether it was there in 1780 seems very much less likely.

Jenner probably first wrote a paper on cowpox in 1796. There are two known manuscripts, one written by Jenner himself, and one written by his brother-in-law, with notes and corrections made by Jenner. Crookshank went to considerable lengths to compare and contrast these two versions and he considered that Jenner corrected a number of his earlier views. We know that he submitted a copy to the Royal Society, but there is no evidence in the minutes that it was ever formally presented. It seems possible that Everard Home took it to the Society and showed it informally at a council meeting. Crookshank alleges that the second copy had alterations in handwriting other than Jenner's, but this is not accepted by most authorities, and Crookshank's own arguments are considerably weakened by incorrect quotations from Jenner's papers. Jenner was hasty in rushing into print with so little factual information to support his complicated theories. The appearance of references in the medical press, particularly by Adams and Woodville in 1796, must, I think, have stimulated him from his rather idle speculations of the previous years.

In the paper he cited three cases of persons who had been infected naturally with "grease". In one, variolation subsequently produced a minimal effect, in a second a normal effect resulted, and a third apparently got smallpox in the natural way. In spite of this obvious lack of connection between grease and cowpox, Jenner concocted his first explanation, that although grease was the cause of smallpox it could not be relied upon until it had been passed through the cow. Because it had been observed that cowpox could occur more than

once in the same person, Jenner had to propound that, "although cowpox shields the constitution from smallpox and the smallpox proves a protection against its own future poison, yet it appears that the human body is more and more susceptible of the infectious matter of the cowpox". Perhaps this statement above all explains why so much criticism could be levelled at Jenner when years afterwards in the face of much evidence to the contrary he still believed that a person who had been cowpoxed properly "shall be for ever immune to smallpox". As well as the three cases of casual horse grease recorded in the original paper, there were ten cases relating to occurrence of casual cowpox in various people and their apparent immunity to infection from natural smallpox and to variolation. The one experimental observation in this original paper was that undertaken on 14 May 1796.

On this date Jenner took material from a sore on the hand of Sarah Nelmes, a milkmaid who had been infected with cowpox from milking cows. He inoculated from it on to the arm of one James Phipps, aged about eight years. The operation is reputed to have occurred in

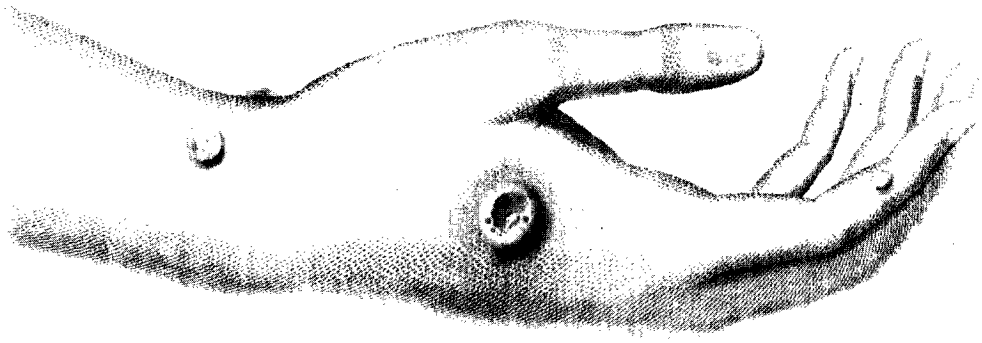


FIG. 214. Cowpox. Hand of Sarah Nelmes, from Jenner's "Inquiry".

Jenner's garden, possibly in the summer house (Fig. 215) which was certainly used for later vaccinations. Two superficial incisions were made, each about three quarters-of an inch long. The boy felt perfectly well until the seventh day when he had slight axillary pain, and a slight fever on the eighth or ninth day. In Jenner's opinion the state of maturation was pretty much the same as when produced in a similar manner by variolous matter except that "around the incisions took on rather more of a erysipelatous look than we commonly perceive when variolous matter has been made use of in the same manner".

On 1 July, just under seven weeks after the cowpox, this boy was inoculated with matter taken straight from a smallpox pustule. "Several punctures and slight incisions were made on both his arms and the matter was well rubbed into them, but no disease followed. The same appearances only were observable on the arm as when a patient has had variolous matter applied after having either the cowpox or the smallpox." With only this one experiment, and the hearsay evidence on both cowpox and horse grease, Jenner submitted this paper to the Royal Society with the following rather pompous comment: "I presume it would be swelling this paper to an unnecessary bulk, were I to produce further testimony in support of my

assertion that the Cow Pox protects the human constitution from the infection of the Small Pox. I shall proceed then to offer a few general remarks upon the subject, and to some others that are connected with it. Though I am myself perfectly convinced, from a great number of instances which have presented themselves, that the source of Cow Pox is the morbid matter issuing from the newly diseased heels of horses, yet I could have wished, had circumstances allowed me, to have impressed this fact more strongly on the minds of this Society by experiments."

It is small wonder that the paper was never presented formally to the Royal Society, but Jenner, who always seems to have been hypersensitive to criticism other than from his old

FIG. 215. Jenner's summerhouse, in which James Phipps is reputed to have been cowpoxed.

friend John Hunter, by now unfortunately dead, set about collecting further evidence as quickly as possible and publishing it himself without submitting it to the Royal Society. The informal rejection of the first paper is completely glossed over by Baron; indeed, he makes a point of quoting a letter of Jenner's of June 1797, that Worthington had recommended publishing it as a pamphlet instead of sending it to the Royal Society. I feel that Baron's action was intentional and meant to deceive.

In 1798 Jenner published his celebrated Inquiry in the form of a book, the full title being *An Inquiry into the Causes and Effects of Variolae Vaccinae, a Disease, Discovered in some of the Western Counties of England, particularly Gloucestershire, and known by the Name of Cow Pox*, the first edition dedicated to his friend Dr. Parry of Bath.

Jenner recorded eighteen cases in which persons contracted cowpox from the cow, and one in which the disease had been accidentally contracted from another person. In all, insus-

ceptibility to subsequent smallpox had been shown by a failure to obtain a normal variolation reaction with material which otherwise produced inoculated smallpox. Most of his cases gave a history of having previously had contact with, nursed or even slept with persons suffering from smallpox without contracting the disease. This was the record of his observations.

His experiments consisted of the inoculation in 1796 of one child (Phipps) with cowpox taken from the hand of a natural cowpox infection, and of a second inoculation, in 1798, with material obtained directly from a cow infected with cowpox. From this child he inoculated another and subsequent cases until it had been passaged through five generations. To only three of the cases had he applied the variolous test.

On 16 March 1798 Jenner selected a child, John Baker, five years of age, and he inoculated him from a pustule from the hand of Thomas Virgoe, one of the servants who had been "infected" from a mare's heel. He became ill on the sixth day and had a well-developed pustule similar in many respects to a crude cowpox lesion. Crookshank places considerable importance on minor differences in the appearance, doubtless to persuade his readers that Jenner would inoculate his unfortunate victims from any kind of vesicular lesion and could not distinguish one from the other. Judging at any rate from Jenner's illustration, the lesion although having a greater erythema, has no characteristics peculiar to it, and is like cowpox. What is rather unfortunate is that in this early account the case is passed over with the comment that on the eighth day the child was free from indisposition, but was rendered unfit for variolation from having felt the effects of a contagious fever, the latter thought to have been caught in the workhouse. In Jenner's later work, *Further Observations on the Variolae Vaccinae or Cow Pox* (1799), he records that the child died, most probably from erysipelas. How this was caught we shall never know, but the suppression of the facts of this death was seized upon by his opponents. In other experiments with horse grease, although the date is not given, at least three cases suffered from extensive erysipelas. The material was transferred from arm to arm with success in some, but was subsequently lost.

Crookshank (1889) suggests that Jenner had discovered nothing. Indeed, he had not discovered that cowpox produced some immunity against smallpox, as this was known, but in these further experiments he had shown that cowpox could be intentionally communicated and carried on from man to man, although Crookshank denies this and erroneously credits it to Jesty and others. Jesty showed that cowpox could be artificially transferred from cow to man—a different matter and similar to the natural disease. Crookshank, with more justification, criticizes the test of exposure to infection—"this had been carried out repeatedly", but it was really only the exposure to chance infection in natural smallpox. All Jenner had been able to show was the apparent insusceptibility of an individual artificially cowpoxed to subsequent inoculation with smallpox. However, without any proof, he assumed that the failure of variolation was good enough to prove protection from natural smallpox, a point of great practical significance.

After the publication of the first book, Jenner waited in London with vaccine material for three months to see if anybody would repeat his experiment. He was disappointed and surprised that the profession should not jump at his discovery, and it was not until he had returned to Berkeley that he heard from Cline, a surgeon and an old student friend, that he had vaccinated a boy with hip disease, in the hope of producing counter-irritation, with some dried lymph that had been left by Jenner. Rather surprised with the result, soon afterwards he variolated the boy without result. The supply of lymph was then lost.

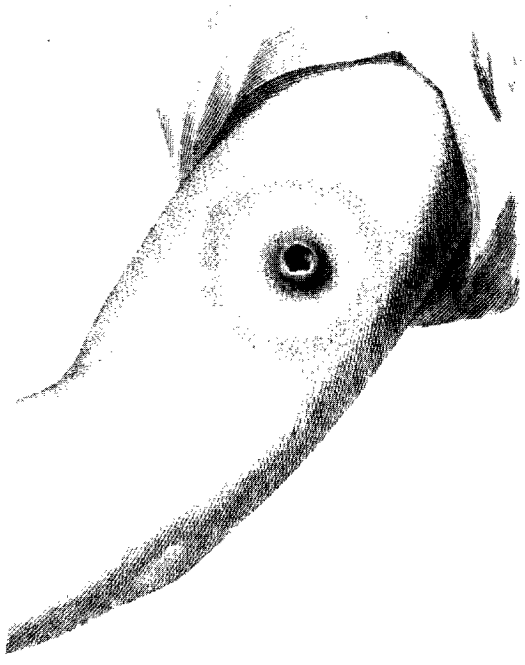


FIG. 216. Vaccination. Arm of William Pead, vaccinated 28 March 1798, with lymph from William Summers (from Jenner's "Inquiry".)

FIG. 217. "Equine" vaccination. John Baker (from Jenner's "Inquiry").

Dr. George Pearson, M.D., F.R.S., a member of the College of Physicians and physician to St. George's Hospital, was greatly interested by Jenner's pamphlet and before the end of 1798 wrote *An Inquiry Concerning the History of Cow Pox*, strongly supporting Jenner. As Greenwood points out (1935), Pearson, in an objective survey of the evidence and supported by a small number of experiments, reviewed the possibility of a number of interpretations, but concluded: "It seems most reasonable to impute the inefficacy of the variolous poison in the above three instances to a state of inexcitability produced by the cowpox poison." He concluded by writing: "I shall be no better contented with those who consider the facts to be already demonstrated than with the opposite extreme opinion, that the whole of the prospects displayed are merely Utopian. The fortunes of the new proposed practice cannot with certainty be told at the present by the most discerning mind, more instances are required to establish practical and pathological truth. Without assumable pretentions, which I think unwarrantable, the number of instances further requisite cannot be stated; but one may safely assert that well-directed observation in a thousand cases of inoculated cowpox would not fail to produce such a valuable body of evidence as will enable us to try our knowledge with much usefulness in practice, and establish, or at least bring us nearer to establishing, some truth", statements better adapted to "have commended the confidence of reflecting persons" than Jenner's rather pompous comment on his paper to the Royal Society.

At the end of January 1799 cowpox was discovered in a dairy in Gray's Inn Lane, and Dr. Woodville, of the Smallpox Inoculation Hospital, armed with a copy of Jenner's illustrations of cowpox, went there with the President of the Royal Society and other eminent persons. Sarah Price, one of the milkmaids, having a typical vesicle, Woodville took the lymph and started to vaccinate. Unfortunately Woodville vaccinated his cases at the Smallpox Hospital, and at least two-thirds of them showed some general eruptions. It is almost certain, that under these circumstances the patients were either inoculated with a mixture of vaccinia and variola virus from contaminated lancets, were vaccinated and naturally infected with smallpox at the same time, or, in some cases, were vaccinated and then variolated from three to five days later, when they again had a double infection. What is important, however, is that Jenner in April 1799 published his *Further Observations on the Variolae Vaccinae*, and instead of leaving this obvious error of Woodville's to rectify itself in the light of experience, concocted a *theoretical* objection that any injurious after-effects of vaccination were not due to the first action of lymph upon the system but to a secondary phenomenon which occurs "if the pustule is left to chance". There is some similarity in Jenner's reasoning with that of Sutton, Dimsdale and the other variolators in stressing the extreme importance of medical care. To Jenner there was some, almost divine, rightness about vaccination, and it could, therefore, never be wrong. One cannot but feel that Jenner wanted vaccination to be a great improvement on variolation, but still sufficiently complicated to require expert and costly medical attention.

> "I shall conclude this paper by observing, that although vaccine inoculation does not inflict a severe disease but, on the contrary, produces a mild affection scarcely meriting the term disease, yet, nevertheless, the inoculator should be extremely careful to obtain a just and clear conception of this important branch of medical science. He should not only be acquainted with the laws and agencies of the vaccine virus on the constitution, but with those of the variolous also, as they often interfere with each other. A general knowledge

of the subject is not sufficient to enable or to warrant a person to practise vaccine inoculation: he should possess a particular knowledge; and that which I would wish strongly to inculcate, as the great foundation of the whole, is an intimate acquaintance with the character of the true and genuine vaccine pustule. The spurious pustule would then be readily detected, whatever form it might assume; and errors known no more."

He was of course aware, however, and warned others, that the vaccination of people in the atmosphere of a smallpox hospital was fraught with considerable danger, but it is a pity he did not leave it at that. Although McVail (1896) suggests that the profession at the time was generally aware of the clinical differences between vaccination and variolation, and quotes Ring and Fosbroke, it seems that many believed the absence of secondary eruption to prove vaccinia and its presence to prove variola, when in neither case is this a satisfactory criterion. Some of his contemporaries were more ignorant and obstinate than we would credit—as the following account shows.

"A medical gentleman who was particularly forward on the occasion, but who was not very well acquainted with the characters either of small-pox or cow-pox, applied to Mr. Wachsel, the apothecary, for leave to charge some threads with vaccine virus, professedly to distribute them to his medical correspondents throughout the island. Mr. Wachsel chanced to be called out of the apartment; during his absence the doctor selected a patient, and was busily engaged in charging his threads. Mr. Wachsel observed on his return that he had fixed on a patient who had a general sprinkling of small-pox pustules, and inquired whether he intended to furnish his friends with the virus of small-pox as well as of cow-pox? He replied 'with the virus of cow-pox only'. 'Then, sir,' said Mr. Wachsel, 'you know not what you are doing, you are taking the virus of small-pox.' The threads thus charged, but for Mr. Wachsel's vigilance, would have been distributed as vaccine virus!!!"

In May 1799, Woodville published his report on a series of inoculations for the "variolae vaccinae" recording a high rate of general eruptions, but he quickly realized his error, and in June 1799 recorded further cases in which, in the last 110, only seven had had a general eruption, and he stated that these did not occur when persons were vaccinated in private houses. In October 1799, Pearson also published reports from correspondents to whom he had sent lymph on threads, which confirmed that quite a large number of vaccinations had been done without any general eruption, although with an occasional practitioner general eruptions occurred sufficiently frequently to make it almost certain that smallpox infection was occurring simultaneously.

By 1 July 1800, Woodville published reports on a further 2,000 cases which had been done in hospital, still occasionally producing general eruptions. Woodville, however, had completely abandoned his original view, that a general eruption was common in vaccination. By March 1801, Jenner in his next work, on the *Origin of Vaccine Inoculation*, stated that at least 100,000 persons had been vaccinated in England alone.

Jenner was content to be not only the pioneer but the "grand old man" of vaccination, the authority on all the theoretical aspects of it, but it does not seem that he practised extensively and much of the early evidence of its value was obtained from the work of Pearson and Woodville. Jenner had ethical standards far ahead of his time. When he evolved an improved method of preparing tartar emetic, he published it in the *Transactions* of the Society for the Improvement of Medical and Chirurgical Knowledge rather than give it a new name and

monopolize its production and sale, as suggested by Hunter. His relatives, however, saw the whole thing in quite a different light. Jenner should not only get glory, but also financial advancement as a result of his discovery. The letter from George Jenner in March 1799 sowed some of the seeds of jealously which led to the subsequent conflict between Jenner and Pearson.

Norfolk Street,
March 11th, 1799.

After what Mr. Paytherus has written to you it will be needless for me to say any thing to urge the necessity of your coming to town to wear the laurels you have gained, or to prevent their placed on the brows of another.

. . . Dr. Pearson is going to send circular letters to the medical gentlemen to let them know that he will supply them with cow-pox matter upon their application to him, by which means he will be the chief person known in the business, and consequently deprive you of that merit, or at least a great share of it, which is so justly your due.

GEORGE JENNER.

It cannot be denied that at this time Pearson had supplies of "lymph", while Jenner did not. Jenner's reaction is hardly that of the humble scientist. He wrote to his friend Gardner:

Berkeley,
Wednesday, 1799.

DEAR GARDNER,

A letter I have just received from G. Jenner informs me that Dr. Pearson on Saturday last gave a public lecture on the cow-pox and that it was publicly exhibited at Sir J. Banks's on Sunday evening. He has also given out that he will furnish any gentlemen at a distance with the virus.

As this is probably done with the view of showing himself as the first man in the concern, should not some neatly-drawn paragraphs appear from time to time in the public prints, by no means reflecting on the conduct of P. but just to keep the idea publicly alive that P. was not the author of the discovery—I mean cow-pox inoculation.

Yours truly,
E. J.

Woodville and Pearson started a vaccination practice in Golden Square which became known as the Vaccine-Pock Institution. Jenner, who expected the directorship of the organization, was offered the title of "extra consulting physician". He was deeply incensed by this and not only declined but attacked Pearson and Woodville as much as he could. Although Baron's (1838) and Underwood's (1949) sympathy appears to be wholly with Jenner, Pearson and Woodville were not only vaccination enthusiasts with far greater experience than Jenner, but they had energy and drive to get on with the practical aspects and as members of the College of Physicians had established London practices. Experience of the Jennerian Institute later strengthens my view that Pearson and Woodville, although not unmercenary—a characteristic of doctors of the time—probably recognized that Jenner was by then an impossible man to work with. He regarded them as "snarling fellows and so ignorant withal that they know no more of the disease they write about than the animals which generate it". Jenner's attitude of complete intolerance was at times rather misplaced.

In spite of the friction, Woodville supplied Jenner with lymph and he used this to vaccinate his grand-nephew and a four-year-old boy. The former had a few lesions on the face. With material from this source Dr. Marshall vaccinated 107 persons. "In only one or two of the cases," he observes, "have any other eruptions appeared than those around the spot where the matter was inserted."

Jenner obtained another supply of lymph from Clark's farm in Kentish Town and sent it to Dr. Marshall, who vaccinated a further 127 people without any secondary lesions. On another occasion a local supply of cowpox chosen by Jenner himself gave some severe reactions and one "supply" apparently gave no protection. It would seem that in spite of meticulous descriptions of the vaccine vesicle, Jenner as well as others occasionally found some difficulty in identifying true and false cowpox when obtaining new supplies.

About this time Jenner was corresponding with Lord Egremont with a view to profiting from his discovery. Doubtless due to pressure from his family, he was also looking for suitable appointments, and in a letter to a Mrs. Walker, he tried to get his nephew appointed to the Embassy in Berlin:

> "... it would be still more gratifying were I to be allowed to appoint a person to Berlin, whom I could with confidence recommend as perfectly conversant with cow-pox in all its stages. My nephew, Mr. Jenner, who has assisted in conducting my experiments on the subject, and who has inoculated considerable numbers, would be very ready to accept the embassy. But on mentioning this, perhaps I presume too much. *My motive is the possibility of making a mistake.*"

Although Baron claims that Jenner offered gratuitous vaccination to all the poor in Berkeley, his practice seems to have been small. When smallpox occurred subsequently in Berkeley, the Guardians of the Poor complained bitterly of the cost of the coffins, and because of this at length asked for his help.

In spite of scant attention from his colleagues in England, Jenner was receiving most complimentary letters from abroad, particularly from Dr. Sacco of Milan, although the latter did not entirely agree with all Jenner's views. By 1801 Jenner was further soliciting financial reward, as the letter from Lord Sherborne shows.

> MY DEAR DOCTOR,
>
> Many thanks for your circumstantial letter; I am sorry to say that I do not know Mr. Addington, even by sight; they tell me the King is recovering very fast, and we may expect a drawing-room soon, which I will attend and I will then speak to Mr. Pitt. If patriot Grattan gets 50,000L. for his patriotism, the true patriot Jenner deserves much more: I am sure not less; and less would be perfectly shabby to think of. I perfectly recollect Grattan's business:—it was settled among his friends to propose 100,000L. for him; determining to ask enough, and fearing that sum should not be granted, one of his most particular friends was to get up afterwards and propose 50,000L. which was immediately granted, and he took 47,500L. for prompt payment.
>
> I am, my dear Doctor,
> Yours most truly,
> SHERBORNE.
>
> Sherborne, April 23rd, 1801.

In 1801 he went to London to assist in the preparation of a petition which was presented to the House of Commons on 17 March 1802. He had much assistance from Admiral Berkeley. Jenner's claim was, "first, the utility of the discovery itself; secondly, the right of himself to claim the discovery; and thirdly, the advantage in point of medical practice and pecuniary emolument which he had derived from it". The latter point was largely a negative one, as it was emphasized that he had not kept the discovery secret and thereby benefited, but had disclosed it to the world. Woodville, it should be noted, gave evidence to the committee, on Jenner's behalf, and that he had vaccinated 7,500 people, about half of whom were variolated subsequently without effect.

The speech by the Chancellor of the Exchequer is a model for pronouncements of this kind and would have given cold comfort to most sensible men.

> "... The Chancellor of the Exchequer said that whatever sum of money the House might vote as a future reward for his merit, he had already received the highest reward in the approbation, unanimous approbation, of the House of Commons—an approbation most richly deserved, since it was the result of the greatest, or one of the most important discoveries to human society that was made since the creation of man. That the value of the discovery was without example, and beyond all calculation, were points not to be contested, for they were made out by convincing evidence; and that he (Dr. Jenner) had precluded himself from great emoluments, by the generosity of his own conduct, was also most manifest; but he (the Chancellor) had also a duty to discharge towards the public in voting away the public money, and when he reflected on the other advantages that the Doctor must derive from this vote, he was for the smaller sum. In saying this, he was rather pursuing the sense he had of public duty, than his own feelings. He had, however, the satisfaction to reflect that this discussion had given to Dr. Jenner a reward that would last forever, and also that the comfort of his family would be amply provided for, *in his extended practice*, by means of that House."

Jenner was voted £10,000, according to Edwardes (1902) not unanimously, but only because a minority felt he deserved more.

Surprisingly enough, Jenner was carried away by the thought of the acclamation that he had received.

> "Elated and allured [he observes in a letter] by the speech of the Chancellor of the Exchequer, I took a house in London for ten years, at a high rent, and furnished it; but my first year's practice convinced me of my own temerity and imprudence, and the falsity of the minister's prediction. My fees fell off both in number and value; for, extraordinary to tell, some of those families in which I had been before employed, now sent to their own domestic surgeons or apothecaries to inoculate the children, alleging that they could not think of troubling Dr. Jenner about a thing executed so easily as vaccine inoculation. Others, who gave me such fees as I thought myself entitled to at the first inoculation, reduced them at the second, and sank them still lower at the third.
>
> "I have now completely made up my mind respecting London. I have done with it, and have again commenced village-doctor. I found my purse not equal to the sinking of a thousand pounds annually (which has actually been the case for several successive years) nor the gratitude of the public deserving such a sacrifice. How hard, after what I have done, the

toils I have gone through, and the anxieties I have endured in obtaining for the world a greater gift than man ever bestowed on them before (excuse this burst of egotism), to be thrown by with a bare remuneration of my expenses!"

Although, with his M.D. St. Andrew's and his F.R.S., he would have cut quite a good figure, Jenner never became a Member of the Royal College of Physicians, as he declined to submit himself to a compulsory test in Latin, and he continued to be shunned by the fashionable physicians of the day.

Honours of many kinds came to him. In 1801, the National Institute of France elected him a corresponding member, and the same body conferred a still higher honour by placing him, in 1811, on the list of foreign associates. The freedom of the City of London was bestowed on 11 August 1803, and he was subsequently made a freeman of the city of Dublin and of the city of Edinburgh. He was given a diploma of LL.D. from the Senate of the University of Harvard in 1803, but it was not until 1813 that the University of Oxford conferred on him the honorary doctorate of medicine. This was a great honour, as it was given very rarely. It was not until 1821 that Jenner was appointed as Physician Extraordinary to His Majesty King George IV. He was, however, never given a knighthood or other civil honour so common today.

In furthering the aims of universal vaccination, several of Jenner's friends resolved to form a Jennerian Institution. His Majesty consented for it to be called the Royal Jennerian Society, and the Queen became patron. On 3 February, 1803, Jenner became the first president of the Royal Jennerian Society, and a Dr. John Walker was appointed as resident vaccinator. Thirteen vaccination stations were opened in London, and in eighteen months over 12,000 vaccinations were done. There is no evidence, however, that any were done by Jenner himself. He was above the mundane, practical aspect. Nearly 20,000 doses of material were supplied to different parts of the British Empire and to foreign countries.

Jenner, however, quarrelled with Dr. Walker in 1806, because of the latter's method of obtaining lymph by removing the scab from the lesion instead of by puncturing the vesicle, although later Jenner himself gave instructions on the use of the scab as a source of virus. The successor to Walker also proved unsuitable. Walker, after his dismissal, founded the London Vaccine Institution, with headquarters at 6 Bond Street, Walbrook, from where he directed the activities of twenty-three stations for free vaccination. Both the Royal Jennerian Society and the London Vaccine Institution seemed to have been under almost identical patronage, which suggests that the patrons at least were satisfied with Walker.

One cannot but feel that Jenner was a difficult man to work with as he glossed over the practical problems and substituted theoretical arguments of his own creation. Further troubles occurred, and by the time the National Vaccine Establishment was founded in 1808 by direct Government action, the Royal Jennerian Society had practically collapsed. On 9 May 1805, Jenner again left Berkeley and arrived in London. On the following day he had an interview with Lord Egremont. His interview referred to the establishment of vaccination and the advancement of his private fortune, which according to Baron "had been so much injured by what promised to be beneficial to him". On 2 July 1806, Lord Henry Petty brought the subject before Parliament. It was partly on account of vaccination itself, smallpox having again become prevalent, but also on Dr. Jenner's behalf. This was the first occasion on which Parliament had discussed the increasing problem of the continuance of variolation, alongside vaccination. The

fact that variolation was still being done was one of the strongest arguments against the complete success of vaccination claimed by Jenner. In spite of obvious reasons why some control of smallpox inoculation was very desirable, it was pointed out, "the liberty of doing wrong was still left among the privileges of free-born Englishmen". It seems that although the practice of vaccination had been taken up by most of the orthodox medical practitioners, a number of the more unscrupulous were playing on the ignorance and fears of the poor, and of the obvious failures of some types of vaccination, by continuing to use variolation. In the end, Jenner was awarded £20,000 by a majority of thirteen votes.

By 1804, failures of vaccination were recorded, almost certainly due to genuine unsuccessful vaccination, although Goldson in 1804 suggested that protection would wane with the passage of time. Jenner published his tract *On the Varieties and Modifications of the Vaccine Pustule, occasioned by a Herpetic State of the Skin* in 1806. Failure to obtain successful vaccination and modification of its progress might be due to malnutrition, an unusual state of the skin, or due to "herpes", a general term applied to a wide range of skin diseases. The emphasis was that vaccination, properly performed on a person in normal health, could never fail to prevent smallpox, that every deviation must be due to some fault other than the principle of vaccination.

Baron himself realized that this view meant that the fate of the new practice was made to hang on the occurrence of a single case of smallpox after successful vaccination. In spite of Baron's attempts to suggest that Jenner really modified his view and only believed that vaccination could prevent smallpox in much the same way as natural attacks of smallpox would prevent second attacks, there is no evidence that Jenner really departed from his original opinion, and his statement written a few days before his death (p. 249), only confirms that he died with this belief firmly in his mind.

A point noted by others, but ignored by Jenner, was that when multiple insertions were made some took successfully and others failed, hence the obvious possibility of good lymph failing to take in a hundred per cent of cases where only a single insertion was done. Many years had to pass before doctors would admit personal failure of technique.

In 1805 a medical practitioner named Jones, writing under the pseudonym of "Squirrel", tried to prove that cowpox did not protect against smallpox, but only produced scrofula, and Moseley in 1805 wrote *A Treatise on the Lues Bovilla or Cowpox*. The cartoonists of the time, such as Gillray (1815), illustrated the effects of vaccination on children by drawing them with cows' faces and horns growing out of their heads, and horrific stories were written of vaccinated children bellowing like bulls and undergoing complete change of personality. Baron (1838) quotes: "There was a Master Jowles, the cow-poxed, ox-cheeked, young gentleman and Miss Mary Ann Lewis the cow-poxed, cow-managed young lady exhibited in all the touching simplicity of graphic delineation by Dr. William Rowley a learned Member of the University of Oxford." Criticisms came from all walks of life and therefore carried much greater weight. Amongst the mass of distortions, with every failing in an individual blamed on the preceding vaccination, there is just the possibility that post-vaccinial encephalitis may have occurred and caused real personality changes in some individuals, particularly as much early vaccination was in older children and adults. Amongst the ignorant and super-sensitive the disgusting nature of transmitting a disease from an animal to man was worked upon, and undoubtedly the idea that cowpox was in some way a venereal disease of animals made it so outrageous as to bring in a large number to the side of antivaccination. In 1806 the Royal College of Physicians, having corresponded with the College of Physicians in Dublin and

Edinburgh, reported in favour of vaccination. Variolation was still being done quite freely, particularly in London, and Jenner himself tried unsuccessfully to have it prohibited. Others, much wiser, realized this was an admission of weakness. It continued at the smallpox hospital on out-patients until 1808, and on in-patients until 1822.

The Government, having blessed vaccination, wished to put it on a firmer basis than that provided by the Royal Jennerian Institution, which had almost collapsed. Jenner produced a plan for the National Vaccine Establishment and he was appointed director. The National Vaccine Establishment was to estimate the value and dangers, if any, of vaccination, but Jenner, because he was not a member of the Royal College of Physicians of London, was not eligible to be a member of the Board. Jenner nominated his friend Moore as assistant director, and wanted Mr. Ring to be principal vaccinator, but when the Board assembled to appoint its officers Mr. Ring was not included. Jenner's nominations for subordinate officers also met with little approval from the Board. Jenner regarded himself as the one and only person who knew anything about the subject at all. The Board, consisting of the president and four censors of the Royal College of Physicians and two governors of the Royal College of Surgeons, thought otherwise, and Jenner, as ever resentful of any criticism, resigned and Moore was appointed director. Moore was very loyal to Jenner, who spent much time in trying to influence him to continue to let the world know that Edward Jenner was really the only person who knew anything about vaccination. He continued to correspond with Moore and expressed his feelings in the following letter. What the latter really thought about him we shall never know.

> "At the time I informed you of my intention to come to town, believe me I was quite in earnest. But while I was getting things in order came a piece of information from a Right Hon. Gentleman which determined me to remain in my retirement. It was as follows. That the Institution was formed for the purpose of a full and satisfactory investigation of the benefits or dangers of the vaccine practice, and that this was the reason why Dr. J. could not be admitted as one of the conductors of it, as the public would not have had the same confidence in their proceedings as if the board were left to their own judgement in doubtful cases.
>
> You intimated something of this sort to me some time since, and now I get it from the fountain head. An institution founded on the principle of inquiry seven or eight years ago would have been worthy of the British nation; but now, after the whole world bears testimony to the safety and efficacy of the vaccine practice, I do think it a most extraordinary proceeding. It is one that must necessarily degrade me, and cannot exalt the framers of it in the eyes of common sense. I shall now stick closely to my own Institution, which I have the pride and vanity to think is paramount to all others, as its extent and benefits are boundless. Of this, I am the real and not the nominal director. I have conducted the whole concern for no inconsiderable number of years, single handed, and have spread vaccination round the globe. This convinces me that simplicity in this, as in all effective machinery, is best.
>
> I agree with you that my not being a member of the British Vaccine Establishment will astonish the world; and no one in it can be astonished more than myself. . . ."
>
> Berkeley, Apr. 4th, 1909.

Although Jenner appears to have been harshly treated, his intolerance of any criticism of his gospel, particularly the principle of lifelong immunity, stimulated his opponents to use any suitable ammunition with which to attack him. He had variolated his own son in 1799, which his critics argued proved his own lack of faith in vaccination. In a letter of 6 November 1810, he states: "However during my stay there in 1799 this boy was accidentally exposed to the smallpox, and in such a way as to leave no doubt on my mind of his being infected. Having at this time no vaccine matter in my possession, there was no alternative but immediate inoculation, which was done by Mr. Cother, a surgeon of this place who is since dead, but this history is well known to many who are living." In 1811, Jenner came up against further difficulties. Up till then he could explain all the failures of vaccination as being due to imperfect technique of some kind or another, but on 26 May the Hon. Robert Grosvenor became ill with smallpox although he had been personally vaccinated by Jenner only ten years previously. Jenner reacted characteristically, as shown in the following letter.

Cockspur Street, Charing Cross,
June 11th, 1811.

MY DEAR FRIEND,—I should be obliged to you to send me, by the first coach, some of the Reports of our association. It will probably be my unhappy lot to be detained in this horrible place some days longer. It has unfortunately happened that a failure of vaccination has appeared in the family of a nobleman here; and more unfortunately still, in a child vaccinated by me. The noise and confusion this case has created is not to be described. The vaccine lancet is sheathed; and the long concealed variolous blade ordered to come forth. Charming! This will soon cure the mania. The town is a fool,—an idiot; and will continue in this red-hot,—hissing-hot state about this affair, till something else starts up to draw aside its attention, I am determined to lock up my brains, and think no more pro bono publico; and I advise you, my friend, to do the same; for we are sure to get nothing but abuse for it. It is my intention to collect all the cases I can of Small Pox, after supposed security from that disease [by variolation]. In this undertaking I hope to derive much assistance from you. The best plan will be to push out some of them as soon as possible. This would not be necessary on account of the present case, but it would prove the best shield to protect us from the past, and those which are to come.

Ever yours,
EDWARD JENNER.

As usual, Jenner had a theoretical explanation. Instead of emphasizing the fact that the other children in the family, who had been vaccinated at the same time, did not contract smallpox, which demonstrated the value of vaccination, he ascribed the failure "to that peculiarity of constitution which probably would have left the patient exposed to a second attack of smallpox had he previously had the disease", a fact which might well be true, but would not be appreciated then. Baron, whose hero could never be wrong, stated that Dr. Jenner "had not been perfectly satisfied with the progress of the vaccination in this child". There is no evidence that this in fact was true. It is just the sort of statement repeatedly made by those who were blind to Jenner's faults and which did so much harm to the cause of vaccination. Jenner himself, of course, was at fault. In a letter to Miss Calcraft of 19 June, about this particular event, he states:

"What if ten, fifty or a hundred such events should occur, they will be balanced an hundred times over by those of a similar kind after smallpox." In other words, two wrongs would make a right. In any case, how inconsistent with his statement both in 1798 and just before his death that "properly performed vaccination gave lifelong protection". "With regard to the mitigated disease which sometimes follows vaccination, I can positively say, it shall be borne out in my assertation by those who are in future days to follow me, that it is the offspring entirely of incaution in those who conduct the vaccine process." Failure in his own vaccinations was due to peculiarity of constitution—failure in others was due to incaution!

In 1814, with the abdication of Napoleon and the restoration of the Bourbon dynasty, many allied sovereigns visited England, and there was a great congregation of influential people in London. As Baron naïvely puts it, "Jenner had occasion to visit London in the end of April, 1814, and took up his residence at number 7, Great Marylebone Street". He stayed there for more than three months, during which time he endeavoured to meet all the persons of importance, including the Duchess of Aldenberg, sister of the Emperor of Russia. Count Orloff, the Russian Ambassador, suggested that Jenner should memorialize the assembled monarchs on the score of his claim as a universal benefactor. Baron discreetly says that Jenner shrank from such a project, but when Count Orloff asked if he would accept a Russian order, he replied that he thought this belonged exclusively to men of independent means.

There is very little doubt that Jenner went to live in London for three months, without his wife, who was very ill, simply to see whether he could not advance himself by way of titles or money. He returned to Berkeley in October of that year.

On 13 September 1815, in the year following, his wife died. This greatly affected Jenner, and from that date he retired from public life, and never went again to London in search of honours or reward. In the semi-seclusion of the Chantry at Berkeley, Jenner continued for some eight years to carry on a lively correspondence with men of learning in many parts of the world. He was particularly pleased to discover the use of equine strains of cowpox virus in France, but this really did nothing to establish his original theories.

Outbreaks now commenced to occur in which considerable numbers of persons previously successfully vaccinated contracted mild attacks, the clinical signs of which, as Jenner himself described, were sometimes midway between chickenpox and smallpox. This element of confusion undoubtedly contributed still further to the ease with which either side could assert that the disease in a vaccinated person was either modified smallpox or chickenpox, depending on the loyalties of the observer. At last smallpox was imported into Berkeley and Henry Jenner, his nephew, contracted smallpox, again a modified attack although a fairly profuse eruption. By now most supporters of vaccination would only claim that absolute protection lasted for a short time, but not Jenner; he wrote on the back of an envelope dated 14 January 1823 (Baron, 1838):

> "My opinion of vaccination is precisely as it was when I first promulgated the discovery. It is not in the least strengthened by any event that has happened, for it could gain no strength; it is not in the least weakened, for if the failures you speak of had not happened, the truth of my assertions respecting those coincidences which occasioned them would not have been made out."

On the 25 January Jenner had a cerebral haemorrhage and died the next day.

Jenner is buried in Berkeley Church, beneath the stained-glass window provided by public

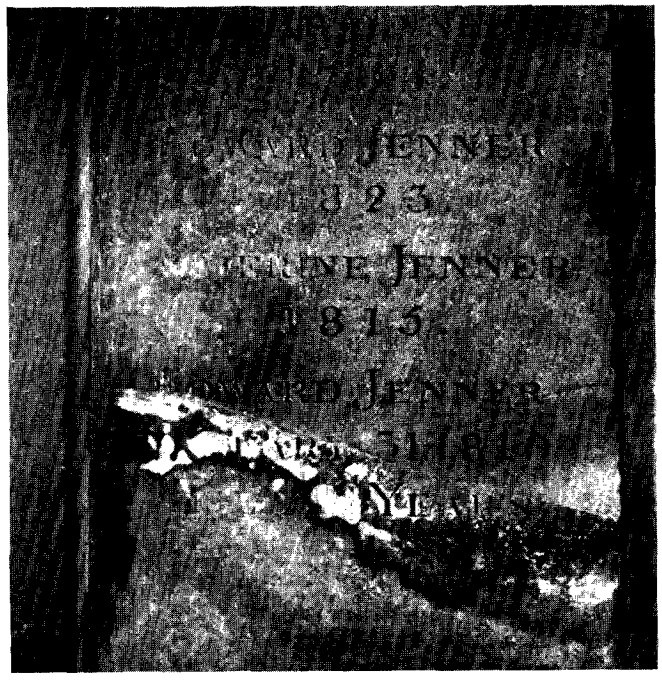


FIG. 218. Grave of Edward Jenner, died 1823. Buried alongside are his wife Catherine and his son Edward.

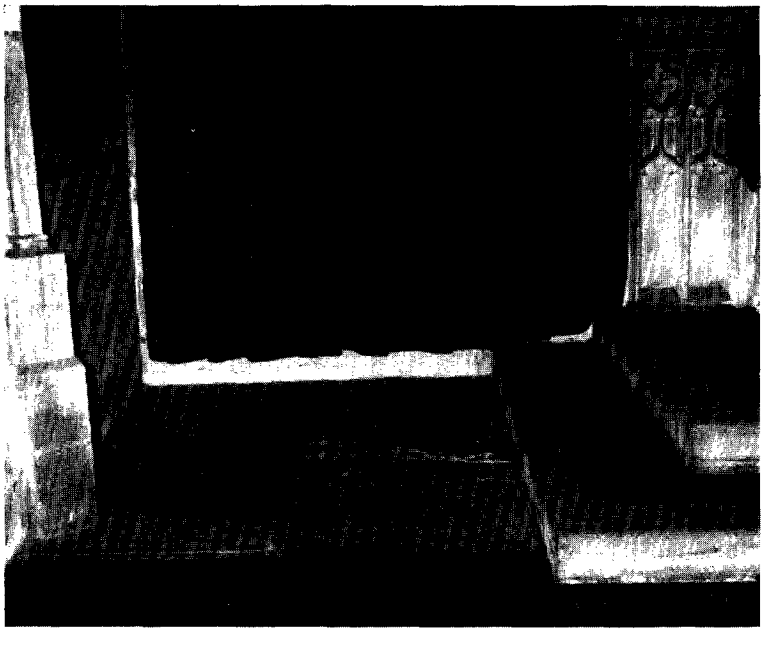


FIG. 219. The grave of Edward Jenner in the chancel of Berkeley Church, Gloucestershire.

subscription. Any visitor to this interesting village can see his house and garden, the greenhouse and the vine planted by Jenner and the old church tower in the corner covered in ivy, grown from a cutting taken from Monmouthshire and also planted by Jenner.

Early in 1799, Benjamin Waterhouse, who was Harvard's first professor of the theory and practice of physic, received a copy of Edward Jenner's Inquiry from his London friend, Dr. Lettsom, and he soon published news of the discovery in a Boston newspaper. By 1800, American physicians were interested in cowpox and were anxious to obtain the material from England. Waterhouse obtained some from Dr. Haygarth of Bath, who himself had obtained it from Jenner. It was probably Woodville's strain or that from Clark's farm in Kentish Town. On 8 July, Waterhouse vaccinated his son and a little while after vaccinated six members of his household. He then requested Dr. Aspin Wall, who ran an inoculation hospital in Brooklyn, to inoculate them with smallpox. The test was successful. At this stage it is pertinent to note that Waterhouse received the report, acted upon it and repeated Jenner's experiment, satisfying himself that the claim of protection from variolation was genuine. From then on, however, his actions were more doubtful. In spite of requests for vaccine he refused to give any to others on the grounds that he himself had undertaken the experiments and that he was not anxious to allow it to be used extensively, and cited as argument the unfortunate accidents which had led to delay in the development of variolation in Scotland compared with England. By 6 September, however, his academic scruples had altered sufficiently to allow him to offer to another practitioner, at Portsmouth, New Hampshire, vaccine material in return for one-quarter of the profits arising from vaccination. Within a short time Waterhouse had allotted the surrounding areas to individual practitioners who in return for a supply of vaccine agreed to pay Dr. Waterhouse a quarter of the profits, or in some instances where he thought this would be relatively small, a flat fee of 150 dollars. Attempts were made by other practitioners to break this monopoly and introduce vaccine from England. In spite of difficulties and failures, a Dr. Manning of Ipswich, who had received "matter" from his brother in London, was prepared to give to other practitioners without payment, and from this point vaccination spread in spite of Waterhouse's attempt to maintain his monopoly. Waterhouse's action in rendering the supply of vaccine difficult, not only gave him financial benefit, but it increased the chances of unsatisfactory material being smuggled in and used in imitation of vaccination. When his monopoly was broken, Waterhouse realized that much spurious vaccination was being done and also the possibility of variolation under the mistaken guise of vaccination, and he wrote many letters in the press condemning this practice. The source of much of this vaccination material was most unsatisfactory. Clothing impregnated with discharges from ulcerating pustules was regarded as a source of lymph and small pieces sold for high prices. Even if originally infective, it was frequently not so at the time when used. As one would expect, this led to public reaction against vaccination, when people who were reputed to have been vaccinated, who might even have had some sort of scar, contracted smallpox in an unmodified manner and died. Perhaps greater credit should be given to Dr. Thomas Manning of Ipswich, who not only imported the vaccine himself and distributed it without payment to other practitioners, but also carried out a variolous test on 16 October 1800. It is perhaps a pity that Edward Jenner, confident in his Berkeley retreat, could not have read the comments of James Jackson, given by John Blake (1957) in his book on Waterhouse. I quote them in full.

"... 'It is also proper for me to declare to those whom I have inoculated for the cow-pox,' he added, 'that my confidence in it is not so perfect as it once was.' He then reported in detail

upon the case of a man named Wheelock who had been vaccinated in October, and who had been inoculated with smallpox in January and probably contracted the disease. Those who knew him, Jackson continued, would readily conceive 'that I have not witnessed these circumstances without mortification. But it will not save my feelings to conceal the facts. It is more pleasing to me to give my evidence in favor of the truth even against an opinion of which I have been an advocate.' The case, he urged, should be independently examined by other gentlemen of the faculty. Should they find him in error, he remarked, 'no person will be more gratified than myself'. He would not say for sure, he concluded, that Wheelock had had smallpox. But his case had 'excited in my mind doubts, which I thought I should never find there'. At the most it could only prove 'that the cow-pox does not always preserve the subject of it from the small-pox; but this is an inconsistency in the operations of nature to which we should not give full credit without the clearest evidence.' . . ."

In all fairness to Waterhouse, by the winter of 1801 he realized his method of distribution was a serious mistake. When he received a further supply of lymph in March 1801, he distributed to all without reward. This led to his being given the unqualified credit for the establishment of vaccination in America. Waterhouse should be remembered, however, for having forced a public body, the Board of Health of Boston, to undertake an experiment. With the town's permission, smallpox inoculations were to be done in an isolated place on individuals who had previously been vaccinated. On 16 August 1802, nineteen young volunteers were vaccinated, and a week later, after they were examined and regarded as fit for the experiment, they were inoculated with fresh smallpox virus along with another person who had not been vaccinated and who was to test that the smallpox matter was active. The test was a complete success. None of those who had been vaccinated contracted smallpox by inoculation. "This decisive experiment", Waterhouse said, "has fixed for ever the practice of the new inoculation in Massachusetts." Unfortunately, of course, the protection tested was against variolation and not against naturally acquired smallpox, and no thought was given to the duration of immunity. It was likely, of course, that Waterhouse, trained in the Sydenham tradition, would regard this alteration of the constitution as irrevocable.

As already mentioned, Jenner was honoured much more on the Continent of Europe and elsewhere than he was in his own country, and this was partly due to the rapidity with which vaccination was taken up, particularly in countries where variolation was never so popular as in England. By 1799 vaccinations were being done in Hanover and in Vienna, by 1800 in Greece, Turkey and even in India and Ceylon. In 1800 France had sent observers to England and a vaccine station was opened. Woodville took lymph to Paris which was reported to be quite satisfactory. By 1805 Napoleon had ordered the vaccination of all troops who had not had smallpox. Vaccination was started in Berlin in 1800. In 1803, out of 17,000 vaccinations done in Germany, over 8,000 had been tested by subsequent variolation. In 1801, Sacco in Italy was vaccinating from a fresh source of lymph from natural cowpox, in which he appears to have had a particularly favourable strain, and probably had better results than Jenner at his first trials. Vaccination was rapidly introduced into Russia and it is reputed that nearly two million people were done between the years 1804–14. Vaccination was commenced in Spain, and in 1803, under the direction of Dr. F. Balmis, introduced to her colonies by taking children on board ship and continuing arm-to-arm vaccination on a small number every week so as to maintain the supply to the end of the journey. Vaccination was made compulsory in Bavaria in 1807, in Denmark in 1810, and in Sweden in 1816. At that time, as we have already seen,

Jenner was still fighting for some recognition that the procedure was an advantage at all, and it took a long time before England moved very far in this direction, although in 1807 the Commission of the Royal College of Physicians had reported strongly in its favour.

As early as 1818, the King of Wirtemburgh had issued enactments which took a very comprehensive view of the function of vaccination, as given below.

"Every child must be vaccinated before it has completed its third year, under a penalty annually levied on its parents so long as the omission continues; and if the operation fail, it must be repeated every three months until a third trial. No person to be received into any school, college or charitable institution; be bound apprentice to any trade; or hold any public office, who has not been vaccinated. When small-pox appears, all those liable to take it must be vaccinated without delay; and, the operation not succeeding, it must be repeated every eight days to the third time, under a penalty. The superintendence of vaccination is limited to medical men, each of whom takes charge in a given district; and a fine is levied on all who undertake to vaccinate without being duly qualified. The name of every child is to be enregistered the day after its birth; and if it die before vaccination, notice must be given. Provision is made for a supply of fresh ichor annually from the cow: and for vaccinating from arm to arm, the parties being recompensed for the time thus taken up. Variolous inoculation is prohibited when small-pox is not present; and when it is, the practice can only be done by a medical man, and under proper precautions of seclusion, &c., to prevent the disease from spreading: all expenses incident to the isolation and care of variolous patients, whether the disease has been taken by contagion or inoculation, is to be borne by the parents, unless the individual had previously gone through the cow-pox, or been thrice vaccinated without effect."

Much sound advice, but I wonder how much was really put into effect.

Apart from the financial grants made to Jenner in 1802 and in 1806, and at the latter date the abortive attempt at legislation to control variolation, the British Parliament took little interest in furthering the cause of vaccination. Annual grants were paid to the National Vaccine Establishment from 1807, but it was not until 23 July 1840 that an Act was passed to "extend the practice of vaccination". By this Act, the guardians or overseers of every parish or union in England and Wales were empowered to contract with registered medical practitioners to perform vaccinations. This was the first free medical service. The procedure however was optional. It is of interest that this provision specifically stated that payments were to be made to the medical practitioners for vaccinations carried out on persons not previously vaccinated, so making it appear that revaccination was discouraged. The eighth section of this Act made inoculation of smallpox, variolation, illegal. A further Act in 1841 clarified certain points, making it clear that the expenses in carrying out the Act were a charge on the poor-rates, although a person so vaccinated or requiring medical care resulting from it, should not be stigmatized as having had "parochial relief".

The next Act of importance is that of 1853, the second Vaccination Act, which was partly the result of pressure from the newly formed Epidemiological Society. The title was "An Act to Extend and Make Compulsory the Practice of Vaccination". It is not without interest that compulsion was introduced through the House of Lords, and on the recommendation and at the suggestion of the Epidemiological Society whose members were medical. The Act gave further instructions to guardians as to how to divide their areas into convenient districts for

vaccinators so as to increase the facilities for the vaccination of the poor. Vaccination was limited to those persons who had not already been successfully vaccinated.

The second section dealt with compulsion. Within three months of birth the parents of a child should take it to the appointed vaccinator unless the parent could obtain a certificate of previous vaccination from some other practitioner. It was also enacted that on the eighth day after the vaccination it must be inspected. A certificate must be given by the vaccinator and submitted to the Registrar of Births and Deaths. A saving clause provided that a medical practitioner could give a certificate that the child was unfit for vaccination; this was good for two months, but was renewable indefinitely. The penalty for failure to have a child vaccinated, or failure not to take it for inspection at the eighth day, were both twenty shillings, a large sum in those days. It should be noted that this legislation made no provision for, or gave encouragement to, revaccination, although as early as 1825 the epidemic in Paris had made clear the necessity for it, and Gregory (1838) and others had recommended it.

A further Act of indirect importance was the Public Health Act of 1858, vesting in the Privy Council certain powers for the protection of public health. The General Board of Health which had been set up ten years before was due to expire on 1 September 1858. The importance of this was that the Privy Council could appoint medical officers and was concerned with what might be termed the medical aspects of vaccination, whereas the Poor Law Board still continued to exercise control over the non-medical aspects, the contracts with public vaccinators and the problems relating to enforcement. The Privy Council was given power to issue regulations as to the qualifications of persons who could be public vaccinators. In 1867 a consolidating Act was passed, the qualifications of public vaccinators were laid down, and a certificate of competency in vaccination was required of medical practitioners who wished to undertake this work. This certificate was required until the Act was repealed by the National Health Service Act, 1946. The inability to repeat the fine for non-compliance under earlier Vaccination Acts was altered so that the fine could be repeated if the parents persistently refused to have their children vaccinated. The Privy Council were authorized to increase the payment to public vaccinators, this doubtless because with arm-to-arm vaccination the supply of lymph was dependent on their satisfactory work. Regulations could be made by the Privy Council for persons wishing to be revaccinated, but little encouragement was given as the fees were to be two-thirds of those given for primary vaccination. The public vaccinator was also empowered to take lymph from any child who was being inspected, and could also repeat the vaccination on any child whose first attempt had failed. Minor details in the administration were tidied up and the Boards of Guardians were able to receive their expenses for prosecutions made under the Act. In spite of attempts to make the working of the Act easier, it was in many ways made more difficult and it roused opposition because of its ambiguity. The parent was guilty of an offence if he had not rendered a reasonable excuse for his neglect, but there is nothing in the wording of the clause to suggest whether the excuse should be formally given to some administrative body, or whether kept and used as a defence when the parent was ultimately prosecuted. A further clause intent on hounding the parent who had refused to have the child vaccinated made it necessary for the parent and child to be brought before a magistrate, and for the magistrate to then issue a directive that the child was to be vaccinated. If this was carried out, then no penalty could be inflicted. If it was not, a penalty could be inflicted, not for failure to vaccinate, but for disobedience of the magistrate's order to be vaccinated. After the penalty had been paid the child was again brought before the magistrate

for direction as to whether another order should be made for the child to be vaccinated. The clause gave absolute discretion to the magistrate. It was therefore possible for widely differing practices to occur under the jurisdiction of different magistrates. It should be noted that although the punishment for failure to vaccinate was a fine, the punishment for not carrying out the order of a magistrate could be imprisonment, and in a test case it was decided that this was a criminal act and that the prisoner had no right to the more humane treatment of a civil debtor. The Vaccination Act of 1871, which came into effect on 1 January 1872, made it obligatory for guardians to appoint officers for prosecutions under the Vaccination Acts and to enforce their provisions, except those carried out by the Registrars. One section gave an important new duty to the medical officer of the union acting as public vaccinator in that he could be paid for vaccinating or revaccinating smallpox contacts.

The Vaccination Act of 1874, along with sections of the Vaccination Act of 1871 and the Local Government Act of 1871, clarified the position whereby the Boards of Guardians carried out certain functions amongst the poor under their powers under the Poor Law, whereas, although they were the same body, they carried out functions under the Vaccination Acts for the whole population. It was this double responsibility which caused so much controversy over the enforcement of the compulsory vaccination of infants.

In 1888 a Bill was brought in Parliament to abolish compulsory clauses in the Vaccination Act but it failed to pass. However, people were worried about vaccination, particularly the implementation of compulsory infant vaccination alone as a method of controlling smallpox, and in 1889 a Royal Commission on Vaccination was appointed. In 1896 the Royal Commission issued its final report recommending modification of compulsion by recognition of the conscientious objector. Although the 1898 Act passed legislation giving the conscientious objector legal status, it is of interest that the Parliamentary Bills Committee of the British Medical Association in 1898 urged a change in the law so that the failure of Boards of Guardians who were not enforcing the Act might be got over by providing some official whose duty was to take legal proceedings without receiving any instruction from and notwithstanding any opposition by the local authority. It is of interest that again the medical profession seems to have been wholeheartedly in favour of compulsion.

Pressure from antivaccinationists was increasing greatly, partly on the grounds of their objection to the procedure, but very largely because of the methods of compulsion under the Acts, particularly in the use of the Poor Law machinery. Under the 1898 Act, along with the conscientious-objection clause, the age period was extended from three to six months, but a person had to satisfy the justices within four months that his conscience was indeed troubled, with the result that in some areas justices would accept any statement to this effect and almost automatic exemption would be granted, whereas in those areas where the justice was a staunch upholder of the law or wished to exercise his power and authority, he would not listen to any claims of conscience and the objector would get no relief.

At long last, arm-to-arm vaccination by public vaccinators was prohibited, although this was still legal for private medical practitioners. The use of calf lymph for public vaccination was made compulsory, and this removed the risk of syphilis, possible with the arm-to-arm technique. In 1903, as a result of a large outbreak of smallpox in the country, a departmental committee was appointed to inquire into the cost of public vaccination, which had become very heavy, but not whether it was achieving its object. This committee reported in 1905, and the Local Government Board issued an order reducing the minimum fees for vaccination.

In 1907 the Vaccination Act was passed, enabling the parent to claim exemption by making a statutory declaration, on the grounds of conscience, that they did not wish to have vaccination done, and they did not have to satisfy the justices. We have the situation of infant vaccination legally compulsory, but the parent able to contract out by making a statutory declaration. Although Government calf lymph treated with glycerine was supplied to public vaccinators, it was supplied to them only. Private practitioners had to get theirs from trade sources. Acland (1912) states: "It is most incredible that a nation which is so particular that margarine should not be labelled butter, permits any preparation to be imported and sold as vaccine lymph, without requiring a guarantee as to its source, origin or nature. It cannot be unreasonable that all individuals vaccinated in compliance with the law should have the right to the use of lymph prepared by the most scientific methods, in laboratories kept up at the expense of the nation, whether they are vaccinated by a private practitioner or by the public vaccinator. As long as the present state of things continues, there can be no certainty that vaccinations performed by others than the public vaccinator at the public expense are done with lymph which is either efficient or prepared with all the safeguards which are universally admitted to be necessary." It was not until the Therapeutic Substances Act in 1925 came into effect that this unsatisfactory situation was remedied.

In 1946, the National Health Service Act came into force. All the sections of the Vaccination Act were repealed, and free, voluntary vaccination, organized but not necessarily carried out by the local health authorities, was substituted.

The history of the development of legislation dealing with vaccination in England and Wales has been given in some detail as the changing approach from the time of Jenner to the present day makes an interesting study in relation to our modern ideas on smallpox control. The vaccination laws of other countries are, however, of considerable interest, and have been briefly surveyed in the *International Digest of Health Legislation* (1954). Compulsory vaccination was introduced very early in Italy, the principalities of Piombino and Lucca in 1806, and in Bavaria in 1807, France 1809, and Norway 1810. In most countries, these original laws have been repealed or considerably altered, but that of Norway is much the same today as when first promulgated. Amongst some forty-seven countries listed as having vaccination legislation, the vast majority have some clauses in which infant vaccination is compulsory, and a few have conscientious-objection clauses. It is much more doubtful, however, whether compliance is in fact anything like so complete as the advocates of compulsory infant vaccination would assume. In some countries, vaccination is compulsory, for certain types of work, for example nursing, merchant seamen, or for attendance at school, while in Norway it is still required for intending parties to marriage. Compulsory infant vaccination has been based on the mistaken belief that this would control smallpox in a community other than one in which the adults were already immune. Compulsory revaccination has had much more limited application. As early as 1835, compulsory revaccination was instituted in the armies of some German States, and in a number of countries revaccination is still required for children at the age of twelve years. One wonders, however, how much of this legislation is really effective. In the W.H.O. *Digest*, 1954, it stated that in France children are revaccinated at eleven and twenty-one years, but this is not strictly correct. Although both vaccination in infancy and revaccination at eleven occurs in the large towns, it is not carried out so efficiently in remoter areas, as outbreaks of smallpox show. Revaccination at twenty-one years is not laid down in any legislation, but only occurs in males who are called up for military service.

CHAPTER 13 | *The Vaccination Controversy*

Although today views on the best use of vaccination in the control of smallpox are not entirely uniform, in England in the nineteenth century vaccination was the subject of the greatest controversy in the history of medicine. The literature on the subject is enormous, and one can only attempt a review of some of the principal arguments which have a bearing on our modern concepts of smallpox control.

The first part centres round Jenner, and the discovery of vaccination and its use, and this continued through the whole century, to be merged after 1850 with the State's interference in the liberties of the subject, by implementing the policy of compulsory infant vaccination, made doubly odious by its administration through the Poor Law authorities. Our main characters, Jenner, Baron, Simon, Creighton and Crookshank, lived in the nineteenth century, the century in which bacteriology had only just emerged, in which there was no laboratory confirmation of diagnosis of cowpox, smallpox or vaccinia, or other conditions which might be confused with any of these. Entire reliance was placed on a clinical diagnosis. In an authoritarian age, the eminence of the person making the diagnosis was the most important factor in accepting its accuracy. The diagnosis of syphilis, the great fear in arm-to-arm vaccination, was also based on clinical findings, and its cutaneous manifestations were frequently confused with other diseases. Small wonder that emotions and rhetoric rather than scientific facts have been the principal weapons in the battle during the whole of the century. Baron and Simon regarded Jenner as a saint who could do nothing wrong, Creighton and Crookshank regarded him as a cunning charlatan who could do nothing right.

In Creighton's eyes, Jenner's greatest crime was to call cowpox "smallpox of the cow", and in particular to have the audacity to give it a Latin name, variolae vaccinae, which he felt was given to this condition entirely to bluff the general public, particularly as Jenner's Latin was poor, and not up to the erudite Creighton's standards. Jenner, however, believed that cowpox was in fact smallpox of the cow, but I don't think he had the idea that it was an irreversible mutant in the way that we believe it to be today. In the Sydenham tradition, unless cowpox was smallpox, the constitution could not be permanently altered so as to render it insusceptible to further smallpox. In a sense, however, he regarded it as a variant, in that it did not generalize, and the patient was not infectious to others, a point he could have emphasized more, although Suttonian variolation was regarded by many as "almost" non-infectious. This was a fundamental truth which in spite of all Jenner's faults must stand to his credit.

But what of Jenner's research, the "thirty years he thought and watched and experimented on the subject" (Simon, 1857). Jenner recorded some observations which suggested that persons who had had cowpox, even many years before, appeared to be insusceptible to smallpox, although they had no history of a previous attack of that disease. Amongst those few cases, however, this might have been a chance association in a dairying district where cowpox might be common. The immunity to subsequent smallpox might well have been due to a

previous attack which was unrecorded. It must not be forgotten that some adults who had no history of smallpox or cowpox appeared to be immune. Jenner, as the careful scientist, would doubtless check that people had no evidence of scars, but we know that mild attacks and resultant immunity can be obtained without permanent scars. Failure therefore to variolate some individuals after cowpoxing might have been due to a previous unknown attack of smallpox, and not due to any protective power of cowpox. This part of his evidence, the nineteen cases of natural cowpox, only gave slightly more backing to the opinions already held and noted by Adams (1795) and Woodville (1796) in their books.

Jenner's attempt to prove it experimentally deserves great credit, but it was eight years after he had shown the drawings of human cowpox to his friends in London. Was he really very uncertain of the outcome and selected James Phipps, a poor little specimen who was

FIG. 220. House built by Jenner for James Phipps in 1818.

believed to have a tuberculous hip or spine, who he may have felt was not a very valuable individual if the experiment went wrong? On the other hand, one must admit that Jenner had had the courage to inoculate one of his own children previously with swinepox, a variety of smallpox, and in subsequent investigations he also used members of his own family. His sense of gratitude to James Phipps was shown by the cottage he had built for him in 1818, and which still stands today. Jenner cowpoxed James Phipps with material taken from a typical case of cowpox in a milkmaid. Despite objections by Crookshank and others that Jenner used a mild strain of smallpox, and therefore variolated and did not vaccinate, there is no evidence that the material used was not from a typical case of human cowpox. The cowpoxing took well, but this did not exclude the possibility that James Phipps had had smallpox mildly at an early age. The critic could say, believing that cowpox and smallpox had nothing in common, that Jenner selected a boy who had had smallpox mildly in infancy, whom he believed he could infect with cowpox at the age of eight, which he did, and in whom the

insusceptibility to variolation some seven weeks later could not be proved to be due to the cowpoxing on 14 May.

The only other experimental work was the cowpoxing in 1798, direct from the cow. Several children were inoculated from arm-to-arm, up to the fifth remove from the cow, but in only three of these, including the last remove, did he bother to carry out the variolation test. From the experimental point of view Jenner stopped much too soon. The whole course of events might have been different if John Hunter, who had died in 1793, had still been alive to guide and criticize Jenner. His earlier advice, to speculate less and experiment more, was never more needed than at this time. Compared with this, Pearson, as soon as Jenner's pamphlet was published, collected by the questionnaire technique as much information as possible on the supposed immunity to smallpox of those who had been accidentally infected with cowpox, and tried inoculating smallpox on five persons, three of whom had had, and two had not had, natural cowpox. In the latter normal variolation occurred, while the three former appeared insusceptible. To add to these experiments of Pearson's, Woodville at the latter's suggestion had in 1799 vaccinated and subsequently variolated some 450 people. By 1802, Woodville had vaccinated 7,500, about half of whom were subsequently variolated without any effect. It should be noted that in 1799 Waterhouse repeated Jenner's experiment, but on a larger scale, by cowpoxing and subsequently failing to variolate.

Jenner's "discovery" was based largely on intuition rather than experiment, but in the days when much pathology was based on the idea of "laudable pus", Jenner's comment on the reason for failure of cowpox to take and produce immunity is quite masterly (1799): "I shall proceed to enumerate the sources, or what appear to me as such of a spurious cowpox. First, that arising from pustules on the nipple or udder of the cow, which pustules contain no specific virus. Secondly from material, although originally possessing specific virus, which has suffered a decomposition, either from putrefaction or from any other cause less obvious to the senses. Thirdly, from matter taken from an ulcer in an advanced stage, which ulcer arose from true cowpox." His capacity to visualize the properties of a specific infective element distinguished from that producing ordinary septic lesions and capable of loss through defective storage or not being present in a lesion too advanced, is quite remarkable.

His description of inoculation allergy also shows his great powers of observation and uncanny ability to interpret what he saw. "It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the smallpox. Indeed, it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable, too, that whether this change has been affected by the smallpox or the cow-pox that the disposition to sudden cuticular inflammation is the same on the application of variolous matter."

One of Jenner's earliest problems was that although he claimed that cowpox gave complete protection against subsequent infection with smallpox, natural cowpox could occur more than once in the same individual, and could also occur in those who had previously had smallpox many years before. Jenner shows great resentment to Dr. Ingenhousz's quite logical comments, made to T. Paytherus, who interviewed him on Jenner's behalf. "That it should render the habit insusceptible of smallpox, and not of its own specific action, is to him incredible. He desires that you will not be in haste to publish a second time on cowpox, and wait

until you have collected a sufficient number of facts, and to secure your ground as you advance. He remarked that you would not be permitted to be judged in your own cause; that you were now before the tribunal of the public, and so long as *sub judice lis est* ought not to risk an opinion." Much of this was prophetic. Even the National Vaccine Establishment would not let him judge his own case. It was a pity that Jenner could not or would not understand and wrote in high dudgeon: "At present I have not the most distant doubt that any person who has once felt the influence of perfect cowpox matter would ever be susceptible of that of the smallpox."

Jenner himself was not particularly lucky with his vaccinations following the experimental ones. He lost his original virus strain and had to accept some from Woodville, in spite of his criticism of Woodville's technique. He obtained what he thought was a new source of virus in the village of Stonehouse in Wiltshire, but unfortunately this strain gave rise to severe reactions, sordid ulcers and no immunity to variolation. It would seem that Jenner himself had difficulty in recognizing true cowpox lesions, and much of the credit for the early popularity of the procedure should go to Pearson and Woodville. Jenner, and particularly his relatives and friends, resented this, as shown by the correspondence. Pearson's and Woodville's work probably more than anything, influenced the clergy and other laymen to try vaccination themselves. 1798 was also a bad year for smallpox in London, and there is no evidence to suggest that it was not also an important disease in many other populous centres. One sees a situation not unlike that which occurred in 1720, on the introduction of variolation: considerable enthusiasm amongst lay people, under the threat of smallpox, and a section of the medical profession who saw in it a lucrative practice; opposition from some, who quite rightly questioned the validity of Jenner's sweeping and unproven assertions, and from those who derived no small part of their income from the treatment of smallpox.

Although some feel that Jenner became embittered because of the way he was treated, his attitude towards Ingenhousz's criticism is typical and occurred so early. Although Baron blames Pearson and Woodville as the cause of much of the controversy, Jenner obtained good advice from many people. Dr. Percival wrote on 20 November 1798: "The facts which you have adduced incontestibly prove the existence of the cowpox and its ready communication to the human species, but a larger induction is yet necessary to evince that the virus of the variolae vaccinae renders the person who had been affected with it secure during the whole of life from the infection of smallpox."

His fatal mistake was of course the claim that vaccination produced lifelong immunity. It is difficult to understand how in the face of increasing evidence Jenner should continue until the day of his death with this belief. It was, however, his idea of the effect on the constitution which caused him to develop the first explanation of true and spurious cowpox, and doubtless in the early days, with some good reason for the latter, as both medical practitioners and lay people were experimenting with any pustular lesion of the cow and calling this vaccination. Later, however, even when his own vaccinations were seen to fail to give permanent immunity, he countered this by pointing out that vaccination was not at fault, but the constitution of the individual, citing as an example the failure of an individual to remain insusceptible to smallpox, even after a previous attack of this disease, particularly by inoculation. At no stage did he believe that immunity, in the sense that we understand it today, was a quality which could change, as this was alien to his idea on the permanent change in the constitution occasioned by disease. That the mistake should have occurred at first is not unexpected, in view of the fact that Jenner was concerned in the vaccination of the young in a population whose adults were

largely immune to smallpox as a result of previous variolation or contact with the natural disease. His mistake was in not recognizing that after ten or twelve years the immunological balance of the community was being altered, and the apparent immunity of vaccinia was of much shorter duration. On the continent of Europe the medical profession recognized Jenner's contribution for what it was worth, but also recognized that as smallpox occurred in the vaccinated it was necessary to revaccinate. In England the profession and even the lay public had to be either wholly pro-Jenner or were regarded as anti-Jenner, with the result that the 1840 legislation providing for infant vaccination, and the subsequent Acts providing for compulsory infant vaccination were founded on the entirely false Jennerian concept that infant vaccination produced lifelong immunity, and revaccination was really unnecessary. As late as 1889, the Royal Commission on Vaccination stated that *only in very exceptional circumstances* did infant vaccination not give lifelong protection, and even as late as 1896 Hime stated that smallpox was predominantly a disease of childhood, and could be overcome by infant vaccination.

It is unfortunate that Jenner's dreams and his quite unsubstantiated theories were always at the back of his mind, and prevented him from developing a more realistic appreciation of the facts, derived from field observations on practical vaccination as they appeared. He lacked the large-scale vaccination experience of Pearson, Woodville and many others. Jenner, I think, was inherently a lazy man, as his early correspondence with John Hunter suggests. He was a dreamer who, having made a rather lucky discovery, wanted to retire and continue to dream about natural history and its relation to disease in man. He also wished to be honoured and to be paid substantially by the community for the work which he felt he had done for it. He never shows that he had any inclination to embark on large vaccination campaigns himself. He never toured the country, carrying out the original Jenner vaccination. He sent large quantities of vaccine to other countries, which was called "Jenner's Original Vaccine", although this had been lost years before and much of the material that he subsequently used had been obtained from the strains Pearson and Woodville used, and from Clark's farm. Jenner's supporters felt that he went back to the country to practise, rather than remain in London, because he was the true scientist. He was certainly disillusioned, but his later remarks on the ingratitude of the people suggest, I think, that the financial side was not far from his mind. He may well have wished for other than financial honours, particularly by his attendance in London in 1814 while his wife was practically dying. His £10,000, although subsequently increased by a further £20,000, did not compare well with Baron Dimsdale's rewards on a few inoculations in Russia, when he received titles, money and annuities.

Jenner discovered that the very real simplicity of vaccination, compared with variolation, meant that every apothecary, preacher, layman, could carry out the procedure, and the expert solely practising vaccination as a speciality was not an economic possibility. Having told the world of the simplicity and of the success of vaccination, compared with variolation, it was increasingly unconvincing of him to meet every difficulty, particularly over duration of immunity, by blaming every other operator, and making the problem appear more and more complex. "A great number, perhaps the majority, of those who inoculate are not sufficiently acquainted with the nature of the disease to enable them to discriminate with due accuracy between the perfect and imperfect pustule. This is a lesson not very difficult to learn; unless it is learnt, to inoculate the cowpox is folly and presumption."

It is interesting to speculate what might have happened if Jenner had taken the alternative

course to publicizing the results of his work. If he had set up as a private inoculator, like Sutton or Dimsdale, had used cowpox material and maintained satisfactory and safe "inoculations" for the ten to fifteen years in which he would have been able to have claimed complete success, he would have made a very large fortune. It seems probable that the medical profession of the day would have been more influenced and more likely to imitate his practice on the evidence of professional success and a very large bank balance than on a few scientific experiments and much learned philosophizing.

Apart from the controversy over Jenner himself, there was some doubt in the early part of the nineteenth century of the desirability of vaccination on ethical grounds. Not infrequently members of the Church raised objections that vaccination was interfering with the will of God, and that smallpox was sent to chasten the population. Rowley (1805) asked was it not "impious and profane to wrest out of the hands of the Almighty the divine dispensations of Providence"? whilst Birch (1806) takes a somewhat more practical view that smallpox was "a merciful provision on the part of Providence to lessen the burthen of a poor man's family". These arguments continued to be raised from time to time throughout the century, but were later incorporated into the anti-vaccinators' dogma, much of which lies outside the scope of rational discussion. Paul (1903) quotes Brown as saying in 1893: "this ungodly and awfully impure method of fighting a disease which is amenable to cleanliness . . ." and ". . . a whole multitude of unclean and sinful experiments, each one seemingly more vile and filthy than those that preceded it. . . ." Their belief in mysticism, akin to that of present-day colour therapists, is shown in their failure to accept any orthodox theories on the pathogenesis of disease. "You cannot change the constitution in relation to one invading agent and leave it unchanged to all other invading agents."

From about 1830, the major arguments centred around the belief that infant vaccination was all that was required and that revaccination was hardly necessary. A few, like Gregory, were years ahead of their time, and proposed not only that persons ought to be revaccinated, but that there was quite a strong case for vaccinating in infancy and variolating in adolescence. On the continent of Europe, particularly in Germany, the need for revaccination was recognized, and carried into effect, but having put compulsory vaccination on the statute book, Sir John Simon and his successors spent much of their energy in trying to prove that infant vaccination alone was all that was necessary to control smallpox. In 1857, Allison stated: "Absolute protection is the rule and the occurrence of any disease the exception." Simon himself, at the same time, said: "With uniformly thorough infant vaccination, such attacks would be extremely infrequent as well as extremely mild." The increasing proportion of smallpox cases in the vaccinated, however, brought forth the claim that imperfect vaccination was the cause of most of these cases, and Marson, writing in 1857, stated: "Apart from the value of infant vaccination and revaccination, it is desirable to revaccinate on smallpox existing in a house—a precaution however that will *cease to be necessary* to advise when all persons have the benefit of proper and efficient vaccination." The controversy over the failure of many vaccinations to protect, after a number of years, and the arguments over imperfect vaccination continued for the next sixty years. With arm-to-arm vaccination, it was easy to blame failures on to lack of care and skill of the operator in choosing his lymph. Even in 1889, Barry was able to show that there was a much lower vaccination take rate in those done by private practitioners compared with those done by public vaccinators, who undoubtedly had much greater experience. Seaton, writing in 1870, stated: "The one important practical fact being that a vaccination

presenting any deviation from the perfect character of a vesicle, and the regular development of the areola is not to be relied on as a protective against smallpox." Even as late as 1901, a fatal case of smallpox in a vaccinated child of two years, who had a discrete attack and might well have died of a respiratory complication, was not explained in any way in the official report, but simply dismissed by stating that the vaccination scar was 0·04 of a square inch in area, and was glazed and not foveated and could not therefore be regarded as evidence of satisfactory vaccination. To some ardent vaccinationists, it seemed that the only satisfactory vaccination was the one which was never followed by smallpox—the rest were imperfect.

With the difficulty imposed by these arguments over perfect and imperfect vaccination, it was small wonder that much criticism was levelled against doctors by those who were not in favour of vaccination, either on religious or political grounds, and who were entirely unconvinced by this sort of explanation for the failure of vaccination to protect against attacks of smallpox after the passage of time. The emotions dominated the scene, and a vast mass of contradictory statistics and half-truths were published on both sides. It is not my intention to delve into these, as the bias is so great that the finer points in distinction are valueless. However, satisfactory statistics can be produced to show that, *group for group*, those who have been successfully vaccinated at any time through life suffer a lower mortality from smallpox. Under the age of ten, the difference is very great, and as the age increases the difference becomes less. As the years went on, an increasing proportion of the total smallpox deaths occurred in persons over ten years. For example, during the 1857–8 outbreak, 85 per cent were under ten years, while by 1887 the figure had fallen to 27 per cent in this age-group. Vaccinationists hailed this as a great success for vaccination, whereas the antivaccinationists pointed out that deaths in adults were important to the community as well as the saving of child life. The misuse of statistics, although a great art of the antivaccinationists, was not limited to these people. Guy, an F.R.S. and F.R.C.P. (London), writing in 1882, stated that the only way to test the effect of vaccination was to compare the mortality from smallpox in one period of history with the mortality in another, quite oblivious of changes in age of attack, social conditions or population structure. He assumed that the disease was automatically present and part of society for all time. The Royal Commission of 1889–97 also handled statistics in a way to suit its own convenience. In pointing out the evils of neglecting infant vaccination, the towns of Warrington, Sheffield, London, Dewsbury, Gloucester and Leicester were listed, and the proportion of the smallpox deaths borne by children under ten years of age was 22·5 per cent, 25·6 per cent, 36·8 per cent, 51·8 per cent, 64·5 per cent, and 71·4 per cent respectively. Warrington, Sheffield and London were all "well-vaccinated" towns, and Dewsbury, Gloucester and Leicester, the last of course the black sheep, were "poorly vaccinated" towns. There is an inverse correlation between the deaths from smallpox in this age-group and the proportion of children vaccinated, and we are expected to agree that the beneficial effect must be solely due to infant vaccination, although it is based on proportion of deaths and not age specific death-rates. Some fourteen pages later, in analysing the case fatality rate in all persons over twenty years of age, we find Gloucester with 14 per cent, a poorly vaccinated town, Sheffield with 10·9 per cent, a well-vaccinated town, Warrington with 10·3 per cent, a well-vaccinated town, Dewsbury 8 per cent, a poorly vaccinated town, London 7 per cent, a well-vaccinated town, and Leicester 2·2 per cent, a poorly vaccinated town. The Commission then state that the people in the six towns over twenty years of age were "probably in about the same condition as regards vaccination", which was not likely to be true, in the light of the

infant vaccination figures, and naïvely say: "The history of the disease shows us that smallpox epidemics vary from time to time in the degree of their fatality, quite apart from any question of vaccination." This may well be true, but is a poor argument to an antivaccinationist.

In the latter half of the nineteenth century, the increasing pressure of compulsory vaccination in infancy, administered by the Poor Law, and the ruthlessness of some of the administrators in prosecuting parents who refused, even if they had lost a previous child from the effects of vaccination, converted many intelligent people to the antivaccination cause. This was further stimulated by a factor of great emotional importance, the possibility of a transfer of syphilis in arm-to-arm vaccination. In official circles, it was claimed that syphilis could not be transferred by arm-to-arm vaccination, unless the vaccinator was particularly negligent in selecting lymph from a child who had *evidence* of syphilis, and much of the structure of the vaccination administration, the inspection of public vaccinators, its inclusion in the medical curriculum, was based on this, quite ignorant of the fact that it gave no absolute protection. It was claimed that government-sponsored and enforced vaccination by government-inspected vaccinators could never be wrong.

Even when calf lymph was introduced, syphilophobes such as Creighton claimed that vaccinia could give rise to this condition as there was some mystic connection between the two. Coroners supporting infant vaccination dealt harshly with mothers by correctly refusing to accept this possibility, but only too readily the diagnosis of syphilis, claiming it to be congenital, so absolving vaccination from causing the death and planting the blame most unfairly on the mother. It would seem that many of the supposed vaccino-syphilis cases, including the celebrated Leeds case, were probably vaccinia gangrenosa. The antivaccinationists claimed that any type of severe reaction of the arm was probably syphilitic, and that therefore many cases of syphilis showing the stigmata later in life were not congenital but due to vaccination. Accurate assessment of the situation was impossible, with the absence of serological tests for the diagnosis of syphilis, and the truth of course lies between these extreme views. Cory in 1880 heroically demonstrated on himself that it was possible to transfer syphilis at the same time as vaccination, when the lymph was taken from a child who was suffering from syphilis (Bristowe *et al.*, 1882). He had made previous experiments, when the lymph had been taken from the arm of a child known to have syphilis, and yet the disease had not resulted. It would appear that with arm-to-arm vaccination, although syphilis could be transferred, even when lymph was taken from syphilitic persons the chance of the disease being contracted was very much less than popularly supposed. One wonders what would have been the fate of compulsory vaccination if calf lymph had been introduced fifty years earlier.

What infuriated antivaccinators was the insistence of most members of the medical profession that severe complications and deaths from vaccination were either due to failure of the individual vaccinator to take sufficient care, or more usually to negligence on the part of the patient or relatives, and was in no way the fault of the procedure itself. Faulty techniques led to some complications, such as erysipelas and other forms of secondary sepsis, as the lancets were not sterilized between patients but merely washed in warm water. Even thirty years ago one of the old public vaccinators in London had, to his students, the nickname "Septic Sam".

Those who had experience of variolation claimed that vaccination had no advantages whatsoever over variolation, whereas those in favour of vaccination claimed that it was always an innocuous process.

I have taken four illustrations from various sources, and had them painted as correctly as possible, and in a similar style, to show some types of vaccination and a variolation for comparison. Fig. 221 shows a vaccination of 1802 at the seventh day, a single insertion which was expected to give lifelong immunity (from Kirtland, 1896). Fig. 222 shows a typical four-insertion "cross-hatched" vaccination of 1902 at the twelfth day. There has probably been a good deal of general reaction and there are two satellite lesions, but this was not expected to give lifelong protection from attack or death. Fig. 223 shows variolation at the thirteenth day in 1802, from a drawing by Kirtland, whilst Fig. 224 shows a severe coalescent vaccination at the sixteenth day (Acland 1912). To a public ignorant of the problems of clinical variation and of pathogenesis, the overall picture and the arguments of pro- and anti-vaccinationists, medical and lay, could be very confusing.

Even today, we still have writers stating that vaccination "properly performed" is entirely devoid of risk. This aspect, and the problems encountered in the production of herd immunity, are discussed in Chapter 14.

Towards the end of the nineteenth century, it was obvious that vaccination, even performed according to the rules of the public vaccinators, was not an absolute protective against small-pox, or against death from the disease, and we have much argument on the effect of single or multiple marks. In the minds of some medical officers of health, such as Low (1905), a single insertion vaccination was hardly a proper vaccination at all—we had certainly come a long way from Jenner. Practically every clinician of note produced figures in an attempt to show the beneficial effect of (*a*) multiple as against single vaccination scars, and (*b*) the effect of the area of the scar and the presence or absence of foveation, which to many was the hall-mark of the "proper" vaccination. The studies of Cameron (1903), Turner (1905–6) and Brownlee (1905–6) were examined by Greenwood (1928), and I think little can be added to his considered opinion. Greenwood stated: "Other things being equal, the fatality rate increases *pari passu* with the diminishing in the number of vaccination cicatrices, and the same holds good with regard to the cicatricial area. The correlation is of the order of 0·2 to 0·3. It is thus not high, but quite significant." Greenwood thought "that there was a definite but not very high association between fatality rate and area of scars, and also between fatality rate and number of scars, four or less, but little or no distinction between the smaller numbers, but the latter relation is more dependent on the association of area and number than is the former; it does however still exist, when the area is kept constant, so that for a given area there is rather more probability of death, with only one or two scars than with four." The area of a single vaccination equal to four separate ones is more likely to have been increased by sepsis and the error in reading four small scars might well be different from one large one. Brownlee took the London cases for 1902–3, and calculated the death-rate for each type of vaccination at each age, and applying them to a standard population, obtained the following rates: one scar, 137·4; two scars, 90·7; three scars, 59·5, and four scars, 56·8.

No concrete evidence has since been produced to suggest that these facts are not true. On the other hand, there are some who claim that whether one is infected at one site or more than one site with vaccinia, the same degree of immunity should be produced, forgetting that most clinicians are of the opinion that variation in size of infecting dose will alter the reaction of the individual. What has never been satisfactorily explained is why some individuals have one, two or three scars, when it would appear that for many years after the 1850's four insertions was the normal practice. It has been suggested that persons who were given one or two

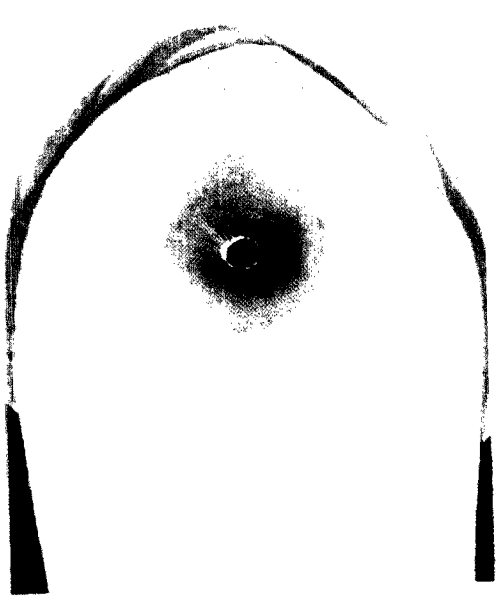


FIG. 221. Vaccination at the seventh day, 1802.

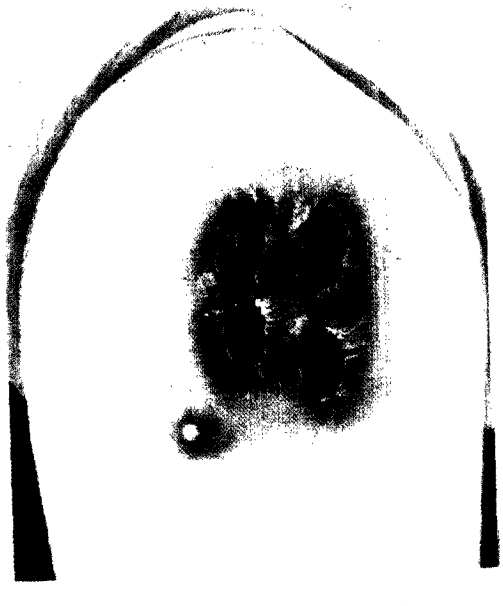


FIG. 222. Vaccination at the twelfth day, 1902.

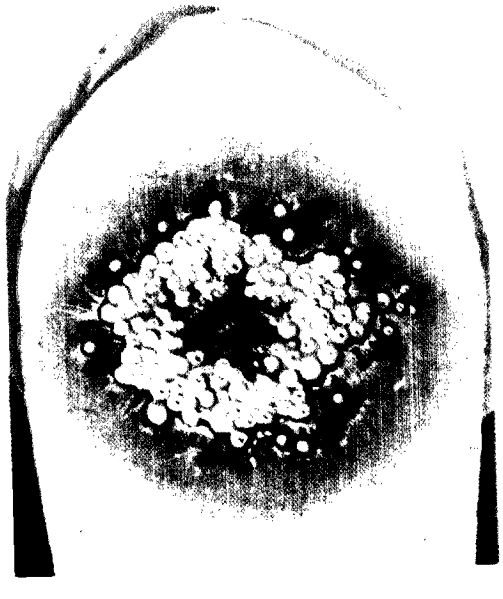


FIG. 223. Variolation at the thirteenth day, 1802.

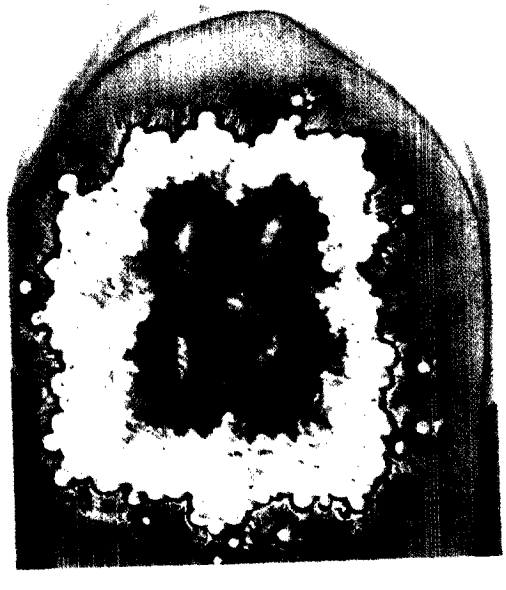


FIG. 224. Vaccination at the sixteenth day, late 19th century.

To face p. 290

Ages	Vaccinated with good marks			Vaccinated with imperfect marks			Vaccinated but no marks visible			Not vaccinated		
(Years)	Cases	Deaths	Per cent	Cases	Deaths	Per cent	Cases	Deaths	Per cent	Cases	Deaths	Per cent
0–2	4	0	0	32	3	9	22	9	41	276	181	66
2–5	57	0	0	150	18	12	96	38	40	401	202	50
5–10	206	2	1	532	27	5	207	40	19	510	180	35
10–15	439	5	1	939	32	3	214	42	20	317	74	23
15–20	606	12	2	1,037	66	6	205	39	19	204	86	42
20–25	389	11	3	843	100	13	167	56	34	174	83	48
25–30	189	12	6	529	80	15	116	35	30	105	56	53
30–40	147	14	10	526	78	15	137	49	36	103	42	41
40–50	29	4	14	186	33	18	85	24	28	49	21	43
50	19	2	11	80	18	22½	46	20	43	30	13	43
All ages	2,085	62	3	4,854	455	9	1,295	352	27	2,169	938	43

FIG. 225. Table giving case fatality by age groups and vaccination state (From Gayton, 1885)

insertions may have had their vaccinations reduced because of a feeble constitution, or for some other reason likely in itself to affect mortality, but in most instances it seems probable that four insertions were made, but only one or two took, indicating some constitutional difference between these individuals and those in whom all four insertions were successful. The possibility of this is supported by the different severity pattern in the failed vaccinated, compared with the unvaccinated (see p. 333), and the mortality in these two groups (Fig. 225). Unfortunately for the cause of infant vaccination, numbers of individuals with four perfectly good vaccination scars contracted both severe and fatal smallpox.

In the last quarter of the century, many were looking to other methods of smallpox control than reliance on infant vaccination. Sir James Simpson in 1868 pressed for the isolation of smallpox cases, to assist in protecting the unvaccinated, and George Buchanan, in 1874, and Dr. Thorne Thorne were also strong advocates of isolation. The antivaccinationists at this time were against notification and against isolation, largely because of the idea of compulsory removal. Their views, however, changed, as isolation of cases, the so-called "sanitary" control of smallpox, appeared to offer an alternative to any form of vaccination, but the Imperial Vaccination League argued that smallpox hospitals were an unnecessary and expensive alternative to infant vaccination.

The experience of smallpox hospital staff was used as an argument on both sides. Many observers showed that staff revaccinated before entering the smallpox hospital did not contract the disease, and any who were missed almost invariably did. This was countered by the

antivaccinationists, who claimed that their immunity was due to the nurses' gradual acclimatization in hospital (Paul, 1903), as would occur with other diseases, quite ignoring the fact that staff go straight from an uninfected to a highly infected environment. Paul, like other antivaccinators, is content to quote the example of one unvaccinated member of the Metropolitan Asylums Board who visited the smallpox hospital with impunity, but does not state how old he was or whether he had had smallpox.

One of the most ridiculous aspects of the controversy were the two ideologies, control by infant vaccination and possibly revaccination, also compulsory, or control by sanitation or isolation. It was difficult to be acceptable to either side if one suggested that possibly the benefits derived from both might be of greater value than either separately. Perhaps an amusing example of the different ways of interpreting the same incident is shown by the description of the outbreak of smallpox on the steamship *Preussen*, bound for Australia. According to the vaccinationists there were 312 persons on board; of persons both vaccinated and revaccinated there were fifty-five, four of whom were attacked by smallpox and none died. Of persons vaccinated but not revaccinated there were 209, forty-five of whom were attacked by smallpox and three died. Thirteen persons had previously had smallpox, of whom three were attacked by smallpox and none died. Of persons stated to be vaccinated but showing no scar, there were sixteen, two of whom were attacked and none died, and lastly there were nineteen unvaccinated persons, fifteen of whom were attacked by smallpox and nine died. The report stated: "This evidence is showing that sanitary circumstances have little or no control of smallpox, when compared with the condition of vaccination or no vaccination."

The antivaccinationists, however, stated that the ship had 723 passengers, was grossly overcrowded, and in addition to the cases of smallpox already referred to, there were twenty-nine cases amongst 235 passengers who were disembarked at Melbourne, of which twenty-one were vaccinated and of whom one died. There was also in addition the crew, numbering 120, who had been vaccinated and revaccinated, and of these fourteen were attacked and one died. The ship was apparently grossly overcrowded, and pronounced to be the filthiest ship the authorities in Sydney had ever had to do with. They quote the view of the medical officer of the Sydney Board of Health, "that had the authorities at Albany immediately on the ship's arrival removed the smallpox patient ashore, and suitably disinfected the ship, it is reasonable to conclude that the terrible amount of suffering and danger which has since ensued might have been almost if not altogether averted". The final remark of the antivaccinationists was: "The fact does not appear to us to indicate that means other than vaccination have not a very potent influence over the spread of smallpox, and in this particular case it would seem that while smallpox paid little attention to vaccination or revaccination, sanitation was conspicuous by its absence." The vaccinationists would not admit that the attack rate amongst those that were "vaccinated" might still be appreciable, whereas the antivaccinationists would not admit that the unvaccinated suffered a very much higher mortality when they were attacked.

The blind faith in the adequacy of infant vaccination to control smallpox resulted in the most extraordinary attitude towards revaccination in England and Wales, compared with that on the Continent. In 1857 it was regarded as quite unnecessary to perform revaccination under the age of eighteen. In 1867, revaccinations were only paid for at the rate of two-thirds of the fee of a primary vaccination. In 1871, we have the official statement that by vaccination in infancy, "if thoroughly well performed and successful, most people are completely ensured

for their whole lifetime against an attack of smallpox, and in a proportionately few cases, where the protection is less complete, smallpox, if it be caught, will in consequence of vaccination generally be so mild a disease as not to threaten death or disfigurement". Revaccination could be performed "so far as is not inconsistent with the more imperative claims for primary vaccination". How this hampered smallpox control can be imagined. Public vaccinators were subsequently discouraged from revaccinating anyone under the age of twelve, even if they were smallpox contacts, and in official memoranda from the Privy Council they were warned of the dangers of wasting their supply of lymph on revaccination, from which they could not maintain their supply, and that they would not receive further supplies from the National Institute under these circumstances. The public vaccinators, as the poorer of the medical brethren, were very inadequately paid, but were encouraged by official advice from the Privy Council to supply private practitioners with lymph, for which they could charge, rather than to revaccinate. Subsequently, when calf lymph was introduced, the public vaccinators were supplied by the Government Lymph Establishment, but private practitioners had to rely on supplies from private manufacturers, which were of doubtful potency and purity, as until 1925 no standards of any kind were required.

Another point which gave ammunition to the antivaccinationist was the inconsistency in the interpretation and use of revaccination. With Victorian certainty in their ability, doctors pronounced that failure to obtain a result from revaccination "proved" that the individual was still protected against smallpox, but by the end of the century severe attacks and deaths in persons who were revaccinated had to be explained, by stating that the revaccination had failed to take, and therefore it was unreasonable to blame vaccination for any failure to protect.

At the turn of the century, the extensive outbreaks in various parts of the country, particularly that in London in 1902–3, focused attention on the use of mass vaccination in controlling the disease when it occurred, rather than relying on infant vaccination. The introduction of the conscientious-objection clause caused a drop in infant vaccination, although the great variation in acceptance rates in various towns had long been a feature of the situation. The damage to public co-operation by the operation of compulsion had been done, and showed itself by the poor response to vaccination appeals, even in the face of an epidemic of variola major, but many thoughtful medical officers of health recognized that the control of smallpox could be best achieved by producing immunity as and when required, and by the surveillance of contacts. The Local Government Board, approached for permission to provide assistance in money or kind for those contacts kept in their own homes, replied sarcastically that if the Vaccination Acts were efficiently applied, this retrograde step, a form of quarantine, would be quite unnecessary. Until quite recently, this view has remained the official one of the Local Government Board, and subsequently of the Ministry of Health, in its statements on the evils which will befall the community if infant vaccination is neglected. The annual report of the Ministry of Health for 1921 states: "Vaccination statistics indicate that approximately only 40 per cent of the children born are now vaccinated at birth, and it is my duty to say quite explicitly that this condition of things brings with it in a greater or less degree an increased risk of smallpox *to the nation as a whole*" (my italics).

Due to wide differences in the enforcement of the Vaccination Acts, the infant vaccination rate has varied from practically nil in some districts to nearly 100 per cent in others. Smallpox incidence has shown no correlation with these figures. For the country as a whole, the figures

for smallpox deaths and acceptance of infant vaccination is shown from 1870 to 1958 (Fig. 226). The relationship, if any, can be variously interpreted.

The ease with which wrong conclusions can be drawn by those who fail to appreciate that the vaccinial state of a population is only one factor affecting the incidence and mortality of

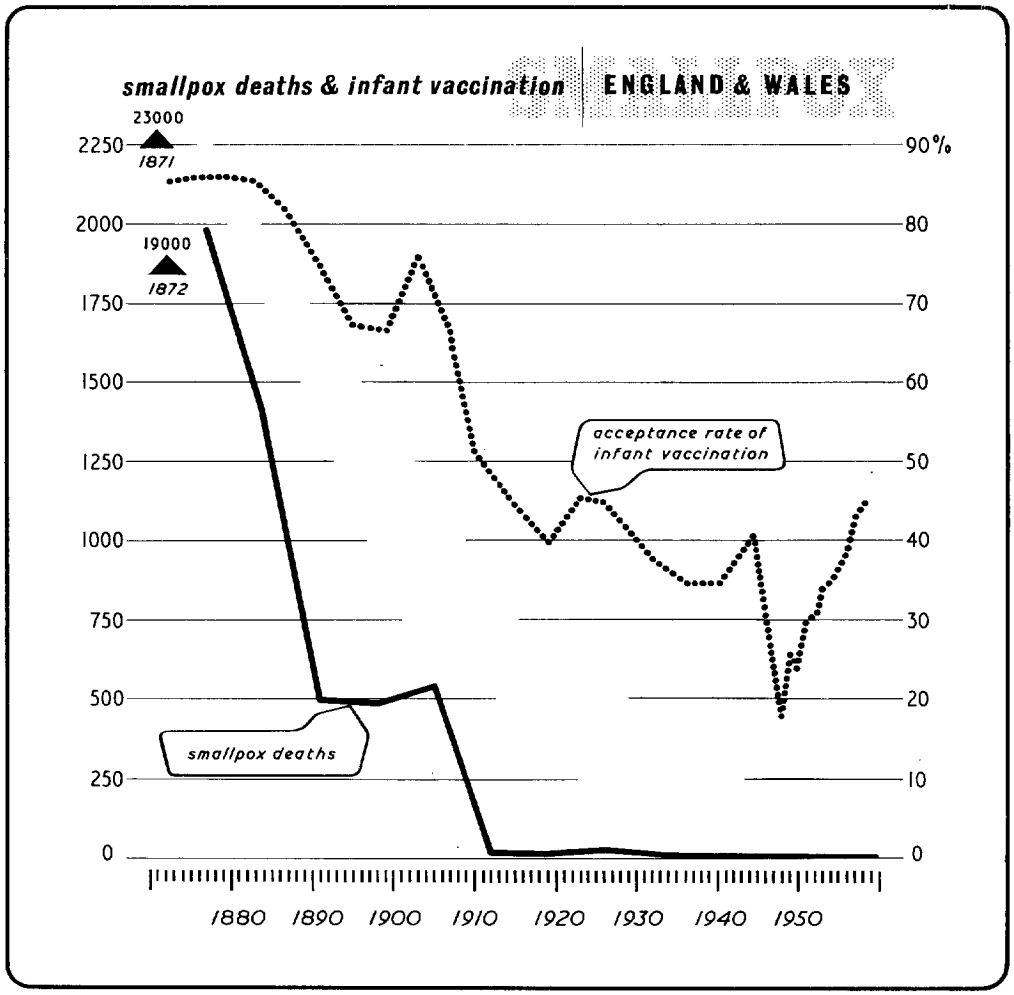


FIG. 226. Smallpox deaths in England and Wales, and infant vaccination acceptance, 1870–1958. (Deaths are seven-year moving averages, except for the years 1948–1958.)

smallpox, is well illustrated by Paul (1952) in abstracting the table from the Ministry of Health Special Report No. 62, in which, taking smallpox deaths from 1900 to 1929, there were 4,729 in England and Wales against 2,334 in Germany. The report of the Ministry of Health comments "that it seems fair to infer from the evidence as a whole that the better vaccinated nation has had to pay a lighter toll, although the current risks of infection were probably at least as great as in England and Wales, but that a more stringent enforcement of vaccination laws (as

occurred in Germany) has not always sufficed to eliminate smallpox from the country". Paul pointed out that if the first six years of the century are omitted, and the table made to cover the years 1906–1929, a totally different picture appears. "In the badly vaccinated country of England, there were 441 deaths, while in the excellently vaccinated country of Germany the deaths amounted to no fewer than 2,151, nearly five times as many, or nearly three times as many in proportion to the total population."

The large outbreak of variola minor in the 1920's and early 1930's, with a large proportion of the cases in the unvaccinated, further stimulated the idea that infant vaccination alone was of great value to the community, and there can be no question that against variola minor its ability to protect from attack lasts very much longer, but the occurrence of the disease in individual areas was not related to the acceptance of infant vaccination. Mass vaccination was still attempted in the control of both major and minor, with increasing apathy of the population in the latter case. While in most countries of the world the control of an outbreak largely depended on this method, Bradley, at the Middlesex outbreak in 1944 (Bradley *et al.*, 1946), strongly advised the abandonment of mass vaccination, for which he deserves considerable credit, in view of the long-established policy of the Local Government Board and subsequently of the Ministry of Health to regard infant vaccination as the first mainstay in smallpox control and mass vaccination the second. This still seems to be the American policy, as shown by the New York outbreak in 1946, and the teaching in textbooks (Maxcy, 1956). I developed the expanding-ring technique in Tripolitania in 1946, and, in France, Boidé *et al.* (1953) now regard mass vaccination as a policy of defeat.

Accepting that mass vaccination is unnecessary where a community has well-organized medical and public health services, and a population who are socially conscious and co-operative, I don't think there is cause for any great controversy over vaccination and its use today. In vaccination properly applied, we have one of the soundest practices in preventive medicine, but it is foolish to exaggerate the long-term protection, or the fact that serious complications may arise which, as far as we can tell, are inherent and can only be minimized if vaccination is performed on a limited scale only when there is a reasonable risk. When the risk of smallpox is great, the risks of vaccinial complications are of little account.

Perhaps the only point of concern today is the ignorance of many medical practitioners on the use and limitations of vaccination, which is a reflection on our teaching of this subject in medical schools. It is particularly regrettable when this leads to incorrect information being given to the public. In *Family Doctor* (1955), a magazine for the education of the public, in reply to a query sent in by a mother about a vaccination scar, this journal informs her that the child has "an honourable scar", and "she is protected from the scourge of smallpox, which you wisely had done in infancy", and that she had something "which would fight against the smallpox germ if she were *ever* exposed to the infection", implying lifelong immunity.

CHAPTER 14 | *Principles of Smallpox Control*

The control of any communicable disease depends on the recognition of possible and probable source or sources of infection, routes of spread, and factors affecting the susceptibility of the individual exposed. In practice our methods make use of all this knowledge.

The ultimate source of the smallpox virus is human. No animal reservoir exists. Cowpox virus, although most probably originally derived from smallpox, is an irreversible mutant and has never given rise to smallpox in man.

The most important source of virus is a case of smallpox. Once a person is known to be suffering from the disease, we can rightly assume that the patient and his immediate surroundings will be a source of infection. It is for this reason that prompt notification of a case of smallpox is an essential part of smallpox control. Delay due to lack of co-operation of the population or of general practitioners, or the inadequacy of medical services has made all the difference between the relative failure in the latter part of the nineteenth century, and the great success in many countries in the last 25 years, of this weapon, especially when supplemented by official or unofficial notification of chickenpox. In many parts of the world notification is still far from satisfactory.

It should be emphasized that by "known case" we mean one that has been diagnosed clinically. Although it is a great advantage to have laboratory aids to diagnosis, there is no method which gives a certain diagnosis rapidly, and the delay in waiting for the results of egg culture can be extremely serious. In one recent outbreak in Europe, two child contacts contracted smallpox, their primary vaccinations having been delayed for three days while waiting for a laboratory report. If the case had been taken to court for damages, it would have been impossible to have justified this delay. Mistakes in smallpox diagnosis must be made on the right side, that is a false positive and not a false negative diagnosis.

The second source of infection is the unknown and often ambulant case. Millard (1914) and others make considerable play on the fact that infant vaccination gives rise some years later to partial immunity, and the attack of smallpox is then so trivial that it is exceedingly difficult to diagnose and very frequently confused with chickenpox. He tended to assume that all the mistakes in diagnosis are the fault of infant vaccination. In recent outbreaks and probably in many earlier ones, fulminating and malignant cases have been misdiagnosed, although these may occur both in the vaccinated and the unvaccinated. Cases diagnosed as purpura, acute leukaemia, meningitis or the acute abdomen have all been the source of infection to others. In those countries with well-organized medical services, the greatest danger is that these cases will be admitted to general hospitals, and an outbreak of smallpox is likely to occur in both patients and staff. Maintaining a high immunity in hospital staff would go a long way towards protecting them, but it is obviously impracticable to maintain a similar high level of immunity amongst the general population who may be patients.

No long-term human carriers of the virus exist. Verlinde and van Tongeren (1952) recorded

a case of a twenty-year-old unvaccinated girl from whom virus was recovered on the eighteenth day after contact. General epidemiological experience does not support this finding, but there is a strong possibility that a person may passively carry virus in the nose or throat for a few hours on the day of contact, and so transfer virus from the source to a third person, but one cannot be sure that the infection is not conveyed on the clothing.

INFECTIVITY OF THE PATIENT

Type of Attack. It is my belief that virus from the respiratory tract is by far the most important from an epidemiological point of view, and this has already been stressed in other parts of

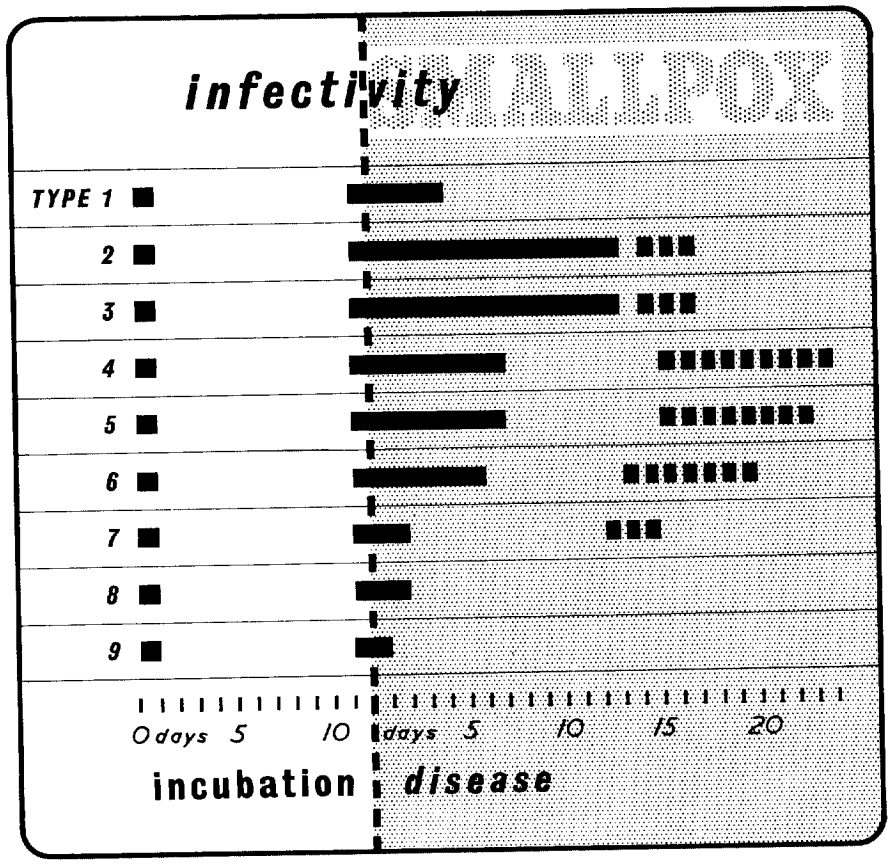


FIG. 227. Infectivity of different types of smallpox.

this book. Apart from having virus in the respiratory tract on the same day that he is infected, a passive carrier state, the patient is not infectious during the incubation period, and many observers have found that he can be allowed to continue in contact with people up to at least the tenth day of the incubation period, without giving rise to infection. The patient appears to be infectious from the onset of the acute viraemia, and although some observers still believe that he is only infectious when the rash appears, many instances are

on record of smallpox resulting from contact with persons in the first twenty-four hours of the pyrexial phase. In my opinion virus is liberated for a period of time, depending to a considerable extent on the type of attack, and in some the necessity to build up a quantity of virus makes many patients appear to be most infectious at about the end of the second or the beginning of the third day, which generally coincides with the appearance of the rash. The quantity and continuance of liberation of respiratory virus would appear to vary markedly with the type of attack, and Fig. 227 shows what I consider to be the period of infectivity in various types of variola major. It seems probable in types 8 and 9 that the period of infectivity is exceedingly short, only lasting a few hours, and the quantity of virus small, and if this occurs at night this patient is quite likely to miss infecting any contacts, even those living in the same house. This has been noticed particularly in outbreaks of variola minor, where the cases are commonly type 7, 8 or 9, and the low degree of infectivity has been frequently commented upon (Robertson, 1913; Innes, 1953). Respiratory virus settles on the skin and on the immediate clothing and bedding of the patient, and so leads to the idea of the patient and his immediate surroundings being highly infectious, as they undoubtedly are, at a time when the rash is in

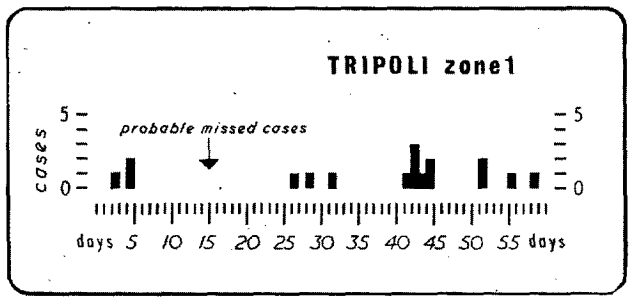


FIG. 228. Thirteen day periodicity under primitive conditions.

the macular or early papular stage. It has been recognized for a long time that the patient is infectious long before the maturation of vesicles and discharge of large quantities of scab material.

The spectacular eruption has focused attention on the scabs, which from their use in variolation from earliest times have been known to contain the infective agent. Downie (1947) and Dumbell have shown that virus is present in the scab for many months, but in practice scab virus seems to lack epidemic potential. I have suggested (Dixon, 1948) that the virus extruded through the skin, perhaps modified by its passage, is in some way different from the virus from the respiratory tract. Experience of the Chinese method of variolation, by intra-nasal inoculation, supports this idea, the severity of attack being very much less than infection with respiratory virus under natural conditions, although the size of the infecting dose is probably very much greater. The thirteen-day periodicity in the occurrence of smallpox cases in outbreaks, even in primitive circumstances, where scabbing cases are continuously present (Fig. 228), also strongly supports the idea that the practical infective period is relatively short, and limited to respiratory virus, disseminated during the initial and early eruptive stage of the attack, and that it may die out relatively quickly.

Priestley (1894) thought the scabbing stage was not very infectious. In many outbreaks, such cases have been discovered who, although ambulant and back at work, have not been found to

give rise to secondary cases except where contact was established in the initial or early eruptive stage. Spencer Low (1905) found a very unsatisfactory state of affairs over the discharge of convalescent cases, who according to the current ideas ought to have been infectious, but on

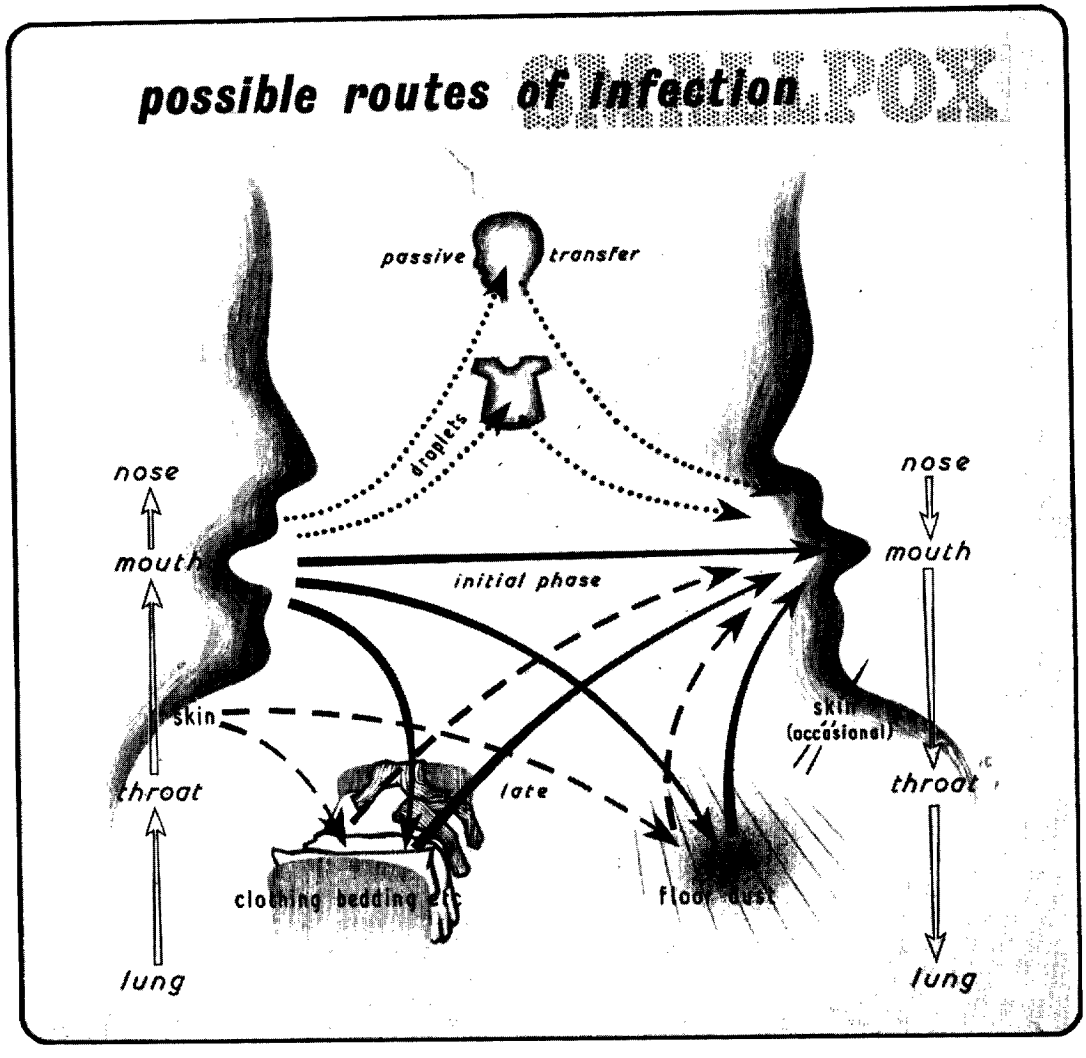


FIG. 229.
Solid line—common route of respiratory virus.
Broken line—route of scab virus.
Dotted line—possible route of "passive transfer on day of contact".

following them up he found that they did not give rise to any secondary cases. McVail (1905) pointed out that "a hospital like Darenth may contain hundreds of convalescent smallpox patients in all stages of desquamation, with crusts and scabs abundantly shed from their whole integument day after day, and yet without any extension of infection from the hospital

whilst on the other hand hospitals containing acute cases, closely confined to bed, and previous to desiccation of the pustules, caused prevalence of smallpox all around them. If the cause were intercourse or immediate infection from smallpox "dust" (scab material) surely a convalescent hospital should be a prime source of danger, instead of being found practically harmless, and, *per contra*, hospitals with acute cases confined to bed, and previous to drying of the eruption, should be much less effective as centres of infection. But experience shows that smallpox has, over and over again, spread from hospitals containing a collection of acute cases."

De Jong (1956) found that an electrician who had quite a severe attack of variola minor, with extensive pustular eruptions and scabbing, had continued his work as an electrician, had visited several office buildings, military barracks and the surgical department of a hospital, infected nobody there, but did infect an aunt and cousin with whom he lived, and who were in contact in the initial phase.

It has been found that early papules, if abraded, yield virus and some writers have suggested that infection, therefore, is derived from the skin, even early in the attack, but this does not explain infectiousness of variola sine eruptione. One would need also to be sure that virus recovered this way was not that deposited on the surface of the skin from the respiratory tract.

Habit dies hard however, and in the light of our knowledge that virus is in the scabs, it has so far proved impossible in practice to ignore this potential source of infection, particularly in disinfection procedures, yet it is of paramount importance to stress that it is the respiratory virus which we cannot see, rather than the more obvious scabs, that really matters.

THE SMALLPOX CORPSE

The smallpox corpse has long been recognized as a source of infection. On a number of occasions it was noted that medical students contracted smallpox from dissecting the unprepared bodies of persons recently dead from smallpox (Chadwick, 1843; Bruce Low, 1902; Charity epidemic, 1894). Depending on the stage of attack, the virus might have come from the skin lesions, the skin surface or from the shroud and, as the fulminating cases were probably more likely to be dissected, presumably also from the tissue fluids, by droplet spray. Undertakers have also been attacked by smallpox, from handling the body (Long, 1893; Spencer Low, 1905; Copeman, 1906), and this has sometimes been recognized only when infection first appeared in their wives.

Photographers, who have been called in to photograph the corpse and have only been present in the room for a short space of time, have also been infected. The source of virus here seems to be probably from moving the shroud. Mortuary attendants have also been infected (Boidé *et al.*, 1953), sometimes having a normal attack of smallpox, presumably from virus dust, or *variola inoculata*, from pricking the finger, as in the case recorded in Yorkshire in 1953 (Lyons and Dixon). Material from known or unknown smallpox cases handled in pathology laboratories may also give rise to infection. In the outbreak in Tottenham in 1958 (Hogben *et al.*), one of the cases was in a person employed as a laboratory cleaner, while in 1949 in Liverpool a laboratory technician, who was employed before he was successfully vaccinated, contracted smallpox from washing glassware.

CLOTHING AND BEDDING

The most important source of infection other than from the patient himself is his clothing and bedding, which is contaminated with respiratory virus during the initial and early

eruptive stages of the disease. It is not surprising that visitors to the patient during this phase are exposed to a very great risk of infection, often enhanced by the habit of well-meaning relatives straightening the bedclothes just before the visitor enters, so increasing the chance of inhaling infected dust suspended in the air. Many instances are on record where a visitor has just put his head around the door, or stayed in the room only one or two minutes without sitting down or touching the patient or bedding and yet has contracted smallpox. Even by the fourth or fifth day of the rash the virus will still have been derived from the respiratory tract, as lesions in the skin will still be closed. If the room is light and well-ventilated, this virus may die out or diminish in quantity so that susceptible visitors coming when the patient has a well-marked pustular rash may not be infected. Systematic laboratory investigations have not been done on the recovery of this type of virus and on determining its persistence. Dust on the bedding is not only a source of infection to visitors, but is probably the source of infection to the clothing of the nurse or doctor who attend an undiagnosed case of smallpox, possibly in a general hospital, and then proceed without washing the hands or changing the clothing to attend another patient so transferring infection, although the nurse or doctor may be adequately vaccinated and present no evidence of infection. It possibly also accounts for the chance infections which have often been recorded, where an individual has had no known contact himself with the case of smallpox, but may have had some contact with known contacts who themselves have had no recognizable attack. It was noticed that although tradesmen calling at smallpox hospitals rarely contracted smallpox, it was not uncommon in their families. As already pointed out, this mode of spread, by a passive intermediary, could occur from the virus being in the nose and throat, or possibly more likely, from the virus being present on the clothing. The number of untraced cases which occur in every outbreak makes it important to look at every possible route of spread, although the likelihood of proving them is very remote.

The great danger from clothing and bedding is in handling and when it is sent to laundries. In the outbreak at Hendon in 1927, the initial case was very mild, like chickenpox, and two of the daughters in the family were probably infected from handling bedding, rather than from direct contact with the original patient, and four laundry workers were infected. The Barnsley outbreak in 1947, the Brighton outbreak in 1951, were also classic examples of this mode of spread. The laundry workers normally affected are those who sort the incoming garments, and in this way inhale dust. Once the garments are wetted no further danger is present, and the ordinary washing process appears to disinfect. No cases are recorded where individuals drying the clothing or ironing it have been infected. The same risk applies to dry cleaners, from sorting of the dirty clothing, as the dry-cleaning process appears to kill the virus. Another group engaged in handling bedding are hotel chamber maids. The outbreak in London in 1923 gave rise to infection with variola major, and the outbreak of variola minor in the Hague (de Jong, 1956) was also due to the infection of chamber maids, who changed the bed linen. In a hotel the sheets are normally changed, but the infection may remain for a few days on blankets, eiderdown or in dust in the room. Years ago, when it was common for persons to occupy a bed without any change of linen, there were numerous instances of smallpox contracted by sleeping in a bed recently occupied by a smallpox patient, who was usually in the initial or early eruptive phase.

Personal clothing worn by a patient who has ultimately been sent to hospital has often been a source of infection. Spencer Low (1905) relates that he had to put sanitary inspectors on

guard to prevent the relatives coming back at night to remove the clothing, and they were frequently caught in the act. An outbreak in Tabriz (Fredericksen and Motameni, 1957) is also presumed to have occurred from taking infected clothing from a cemetery. Inanimate objects, such as toys, metal objects such as money (Copeman, 1920), have sometimes been incriminated as a source of infection, but it is exceedingly difficult to prove this. Kamal Bey (1946, 1951) stated that smallpox was controlled in Mecca pilgrims only when disinfection of objects of this nature was accomplished, but it is indeed difficult to ensure that infection is not being brought in by missed cases in a nominally vaccinated group of travellers. Paper money has been regarded as a source of infection on more than one occasion. Karkeek (1894) relates an outbreak which was spread by letters in Devonshire, and Boobbyer (1901) described how variola minor virus was almost certainly brought from the United States to Nottingham and gave rise to a small number of cases in those handling papers. How long virus remains alive, and whether the recipient infects himself, seems to depend very largely on chance.

FOOD

Although some of the older writers pointed out that infection might be conveyed by food, as variolation can occur from consuming smallpox virus in the form of scabs, this route is of no practical importance.

Boyd (1903) relates how a man milked a herd of cows for a town milk supply whilst he was suffering from smallpox, but it did not give rise to any cases.

ANIMALS

It is surprising how few of the personal effects surrounding a smallpox patient have not at one time or another been incriminated as a vehicle for virus. Cumpston (1914) relates how a community was very worried when a dog from an infected house arrived and was particularly friendly, and in a Liverpool outbreak in 1957 it was suggested by the Medical Officer of Health, according to a daily newspaper, that the infection might have been carried out of the smallpox hospital by a cat. Although neither the cat nor the dog appear to suffer from smallpox, it is possible for virus to be on the fur, and medical officers of health have from time to time been asked about disinfection of these animals.

FLIES

In some parts of the world flies are very numerous and have a habit of alighting on the nares or the corner of the mouth or the edge of the eyes of small children to feed on the secretions. In hot countries particularly, flies are also attracted to the secretions from the eruption of smallpox, and it would seem quite possible that infection could be conveyed mechanically in this way. This was thought possible in the outbreak in Tripolitania in 1946, and seems to have been likely on a number of other occasions. The difficulty, as with so many other routes, is to exclude the possibility of missed cases. At any rate, it would seem to be sufficiently important in tropical or subtropical countries where flies are a nuisance for smallpox hospitals to be adequately protected with fly mesh. In temperate climates, where the number of flies may be very few, and the climate is different, fly-proofing is not required, but fly control should be carried out by contact insecticides, so eliminating any practical risk.

FIG. 230. The housefly as a mechanical vector of smallpox virus.

COTTON

A further vehicle for the spread of smallpox, which has frequently been credited with giving rise to quite important outbreaks, is raw cotton. Corbin (1914–15) described cases of smallpox that occurred in Stockport in 1908, and the reasons why infection was thought to have been due to the import of cotton containing smallpox virus. He pointed out not only the dustiness of the process, but the habit of operators engaged in "piecing"—joining broken fibres—of moistening the hands with saliva. A similar theory was advanced for an outbreak in Heywood, Colne and Chadderton in 1910, Bury in 1911 and Oldham in 1913, Milnrow in 1914, Blackburn in 1934, Oldham in 1936 and Wigan in 1938. In five of these, the first case or cases were in workers handling the early stage of the cotton process, that is in the card room

or previously. In no instance, of course, has the virus been actually traced to the particular cotton.

Cotton has been suspected because of the simultaneous occurrence of a number of cases in a cotton mill or mills, and often in workers in associated processes, dealing with raw cotton. Because the cases are the first diagnosed, it is usually assumed that they must have arisen from the material handled at work. In the past it has not been appreciated that the outbreak may have originated some weeks or even months before the first case was detected. The fact that only cotton workers were affected first is not surprising, as in most of these towns a very large proportion of the population was engaged in one industry. In the outbreak of smallpox in Dewsbury in 1904, out of 320 cases in wage-earning adults, 120 were engaged in the woollen industry, but nobody blamed wool. In the 1953 outbreak in the Pennines (Lyons and Dixon, 1953) it was assumed by some to be due to cotton, and administrative action was taken to quarantine certain batches of raw cotton, until it was discovered that cases had occurred earlier, before the "incriminated" batch had entered the area at all. It is frequently forgotten that the dirtier and dustier processes in any trade are likely to be staffed by people of the lowest social class who may well come into contact with others in whom smallpox has in the past tended to spread, and in whom mild cases are more likely to be missed. In the Rochdale outbreak of variola minor in 1952, the first known case, some months after the first cases really occurred, was in a cotton worker, but he worked as a bobbin carrier at the cotton mill, an occupation which would not bring him into contact with raw cotton, though the official report at the time said: "Such contact could not be excluded". In the outbreak in Blackburn reported by Thierens (1934), a mill worker, a stripper and grinder of Egyptian cotton, developed malignant smallpox and infected twenty-one other people. Out of the twenty-six cases four died and seventeen were "confluent in type", showing that this was certainly variola major. In the absence of a history of contact "with a previous patient", it was concluded that the source must be cotton. It has been said that whenever smallpox occurs in cotton towns in Lancashire, cotton has always been blamed, rather than attempting to discover other possible sources.

MacCallum and Macdonald (1957) have carried out some laboratory investigations on the survival of variola virus in *scabs* in raw cotton. Scabs from a single case of smallpox were stored in the presence of raw cotton at 30° C. at three different humidities, 58, 73 and 84 per cent. The scabs were removed and ground up at intervals and the extracts inoculated on to the chorioallantoic membrane. At the relative humidity of 58 per cent, virus was recovered after 185 days, but at the two higher levels no virus was recovered after 97 days. In the second experiment virus was recovered from cotton stored at 58 per cent relative humidity, after 70 days but not after 112 days; from 73 per cent humidity at 70 and 112 days but not at 91 days, and from 84 per cent humidity at 60, not at 70 or 91 days. Scabs stored at room temperature, relative humidity between 55 and 75 per cent, in indirect daylight still had viable virus after 530 days (eighteen months). These experiments show that smallpox scabs could survive in bales of raw cotton, so that after many months when ground up they provide smallpox virus. In cotton picking by hand the bag is hung round the neck, an ideal way of acquiring respiratory virus from droplets and saliva, and the experiment does not prove that this virus survives for this period of time. Corbin pointed out that bales were wetted and the centre often remained quite warm, due to fermentation, and this was likely to prevent the survival of virus under natural conditions. It was also suggested that the virus was in some way attenuated, and this

would fit in with the lower infective potential possessed by scab virus. However, secondary cases were often also equally mild, which suggests that the outbreak was variola minor, or variola major in a predominantly vaccinated community.

The most difficult thing to understand is why, if cotton is infectious, these outbreaks should have occurred in Lancashire, and not in other countries which use cotton. It may be argued that in these countries vaccination is practiced much more extensively, but the outbreaks of smallpox in various countries in Europe over the last fifty years suggest that if this had been an important source it would have occurred more frequently. On the other hand, the argument might be used that Lancashire has in the past been a very much larger user of cotton. This may be so, but Liverpool and Manchester are both important ports for general merchandise of all kinds, partially from endemic countries such as India, and in the early twentieth century the United States of America, and the opportunities for infection to be brought in by sub-clinical attacks in seamen must be very great, and probably much greater than in most other European countries. It would seem that the case against cotton is not proven.

It has been suggested that cotton workers, particularly those handling raw cotton, should be vaccinated. If these workers could be kept immune by revaccination every three years, it certainly would prevent smallpox in these people, whatever the route of infection. However, once the panic had died away the likelihood of maintaining immunity voluntarily would be small.

Compulsory vaccination of cotton-workers would lead to many administrative problems, objection by mill-owners and pressure from trade unions for danger money, and would be unacceptable in many countries.

RAGS

Another, and more likely source of infection, particularly fifty years ago, was the traffic in old clothes and rags. Clothing bought from the houses of patients is liable to give rise to infection on handling. It is particularly important to appreciate the danger of apparently clean, but contaminated, material. Clothing or bedding grossly contaminated by secretions is recognized as dangerous in many countries, although, in some, conditions may be so primitive that even this is ignored. Corkill (1951) noticed a bitter taste on moistening the lips when handling patients' clothing, and this may be similar to the bitter taste complained of by persons who were variolated. In many parts of the world public health legislation exists to effect some control over the collection and disposal of clothing. In the late nineteenth century in England and Wales traffic in old clothing was quite important, and with the absence of notification, and general apathy of the public towards smallpox, it seems highly probable that infection was spread from the sale of these garments on stalls at fairs and in other places.

The problem of infection introduced from old rags which have been baled and stored for many years is much more difficult to assess. I feel that many accounts are derived directly from similar stories concerning the transmission of plague. All too often the part of the rag-dealer, in most cases a migratory character, was ignored, because he did not present any obvious symptoms. The whole problem of smallpox from infected rags was investigated on a number of occasions in England in the late nineteenth century. Parsons (1886) was quite convinced of the occurrence and frequency of this route. Although rags were handled by collectors, dealers and others, the outbreaks were nearly all associated with paper-mills, and in these premises

mostly rag-sorters experience the disease. Although on occasion foreign rags were blamed for the infection, the dangerous material was apparently "outshots", soiled white rags, mostly personal underclothing, collected in England and Wales and often from fairly local areas. In some of the ten outbreaks listed the first recognized case occurred among the sorters, and occurred simultaneously in two or three workers, showing infection from a common source. The workers often lived in quite different parts of the town and only came into contact at work. In some outbreaks other cases had not been diagnosed for many months, and in some instances even years.

At first sight the evidence appears overwhelming, but it must be appreciated that smallpox was endemic in England at the time. Notification was not compulsory, and the public, particularly the lower social classes, were somewhat apathetic to disease, smallpox included. Rag-sorting is a dirty, offensive job, and amongst the most lowly kind of work, only likely to be followed by the poorest section of the community, who normally experience smallpox to a greater degree, and who are most likely to give incorrect accounts of their movements or contacts. Parsons thought the rag-sorters were no different in social class from other workers in a paper-mill, but I don't think many would agree. It was recognized that some outbreaks assumed to be due to rags occurred concurrently with known and temporarily missed cases in the area. In a population, the majority of whom were vaccinated, the possibility of many missed cases amongst adolescents was very great and only a small fraction would ever be discovered. It is highly probable that missed cases amongst the rag-sorters' companions might just as well be the cause of simultaneous infection. Parsons noted that in some instances inquirers were refused admission to houses where cases were suspected to have occurred some weeks previously. In some of the outbreaks workers in other parts of the mill, where the material is quite sterile, were also infected simultaneously, but this is usually glossed over. From our experience of infection in laundry workers, I do not think there can be any doubt that persons intimately handling and sorting rags from smallpox cases, particularly clean-looking material contaminated with respiratory virus, could be infected if the material finds its way from the patient to the rag-sorter in a relatively short time. The temperature and dryness of the material will also affect viability. If rags are baled and stored for a long time, it would seem that scabs may remain viable, as in cotton, but whether these give rise to infection is another matter. Within the last fifty years, in those countries where notification and isolation are prompt, the possibility of much infected material finding its way into the rag-dealer's hands is very limited. In those countries where cases are not notified and are rarely isolated, the chances of missed cases will also be very much greater. Although it would seem possible for virus under particularly good conditions to remain viable, many if not most of the reported outbreaks due to rags are most likely to have arisen by contact with missed cases. In both infection from cotton and infection from rags, accurate information is difficult to come by today, as the legal-compensation aspect has made the patients anxious to blame this material and through it their employers.

More definite information is available of infection conveyed on lace-making materials. Boobbyer (1895) describes how outworkers who were suffering from smallpox infected a large number of women in a factory, some with *variola inoculata*.

Goose feathers have also been incriminated, and it would seem possible for other materials of this kind to convey infection where transfer is rapid.

At one time in the United States the clothing industry was thought to be dangerous, pre-

sumably through outworkers, and vaccination of employees was advocated, the cost being borne by the industry.

AERIAL SPREAD

Towards the end of the nineteenth century a great controversy arose, particularly in England, on the siting of smallpox hospitals, then frequently situated in the centres of towns. The view was put forward, particularly by Power (1886), on experience at Fulham and other smallpox hospitals, that infection was carried from the hospital by the wind or by aerial movement, considerable distances, even up to a mile. This view was opposed by others, who contended that, in spite of precautions, infection occurred in these areas around the hospital by contact between staff or patients and local inhabitants. It was claimed that infection spread from floating hospitals, such as the M.A.B. hospital ships at Dartford, and was wafted across the river (Thresh 1902). The subject is discussed at considerable length by Buchanan, and most of the contemporary experts, in the *Transactions of the Epidemiological Society of London* from 1904 to 1905.

It had been the practice to site smallpox hospitals or to admit smallpox cases into hospitals situated in closely populated areas of large cities. When a few cases of smallpox were admitted, the incidence of the disease did not appear to be unduly high in that part of the city, but if many acute cases were admitted, the critical number being between thirty and fifty, it was common for a large number of cases to then occur in the area immediately surrounding the hospital, the attack rate per thousand being very much greater than in more distant areas, and in many cases showing a gradation from the highest rate within a quarter of a mile of the hospital to lower rates as one went further away. Even at one mile from the hospital the rate was higher than for the town as a whole. In some instances the high incidence was limited to the leeward side of the hospital, but in most cases it was not so directional. It was on this evidence that the practice arose in Great Britain of siting smallpox hospitals at least half a mile away from any other human habitation, in spite of evidence produced by Hope (1905) that a similar pattern of incidence of smallpox occurred around hospitals that were not admitting smallpox at all. Hospitals, either special or for general infectious diseases, are most likely to be built where they are required on the outskirts of a town but, with the rapid growth of cities in the late nineteenth century they frequently became surrounded by the poorer and more squalid type of accommodation. The better-class inhabitants would not chose a site close to a hospital for somewhere to live. In some areas it is obvious that the site of the hospital therefore coincided with an area of dense population and low social class, where one would expect to get a high incidence of smallpox. The admission of thirty to fifty acute cases in a short time is likely to mean an uncontrolled outbreak in the town with the certainty of many missed cases.

Instances were recorded where infection broke out in areas previously free from smallpox when cases were first admitted to the hospital serving the area. The opening of hospitals for the reception of cases may frequently be determined by the increasing incidence of a disease in the city as a whole, and the rising incidence may not be due to the effect of opening the hospital at all.

To many, however, this seemed clear proof of cause and effect, although other outbreaks were recorded where, in spite of apparently favourable circumstances, infection did not spread to neighbouring areas. Instances were cited where unvaccinated workmen on the boundaries of such hospitals or patients in neighbouring non-smallpox wards never became

infected. Unfortunately, little, if any, information is usually given about the population at risk, particularly its vaccinial state.

In late nineteenth-century England, the population close to smallpox or infectious-disease hospitals was mainly of the lower social classes, people less likely to avail themselves of revaccination facilities in adult life, although a large proportion would have been compulsorily vaccinated in infancy. Once infection had been introduced by whatever means, undiagnosed cases, the real method of spread, would be commoner in such a group than in other areas, and would account for the high attack rate as the outbreak proceeded. It must be remembered that at the time notification was not compulsory in many areas, and even in those in which it had recently been introduced it was not carried out very well.

Although these arguments will explain some cases, they will not explain all. Much confusion arose from the failure to recognize the importance of respiratory virus as a source of infection rather than scab material. McVail's interesting remarks have already been noted (p. 299), that convalescent hospitals, with much scab material, were not a source of infection, although the hospitals for acute cases were.

I think one can accept that a smallpox patient in the initial and early eruptive stage may be contaminated with virus in such a form that a small quantity will produce smallpox in a large proportion, possibly 95 per cent (Barry, 1889), of susceptibles who are effectively exposed. It is only very rarely, and then principally in direct case-to-case infection, under overcrowded conditions, that such a high proportion of susceptibles would be infected. It has been recognized more and more that even in variola major, and particularly in variola minor, fairly close contact is necessary for an infecting dose of virus to be obtained. Although we know from studies of streptococci- and staphylococci-infected dust that the material could be blown considerable distances, it is most likely to be dispersed without giving rise to infection.

To the question, is it absolutely impossible for a virus to be blown a distance of a quarter of a mile and infect someone, the answer, I think, must be no, but to the question, is this likely to cause the pattern of infection seen around the smallpox hospital, the answer is always no. As already indicated, the possibility of infection by missed cases and imperfect disinfection of clothing and other irregular contacts between the sick and the healthy is so much more likely, apart from the epidemiological considerations already mentioned. The owner of a small general shop close to the smallpox hospital in Rochdale was infected in the Milnrow outbreak in 1914; a previous occupant had also been infected in the outbreak in 1903!—very suggestive of unauthorized contact with hospital staff.

The theory of aerial spread has been most popular in Great Britain. Chapin (1910) stated that the evidence in favour of aerial transmission was so slight that it should never influence a municipality in the selection of a hospital site. Chapin's experience was principally of variola minor, in which there appears to be no evidence of aerial spread. In Germany smallpox was nursed in wards in general hospitals (Bruce Low, 1902), and except for the spectacular outbreak in Berlin in 1895 did not apparently give rise to secondary cases. The doctors in charge, however, stated that this was only due to the policy of compulsory infant vaccination and revaccination as practised, and that otherwise they would have felt obliged to nurse smallpox out of the centre of the city. Whatever the reason for spread to the community, if a smallpox hospital has to house many patients it is better situated other than in the centre of a large city. Although it is easy to blame the Victorian smallpox hospitals and the medical and administrative standards of the time, it must not be forgotten that in 1938 a single case of smallpox

was landed at Gravesend from a ship direct to the smallpox hospital, but in the following six months seven cases of smallpox occurred, at a time when the disease was not present elsewhere in the country, and must have arisen in some way from this case. In 1957, cases occurred at Bebington, Cheshire, not for the first time, around the smallpox hospital, the source of infection never having been determined, and many competent medical officers are baffled in finding the link in the chain between the hospital and the community, and therefore consideration of the possibility of aerial spread recurs. The courts accepted the possibility of aerial spread in the late nineteenth century, but today it would be difficult to persuade a court that a chance case of smallpox was not due to some failure of hospital management, and this is a point of some importance.

Although the controversy centred round hospitals, instances have been quoted where aerial spread was thought to have occurred amongst small groups of slum houses opening on to communal courts (Whitelegge, 1905). Evidence was also produced that the direction of the prevailing winds was also consistent with the spread to other houses by this means. On a number of occasions infection has also been spread in hospitals, where it would seem that infected dust could be blown along corridors and, due to the vagaries of air movement, might be directed into certain rooms, so producing a somewhat mysterious pattern of secondary cases. De Jong (1956) found that five patients admitted for observation in a "negative" ward separated from a smallpox ward by two sluice-rooms were, however, infected with smallpox, possibly by airborne infection. De Jong appreciates that indirect infection could have been caused by members of the medical and nursing staff, although he assumes airborne infection to have been the cause of infection of a doctor, who had no contact with patients or nurses on the affected floor, but had to walk along the passage of that floor when going to the surgical wards from his room. Even under these circumstances, as with the ones in houses, it is impossible to rule out direct spread. In many instances patients forget what their movements were some twelve days previously and, in other instances, as they do not want to be blamed for anything, are reluctant to tell what really happened. Although I feel that true airborne infection may occur as an extreme rarity, infection conveyed by passive carriers by dust or the clothing of people, will be the source of most of these infections. Infection from door handles and similar things are again possible routes which we can never ultimately prove, but investigation of other infections has suggested that these cannot be discounted entirely. The efficiency of any mechanism of spread depends not only on the dispersability of the infecting agent, but the susceptibility of the recipient in relation to the size of the infecting dose.

We are on firmer ground regarding the infectiveness of the room which has been vacated by the smallpox patient. Numerous instances are on record where patients have occupied the rooms which have been used by smallpox patients. This was seen in the Tripoli outbreak, where a nurse contracted smallpox after cleaning out the room and removing the bedding following a very perfunctory disinfection some three days earlier, and in the outbreak of smallpox in Hendon (1923) two persons, who subsequently occupied the same hotel room as the first case, developed smallpox. Although the virus is on the bedding or clothing it is inhaled as an aerial suspension.

THE WEIGHT OF INFECTION

It is traditional to call smallpox one of, if not the most, infectious of diseases, but is this really true ? Man has a high degree of susceptibility to smallpox virus, and in the past in grossly

overcrowded conditions, when patients were left in contact with susceptibles throughout the whole course of the disease, the attack rate was very high, but in more recent years, it has been seen that outbreaks of variola major have occurred in which susceptibles have not contracted the disease after fairly casual contact. It is important to bear this in mind in carrying

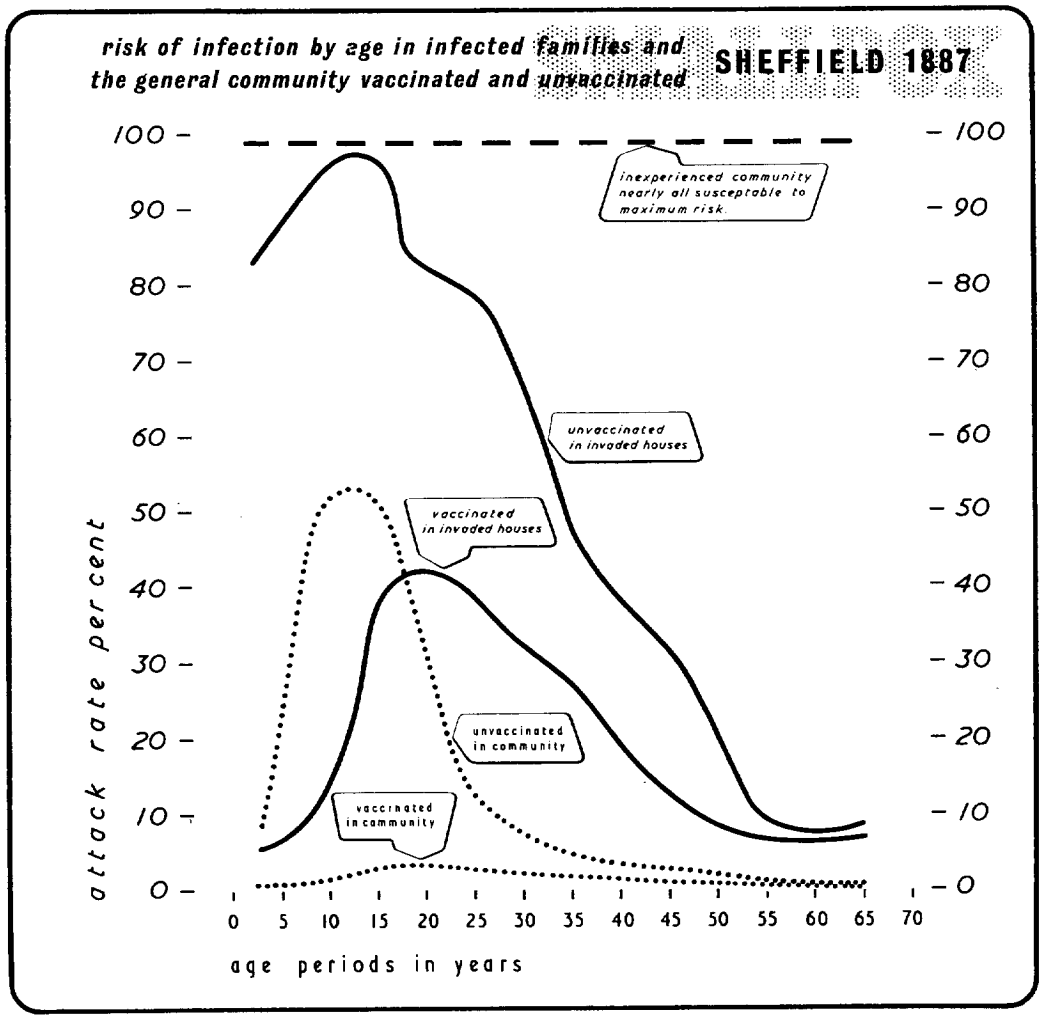


FIG. 231.

out any tests of the value of vaccination, gammaglobulin and other preventive measures, without adequate controls. In the case of variola minor escape seems to be even more frequent, and may well depend on a larger quantity of virus being needed to initiate clinical infection.

It is impossible to get really satisfactory figures of attack rates. In those countries where medical services are good, smallpox is so rapidly controlled that its natural history cannot be studied. In those where the disease is common, facilities for accurate observation do not exist.

Barry's study of conditions in Sheffield in 1887 throws some light on this point (Fig. 231).

It can be seen that in "invaded houses" the attack rate in contacts is very high in the unvaccinated, falling off in old age, probably due to previous contact with the virus; 6·6 per cent of the population had a history of previous smallpox. Even those vaccinated (in infancy) suffered a high attack rate if over fifteen years of age.

As one would expect amongst the unvaccinated, the all-age chance of being attacked if living in an invaded house in 1887 was 75 per cent whilst the chance from casual contact at work or in travelling was 9·7 per cent—about one-eighth. Amongst the vaccinated (in infancy) who lived in invaded homes the chance of contracting a clinical attack was 23 per cent whilst from casual contact in the community it was 1·55 per cent—about one fifteenth. Although antivaccinationists have often been at pains to stress that the attack rate in the "vaccinated" in the invaded houses was higher than in the unvaccinated in the population as a whole, so demonstrating its failure and the importance of undefined factors in the environment, the value of even remote vaccination in lowering attack rates under different circumstances is well shown. Assessment of risk is crucial to the evaluation of preventive measures, and is nearly always incomprehensible to the emotionally motivated layman.

Although the conditions of overcrowding and lack of isolation of cases, as in Sheffield in 1887, still occur in some countries, those with well-developed medical services are never likely to see this epidemic pattern again. Whilst the risk within the invaded family is only slightly reduced, that in the community as a whole is very much reduced. This fact is the basis of our present day practice in the control of smallpox in such communities.

As smallpox is regarded as such a highly infectious disease, it is assumed that a very small dose of virus will initiate an attack. On this we have no information and no method of measuring, but it is interesting to note that occasionally exceedingly mild attacks of variola major occur in the unvaccinated (see Figs. 89 and 90), and even attacks of variola sine eruptione. Possibly these are cases which have received a small dose of virus, although the immunity of the individual (non-vaccinial) could equally well account for it. On the other hand, when individuals such as nurses are exposed very closely to infection, we find that the attack rate is high, and mortality rate exceedingly high. In recent outbreaks in the United Kingdom, where smallpox attacked hospital nurses, seven who were unvaccinated all died from the disease. The same high fatality rate has also been recorded in mothers nursing their sick children. I feel that variation in severity must partly depend on the size of the infecting dose. It would seem that a room which has had a smallpox patient at any stage of the disease, even the earliest stage, may be infectious for at least a week and probably longer, depending on humidity, temperature and the amount of light. It is on this basis that a fairly rigorous disinfection of the room occupied by the patient is normally practised. As previously mentioned, sleeping in the same beds and cleaning the room seem to be amongst the most dangerous occupations.

Chance of infection in the community depends largely on conditions. Wanklyn (1913*b*) recounts an outbreak where one person with smallpox arriving in the country travelled by train to Stalybridge. When he landed he was apparently in the initial phase of the disease, as nobody noticed a rash on his face. He travelled by train to Manchester, and then in another train from Manchester to Stalybridge. Almost every person who travelled with him in the compartment from Queenborough to Manchester contracted smallpox, the ticket collector at Manchester, and those who travelled with him from Manchester to Stalybridge in another train, something like a hundred people being infected from one single case. In the *Tuscania* episode, in March 1938, two cases on board ship gave rise to forty-five further cases. In

general, variola major produces secondary cases in a larger number of susceptible contacts who have close or domestic contact, or contact at work. The chance of infection by more casual contact is impossible to determine. In some instances contact may be most transient, as in the case cited by Stallybrass (1931), where a man walked by an open window of a room in which there was a smallpox patient, and another instance in Berlin (Low, 1902) where the person just looked through the doorway of a smallpox ward and was infected; but in general more and more of the observations in the last twenty years confirm the fact that most of the cases of variola major occur in close contacts of the patient suffering from the disease, or from contact with infected clothing. Cumpston (1914) noted that the marked variation in the attack rates in smallpox outbreaks in ships was largely determined by the arrangements for controlling the spread of infection, rather than any differences in vaccination state.

In the case of variola minor, the infectivity is undoubtedly less. It was noticed by Robertson (1913) and by Innes (1953) that a much closer degree of contact was necessary than would appear to be required for variola major. This is cited by de Jong (1956) as evidence that the patients are not infectious during the initial phase, but the observation, particularly of larger series, suggests it is the actual weight of infection that is less. Even when unvaccinated persons are in the same family, it is quite frequent for them to escape infection from a case of variola minor, and not unknown today in variola major. Changes in housing and environmental conditions have undoubtedly altered the pattern of infection in some countries. In others, particularly the endemic areas in the tropics, "saturation" infection still occurs in the family.

PUBLIC HEALTH ASPECTS OF THE INCUBATION PERIOD

The incubation period has been discussed at some length in the clinical chapter. There is a vast amount of evidence that the incubation period of variola major is nearly always between twelve and thirteen days, and in spite of early accounts that the incubation period of variola minor is considerably longer, observations of Marsden (1936), and more recently of de Jong (1956), confirm that the incubation period is twelve to thirteen days. It has long been recognized that it is very difficult to be certain that a patient only has contact for a short and limited space of time, and the vast majority are in contact with their source of infection for three or four days, sometimes longer. Of more recent years there have been cases cited (Stallybrass, 1947; Eastwood, 1955) where individuals appear to have had shorter incubation periods, between eight and ten days. In many of these cases concurrent vaccination has been performed, and it seems possible that the initial pyrexial attack may well be due to this, and even the appearance of some of the lesions may be vaccinial rather than variolous, particularly where the attack is very mild. On the other hand, occasionally the cases appear to be exceedingly severe, as in that of Stallybrass, and where any other possible source of infection can be ruled out, which is often not as certain as might appear at first sight. It would seem that very occasionally a shortened incubation period does occur. From a practical point of view, however, I think it is justifiable to regard the incubation period as twelve days, and that it is possible to regard contacts as not infectious for ten days of the presumptive incubation period. The other small group of cases have been referred to in Chapter 10, under "illness of contact". In the form of "pulmonary allergy" there is a clinical syndrome with pyrexia, often from about the eighth or ninth day, but lasting about two weeks. I feel that in the light of our present knowledge we can regard these as being non-infectious, so that our public health measures still remain as they have been for the last fifty years, that is regarding the incubation period as twelve to thirteen

days, and basing our administrative action on this assumption. In this way it is desirable to have a quarantine period of sixteen days, particularly if one has to rely on the appearance of lesions rather than the history of pyrexial attack, and the possibility that occasionally persons may pick up smallpox virus on their clothing, and not infect themselves for one or two days afterwards, so apparently giving a longer incubation period.

CLIMATE

Latham (1890) drew attention to what he thought was a connection between climatic conditions and the occurrence of smallpox. He remarked that smallpox was always preceded by a long period of dryness of the ground, measured by the absence of percolation, but he was under the impression that smallpox was propagated in the same way as cholera. Rogers (1928) has published many papers since 1923, dealing with the effects of climate on disease, particularly smallpox, in India. Although a vast amount of work has been done on this subject, much is related to deaths as an index of smallpox incidence, which is much affected by the age of attack and the degree of vaccination. The thesis is that epidemics of smallpox nearly always follow closely on low rainfall and low absolute humidity, and in a study he made of variola minor in England between 1921 and 1927, Rogers (1928) showed that in each year the highest incidence was in the month after the lowest absolute humidity, and lowest incidence in the month after the highest absolute humidity. This might be more connected with social customs of the population than with the climate. The survival of virus, particularly on clothing, might well be affected by the humidity of the air and it would seem possible that, where control is not exercised at all, climate might play some part in increasing the likelihood of spread, but in a community with well-organized medical and public health services, examination of the weather records will certainly not provide the health officer with advance information as to when smallpox is likely to occur.

PREDISPOSITION

The older accounts of smallpox frequently noted that certain families appeared particularly liable to contract the infection and die. This was particularly noticeable in the Stuart and in other notable families. In a number of more recent outbreaks it has been noticed how the maximum weight of infection seems to rest on one family, where two or three of the members may die, particularly blood relations. In the outbreak in Yorkshire (1953) I noticed the similarity of physical type between mother and son, who both died, whereas another son, equally exposed but of a different physical type, had a mild attack and recovered. In the outbreak in Merseyside in 1946, a mother, aged fifty, and three children, aged twelve, fifteen and seventeen, all died, a somewhat unexpected outcome in this age-group. There is no conclusive evidence, but in common with most other diseases the factor of individual idiosyncrasy should be recognized in assessing some of the more unexpected results of vaccination or treatment. Gregory (1838) pointed out that both smallpox and vaccinia affect particularly severely those who appear to be in the best of health, and patients suffering from other diseases tend to escape a concurrent attack of smallpox. Although smallpox and vaccinia frequently occur concurrently, evidence of smallpox associated with other diseases is scanty.

Fifty years ago the high mortality in chronic alcoholics was often noted in clinical accounts. It appeared that a higher proportion of malignant cases occurred in these patients, and maniacal symptoms were particularly frequent. Chronic alcoholics, many of them tramps, belonged to

a very low social class, and would therefore be more likely to contract smallpox. Possibly they were noticed because of fatal attacks in relatively young men who had been successfully vaccinated in infancy.

The effect of anaesthetics is also of interest in view of the fact that the initial stage of an attack of smallpox may be misdiagnosed for the acute abdomen. One contact from the *Mooltan* outbreak was seen by a surgeon as a possible acute abdomen. Fortunately he thought that it might be smallpox, and the case, which proved fatal, was not operated upon. In the outbreak in Yorkshire (1953) one case was operated upon as an acute abdomen, and died shortly afterwards. In the outbreak at Tottenham (1958) a small child was operated upon for acute appendicitis in the initial stage of smallpox, and he also died from the disease. It seems possible that anaesthetics during the initial stage may have some adverse effect on the outcome of the disease, and the alcoholic may suffer in a similar way.

FAMILY SIZE

As the main pattern of smallpox spread is by close contact within the family, it can be seen that the size and composition of the family is important. Barry (1889) carried out a family survey during the Sheffield outbreak and from his tables I have constructed a diagram to show the differences, statistically significant, between the ages of members of infected families and those of uninfected families in the city (Fig. 232). In a community where infant vaccination was practised extensively smallpox occurred more frequently in those families with a larger number of members between the ages of ten and twenty-five, and occurred less in families where a larger proportion of the family were under ten or over the age of thirty. In spite of a different vaccination state, this pattern still tends to occur today, due to the importance of the individual in the 15–25 age-group as the interfamily disseminator of infection.

SOCIAL CLASS AND OCCUPATION

Social class in smallpox has varied over the centuries. In the early days, smallpox was introduced into England from abroad, and principally affected the nobility, the people most likely to travel. Over the years, the upper classes have more and more protected themselves by vaccination, and smallpox has been predominantly a disease of the lower social classes. Particularly at the end of the nineteenth century, a large number of outbreaks were due to the transfer of infection by tramps from one area to another, and Long (1893), Duncan Forbes (1938) and others have pointed out that the elimination of smallpox from a community depended first on eliminating it from the tramp population. It may be fairly said that during the late nineteenth century the tramp carried infection, and those families who had contact with him, either at work, in the public house, or in various other ways, were liable to have smallpox introduced. In the twentieth century smallpox became a disease which was introduced from abroad by merchant seamen or by travellers. In England and Wales between 1935 and 1952, smallpox was imported on thirty-one occasions, spreading to the population on twenty-five occasions. Sometimes the disease was detected on board ship, but inadequate public health measures were taken to prevent entrance into the country, and many missed cases also occurred. Within the last twenty years, the picture has changed, in that the tramp no longer is present in England and Wales to transfer infection, but the modern long-distance lorry driver seems likely to replace him as the method of conveying infection

from the ports into inland towns. The lorry driver belongs to a peculiar social class. Many have been vaccinated and revaccinated during the last war, so that their level of immunity is still fairly high. They tend to be like the traditional merchant seaman—they have a wife in every town, and their somewhat peripatetic existence makes their movements difficult

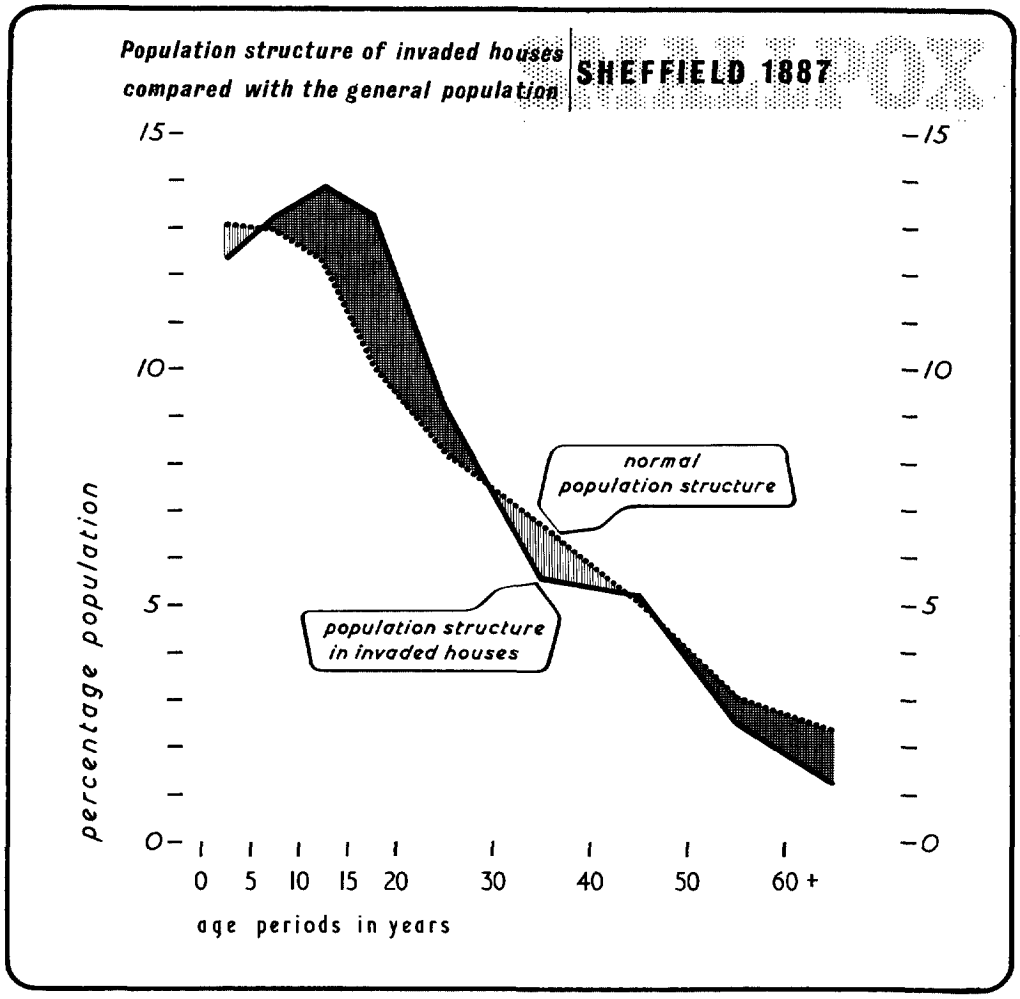


FIG. 232.

to follow, as the investigations in Yorkshire showed. In modern welfare states there is a great tendency for people to remain in their own environment and in the security of their own occupations, and not move from place to place except at holiday periods, but the long-distance lorry driver has innumerable contacts, in loading his vehicle, in seeking his meals and lodgings *en route*, in a way that the railway crews have never done, with the result that the lorry driver is more likely to convey infection than other means of land transport.

Density of population has often been regarded as affecting the incidence of smallpox. Long, writing in 1893, pointed out that it was not so much overcrowding in itself as poverty and the concomitant carelessness about disease that really mattered. Although outbreaks occurred in thickly populated parts, they were not necessarily in the most overcrowded streets, and there were overcrowded places with narrow streets, big houses and very small backyards, such as Bethnal Green, Southwark and Bermondsey, where smallpox often occurred but never produced large outbreaks. My own observations in Tripoli City, which was exceedingly overcrowded, support this view. On the other hand, in places like Glasgow with its single-room tenements, the opportunity for infection is very great, and in towns like Dewsbury, Spencer Low (1905) noticed that because frequent visiting of the sick was the social custom, there was great opportunity for spread of infection. It would seem therefore that in a small town with a single industry, where everybody knows everybody else, spread of infection may be rapid, whereas in a town which is predominantly commercial and has many industries and wide interests, where families to a considerable extent "mind their own business", opportunities for spread of infection will be much less, although the degree of overcrowding may be just as great. It has also been noticed that it often takes some time in an outbreak for infection to "cross" a main road, river or canal. This is because such geographical features are often the boundaries of groups of similar social class having the same schools or occupations. Multiple cases in households were not so common in late nineteenth-century outbreaks as is usually assumed. Variation in the amount of vaccination will also affect the pattern, as seen in Dewsbury, 1904, and Gloucester, 1923 (Fig. 233). In the rapidly controlled outbreaks today, with the small total numbers a proportionately larger number of instances occur with two or more cases in a family.

Dewsbury, 1904. 552 cases. Variola major
1 case only in 280 houses
2 cases in 51 houses
3 cases in 18 houses
4 cases in 14 houses
In 34 households all unvaccinated inmates affected.

Gloucester, 1923. 621 cases. Variola minor.
1 case only in 272 houses
2 cases in 81 houses
3 cases in 28 houses
4 cases in 16 houses

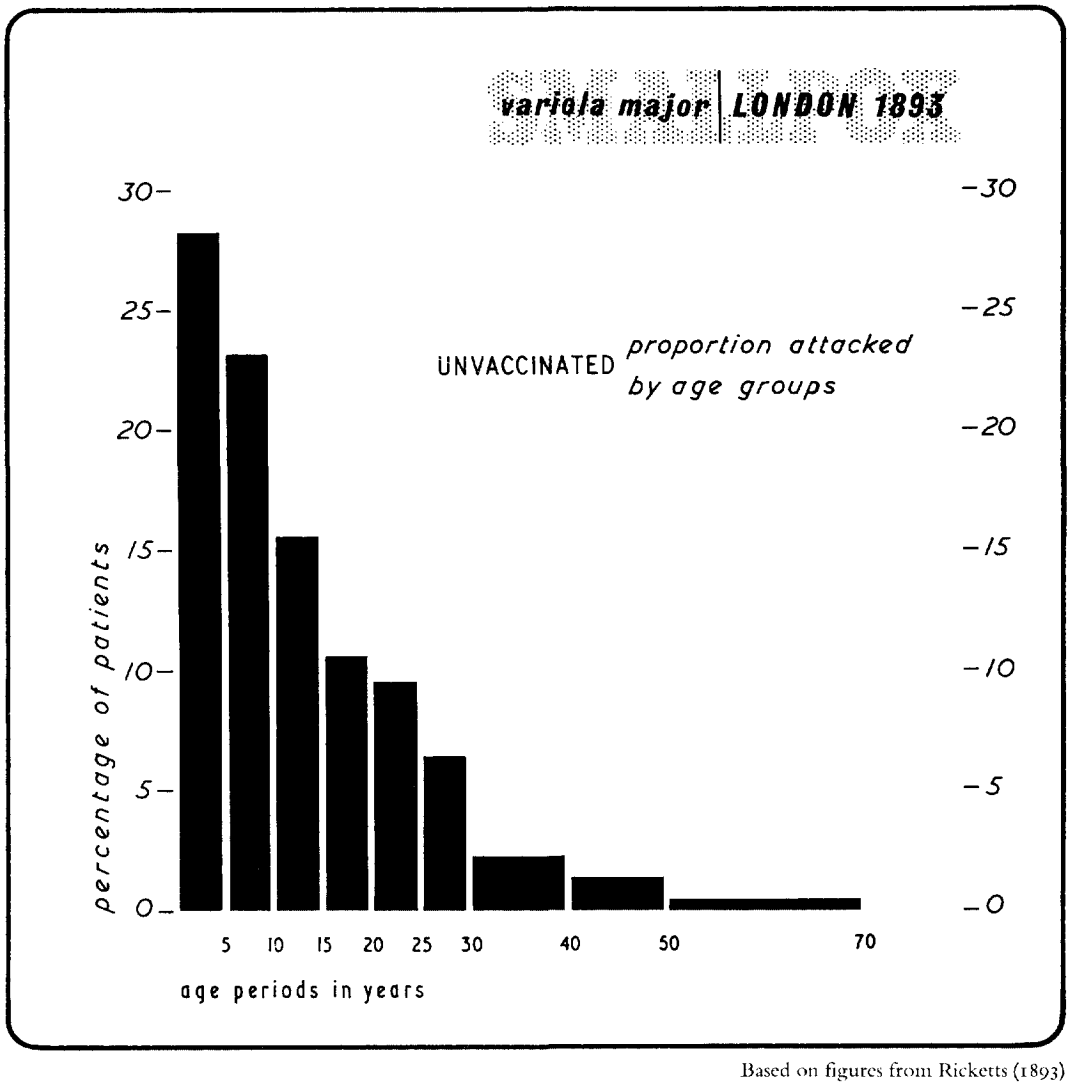
FIG. 233.

It has already been noted that tramps, cotton-workers, rag-sorters, undertakers, mortuary attendants and others have at various times been more likely to contract smallpox, but perhaps the most important occupational group today are doctors, nurses, hospital domestic staff, and medical students, who are frequently and unnecessarily attacked, and have figured largely in outbreaks in England, Scotland, France, Holland and Germany in the last fifteen years.

RACE

It is usual to state that coloured races suffer from smallpox more severely than do white races, from the observation of smallpox in a small number of coloured people, who have been

attacked by the disease alongside Europeans, who might well be living under far better conditions. Neglect, particularly leading to pyaemia and broncho-pneumonia, can undoubtedly lead to increased mortality. Wilkinson (1942) noticed a higher mortality in negroes than in Chinese. There were an unusual number of deaths from variola minor in the Maoris in New



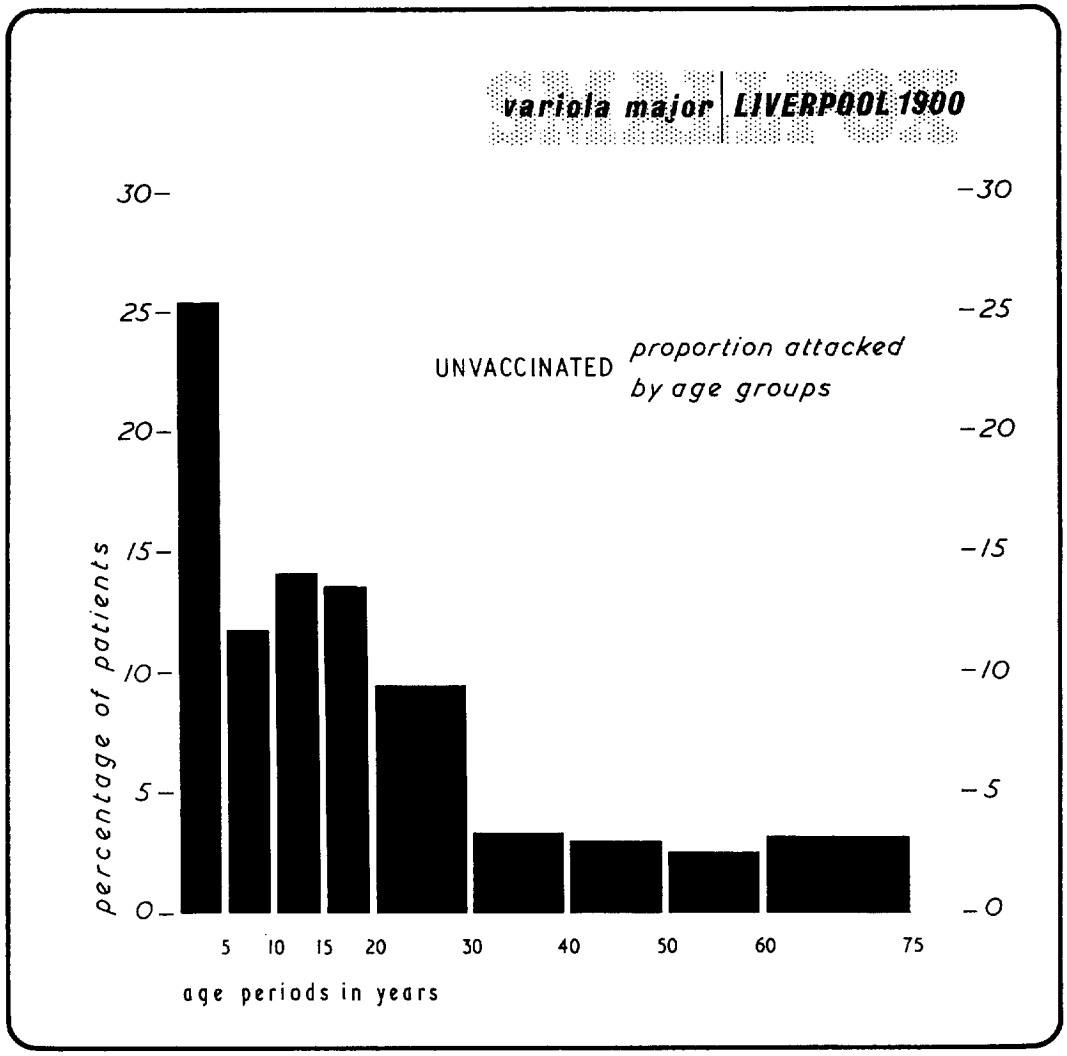
Based on figures from Ricketts (1893)

FIG. 234.

Zealand in 1913. It is very difficult to avoid the bias which is introduced in any small series by the high proportion of vaccinated cases in Europeans, when the same proportion are not present in cases in other races.

Racial predisposition probably does not exist as such, but a population that has experienced the disease for some generations, even if unvaccinated, appears to have a lower mortality

than one that has never experienced it before. This apparent difference may be due to the fact that in those populations, where the disease has been endemic for three or four generations, the present inhabitants have been bred from the survivors.



Based on figures from Hanna (1913)

FIG. 235.

MORBIDITY—VARIOLA MAJOR

It has usually been assumed that man is highly susceptible to smallpox, and that all who come into contact with it will eventually be attacked. The figures obtained from an investigation of the Norwich outbreak in 1819 suggest that the residual population who had not had smallpox and who did not contract the disease in this outbreak was about 2½ per cent. It does seem that, if individuals are repeatedly brought into contact with smallpox, the vast majority

will in time be affected, but this does not mean, however, that the chance of contracting smallpox on any one occasion is nearly 100 per cent. It is very much less.

The natural attack rate of variola major in unvaccinated individuals exposed to the infection is not easy to determine. In Gloucester in 1893 in invaded houses the attack rates were: under

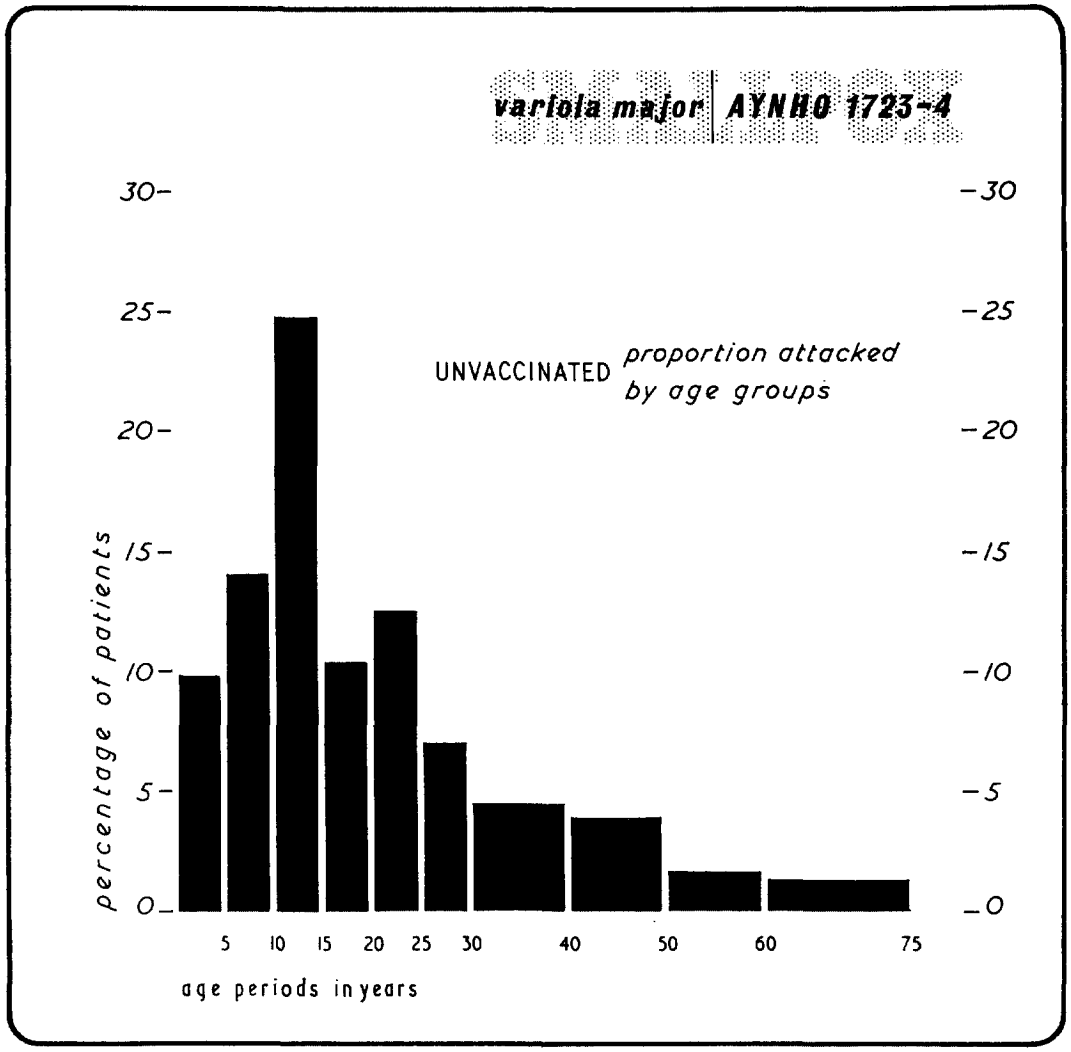
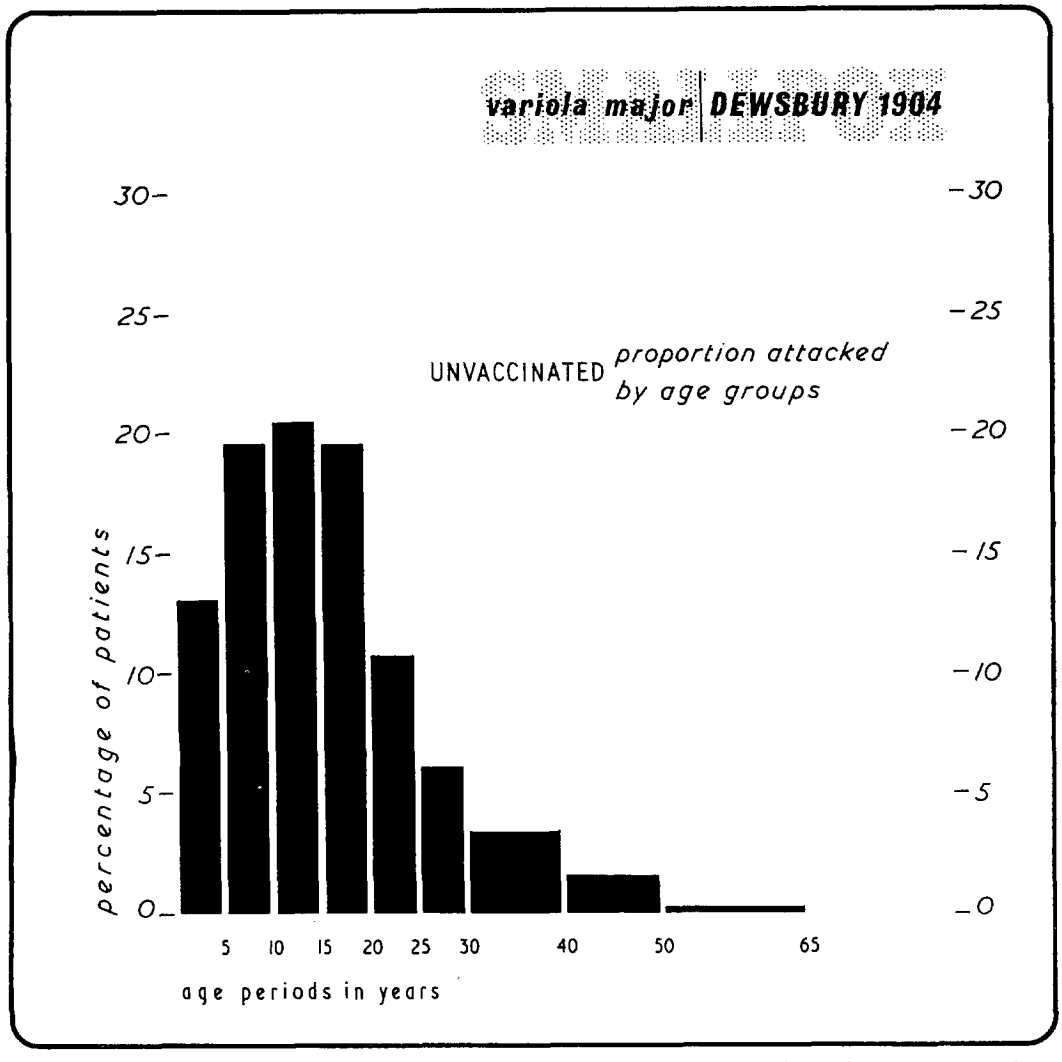


FIG. 236. Based on figures from Creighton (1894)

1 year, 80 per cent; 2–10 years, 75 per cent; 11–30 years, 75 per cent; over 30 years, 46 per cent. The chances of infection were probably maximal, as Gloucester was notorious for its reluctance to isolate cases. In Tripoli in 1946 a number of contacts under five were observed, and about 40 per cent were attacked.

It is impossible to get figures under present-day conditions, because contacts will be immediately vaccinated. However, I feel that the natural attack rate in a modern community, with

good housing, reasonably early diagnosis and removal to hospital, would be about 50 per cent of those "exposed". The degree of contact of members of the family—for example, mother and child, nurse and patient—will increase the chances very considerably, and there is also the



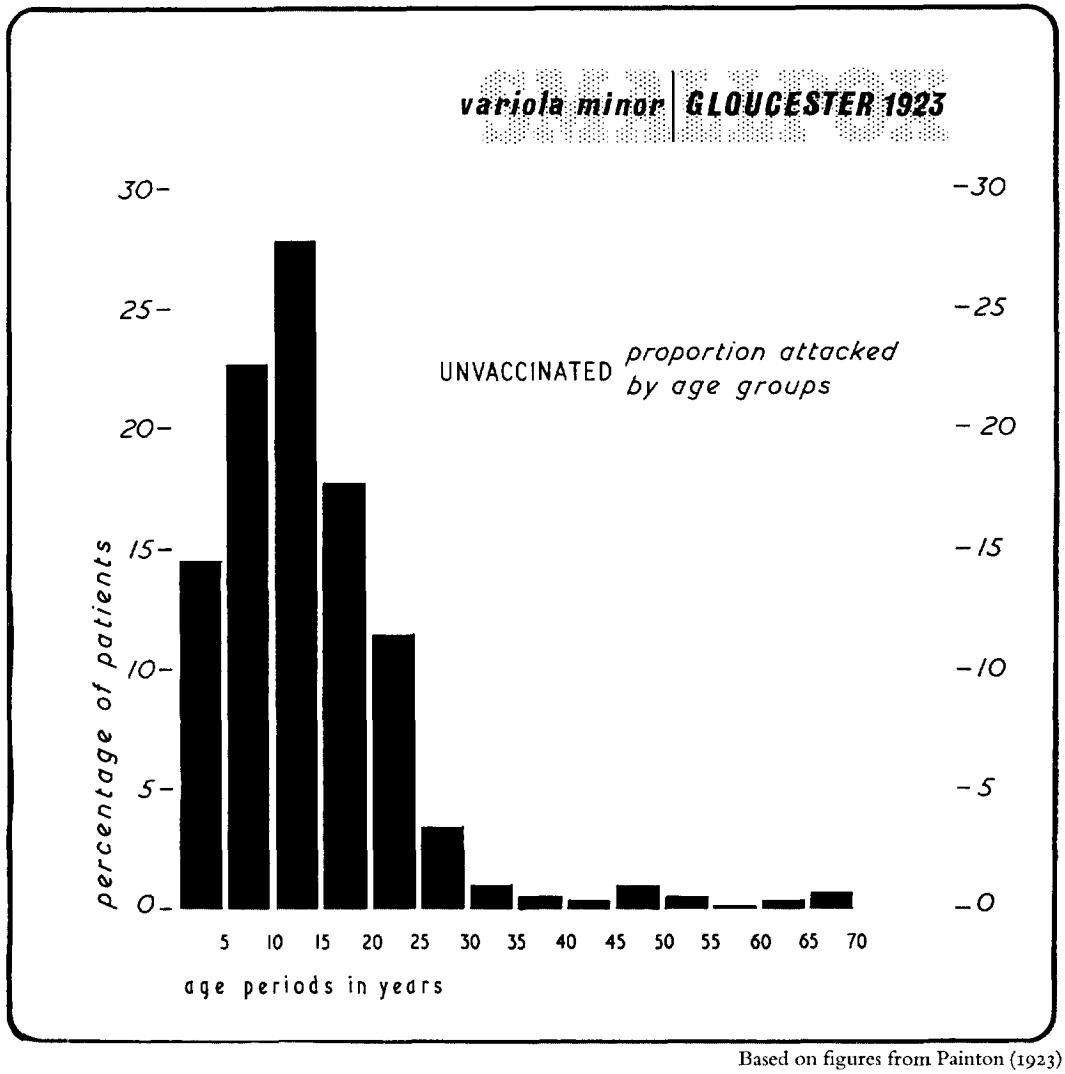
Based on figures from Spencer Low (1905)

FIG. 237.

type of the source case to be taken into account. In some families, all the susceptibles may be attacked, whereas in others, all may escape.

It has, I think, been too readily assumed that the age of attack in smallpox is determined entirely by the previous experience of smallpox or vaccinia, particularly the latter. It has always been customary to regard the disease as having a very high incidence in infancy and childhood, and steadily diminishing with advancing age. This picture is shown very well in Fig. 234,

illustrating the proportional age-specific attack rates for London, 1893, in the unvaccinated. This form of presentation compensates for the usual exaggeration shown in the age-group 0–5, due to an excess at risk, but the pattern is one of diminishing incidence with age. It is usually thought that the lower incidence at older ages is due to previous contact with smallpox

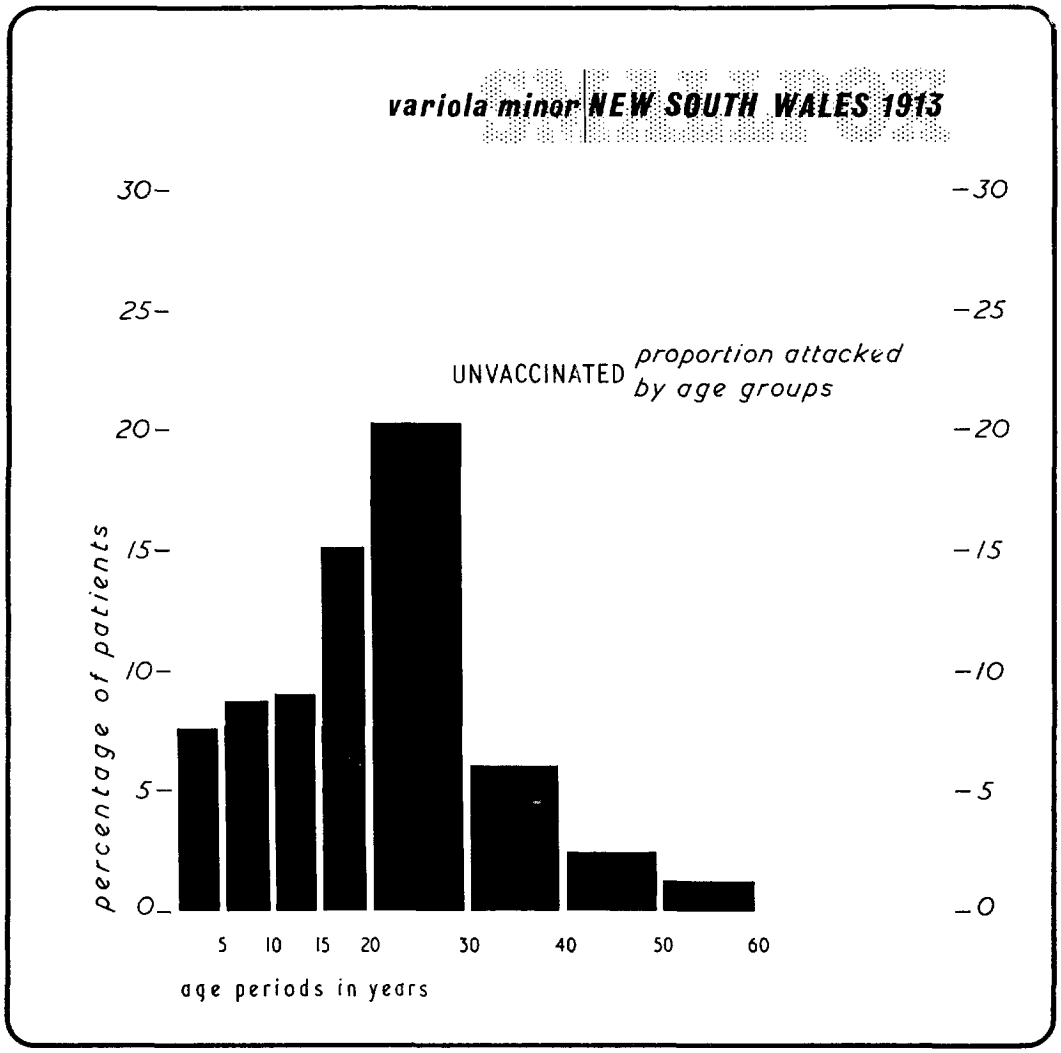


Based on figures from Painton (1923)

FIG. 238.

virus. If, however, one looks at Figure 235, for Liverpool, 1900, the crude age proportion of attacks, one sees that although the age group 0–5 is about the same, the group 5–10 is less than group 10–20. There are probably sociological reasons, possibly a large number of Irish immigrants, which have altered the pattern of age distribution in this particular outbreak. If one then examines Fig. 236, a small outbreak at Aynho in 1723, one sees the rather unexpected

pattern showing a rise in incidence up to a maximum in the age-group 10–15, and then falling away with proportionately quite a large number of cases up to the age of fifty, considering it is the early eighteenth century. Figure 237 shows an outbreak in Dewsbury, where the pattern in the unvaccinated shows a similar peak in the age-group 10–15. It has points of



Based on figures from Robertson (1913)

FIG. 239.

similarity with the Aynho outbreak, and yet why it should be so different from London in 1893 or from Liverpool in 1900 is difficult to explain. Being a woollen town with a large number of people engaged in mills, may have been the factor determining the high incidence between 10 and 20, but this doesn't explain the relatively low incidence in the unvaccinated between 0 and 5.

MORBIDITY—VARIOLA MINOR

Accurate figures are not available, but all the evidence suggests that chance of infection is reduced. Unfortunately recent observations (Innes, 1953) on the feeble powers of spread are derived from a study of all the families and not those where all were unvaccinated. The

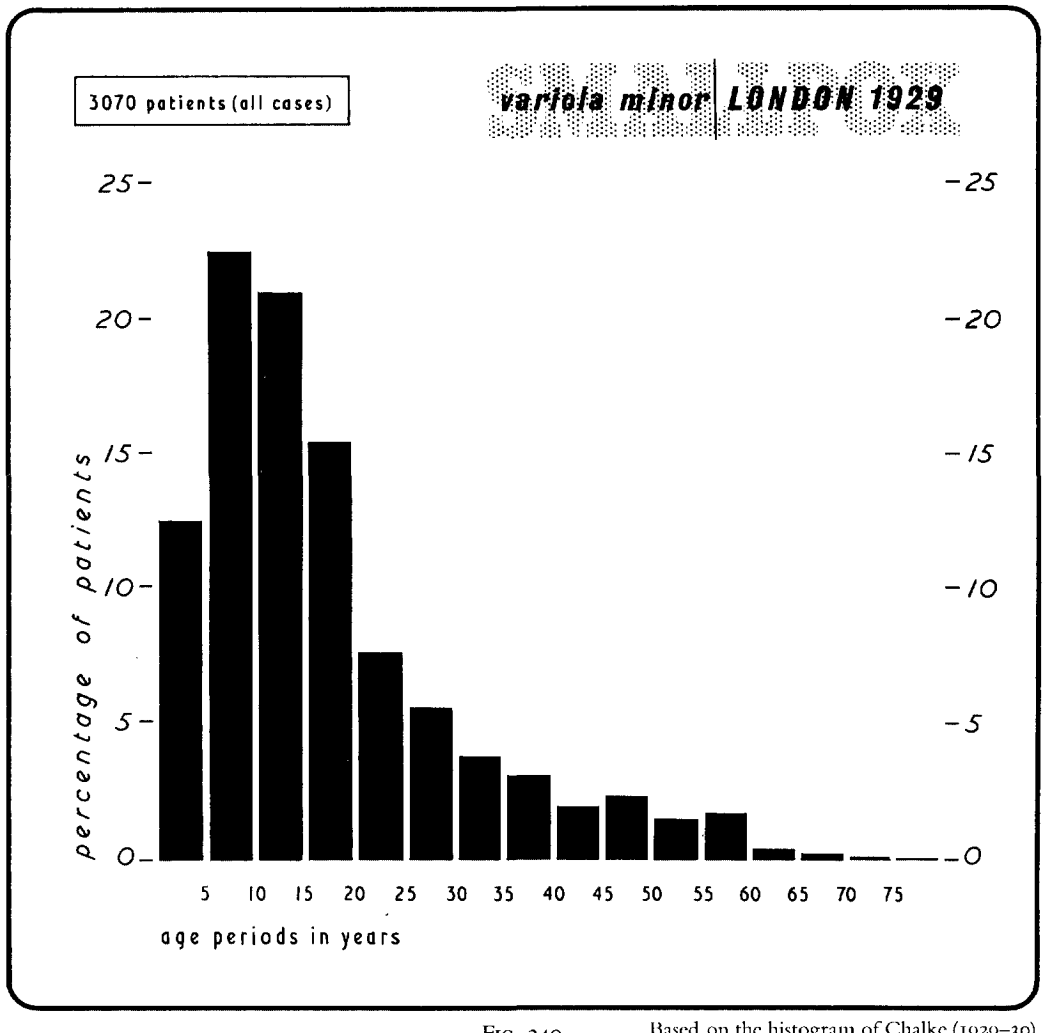


FIG. 240. Based on the histogram of Chalke (1929–30) and figures of Chalke (1958)

view of Robertson (1913) on the frequency of single cases in families is also partly affected by the probability that a fair proportion of older adults were vaccinated, although the majority of children and younger adults were not. I would hazard a guess that 20 per cent would be near to the natural attack rate in variola minor, but the degree of contact within the family has to be greater than in variola major, and there is much greater chance of variation. It is important, however, to remember that families can be involved in variola minor where every unvaccinated susceptible is attacked.

Turning to the diagrams of age incidence in variola minor, we again get some surprises. Figure 238 shows the age of attack in a series of unvaccinated patients in Gloucester in 1923. Although unvaccinated, children under five suffered less than those of 5–10, and the group most affected was from 10–15. The weight of attack rapidly faded away, so that few were involved over the age of twenty-five. This effect may have been due to the relatively small proportion of the population remaining unvaccinated above this age, due to the large outbreak of variola major in 1893, but the lower incidence in young children is in keeping with the earlier observations on variola minor in the West Indies. In Fig. 239 we have the age-groups attacked in the New South Wales outbreak in 1913, where the unvaccinated were much larger in number in all age-groups at risk. Here we see that the age-group 20–30 has been most affected, with a relatively constant and low rate of infection in 0–15. The peak of attack is quite different from the Gloucester pattern, and may be due to spread through young adults at work. Figure 240 shows the distribution of cases by age for all cases, unvaccinated and vaccinated, in London, 1929. The proportion of the latter, however, was only about 13 per cent in the age-groups 15 and over. The pattern for the age-groups 0–5, 5–10 and 10–15 can be regarded as that of the unvaccinated. Variola minor splashes the community with cases, whereas under similar conditions without any control variola major will soak it.

SEVERITY—VARIOLA MAJOR

When a small number of cases occurs, the clinician is often surprised by the fulminating or malignant cases, and regards the infection as being particularly severe. Peters (1909) and Stallybrass (1947) used the term *variola maxima*, but I don't think this is justifiable. Only in a fairly large series of cases is it possible to determine the pattern of severity, and even this will be influenced considerably by the ages of those attacked. Fulminating cases appear more common at the extremes of life and there is a higher proportion of discrete cases in the age-group 10–15, with a correspondingly larger proportion of malignant in young adults. In the series in Tripoli in 1946, about 2 per cent were type 1, 44 per cent types 2 and 3, 26 per cent types 4 and 5, 22 per cent type 6, and 5 per cent types 7, 8 and 9. Figures for Dewsbury in 1904, classified in rather a different way, show about 1 per cent haemorrhagic, corresponding to type 1, 30 per cent classified as confluent, 19 per cent classified as semi-confluent, and 50 per cent as discrete. From examination of the records in England and Wales for the last twenty years, and the pattern in other outbreaks with varying classification of cases, it would appear that given a population similar to that of England and Wales at the present time, with a high proportion of adults, and the probability that smallpox infection will tend to be in the age-group 10 plus, rather than in infants and young children, the pattern of severity might well be as follows: type 1, fulminating, 5 per cent; types 2 and 3, 40 per cent; types 4 and 5, 30 per cent; type 6, 20 per cent; types 7, 8 and 9, 5 per cent. Of those who survive, about 90 per cent will have facial scarring. The inclusion of more of the 5–10 year group would increase the proportion of types 6–9.

SEVERITY—VARIOLA MINOR

The natural severity of variola minor in an unvaccinated community has never been determined, partly because most of the outbreaks occur in people where some vaccination at least has been done, and depending on the availability and astuteness of the medical services, a large

number of milder attacks will be missed. The photograph, Fig. 241, shows very dramatically the pattern of severity in variola minor in Gloucester (Painton, 1923). Five per cent were classed as "severe", 20 per cent "mild", and 70 per cent "very mild". Types 1–3 can occur, but are extremely rare. In about 5 per cent of cases, both in Gloucester and in Pickford Marsden's series (1936), some residual scarring was present.

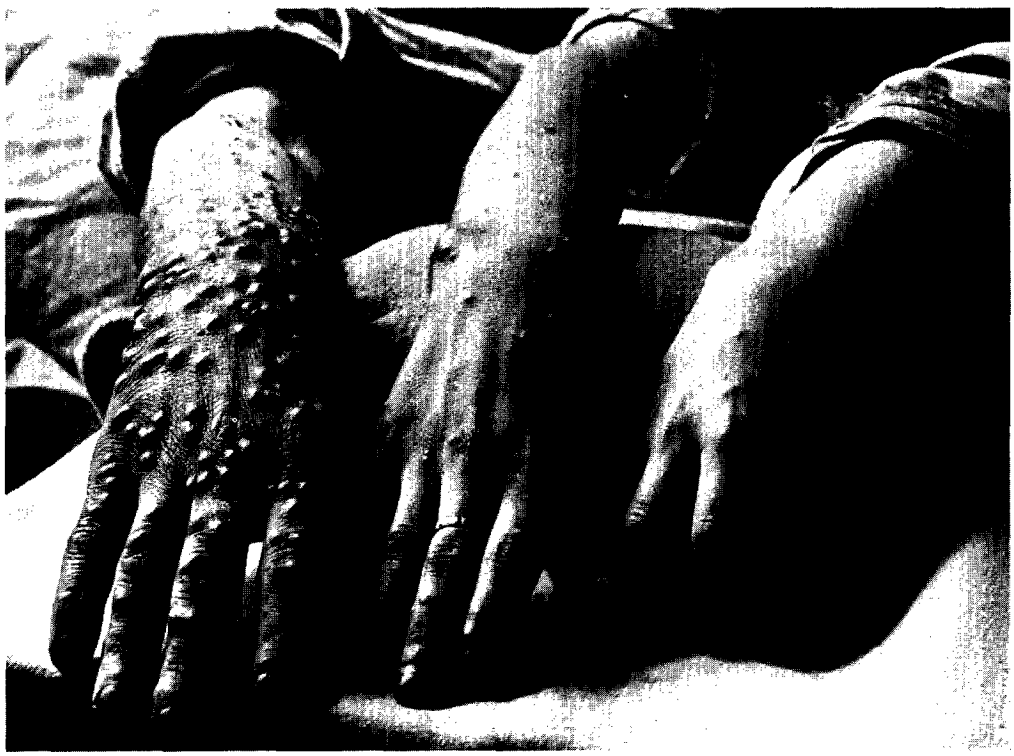


FIG. 241. Severity of attack in Gloucester, 1923. 5 per cent "severe", 20 per cent "mild", 70 per cent "very mild".

MORTALITY—VARIOLA MAJOR IN THE UNVACCINATED

Although it was said in the past that there were some varieties of smallpox which the doctor could not cure, and others which the nurse could not kill, most of the available evidence suggests that variola major is a single entity, and that variations in mortality in the small outbreaks can be accounted for by chance, age of attack and population experience. In some of the earlier accounts from some countries, the inclusion of chickenpox has altered the whole value of the statistics. In the early outbreaks in Mexico and other countries, it was stated that about one-half of the population died, in others it was stated that about one-third of the population died from smallpox. An analysis of the figures for some twenty outbreaks shows that the case mortality of an unvaccinated population is about 30 per cent. If an outbreak contains rather more young children or people over the age of forty, mortality will rise, whereas if a larger proportion of the patients are within the age-group 10–20, the mortality

will be reduced. Figure 242 shows from different sources mortality in the unvaccinated by age-group for variola major. The mortality at the extremes of life can also be influenced by the presence of intercurrent infection, particularly respiratory infection, the general hygiene and poverty of the group. The only other effect on mortality other than age appears to be pregnancy. Mortality of those who are pregnant is appreciably higher than in those who are not. In some instances this may be partly due to the occurrence of abortion, but the frequency of fulminating and malignant types appears to be greater in those of the same age who are pregnant. It would seem that the mortality of variola major in the unvaccinated pregnant woman is in the region of 50 per cent.

Variola major. Percentage mortality in the unvaccinated

	Gayton (1885)	Marson (1857)	Barry (1889)	1960 estimate (plus for poor social conditions)
0–4	60	50	42	30+10
5–9	35	27	21·2	20+5
10–14	23	23	19·6	20
15–19	42	26	28·6	25
20–24	48	40		
			38·1	35
25–29	45	45		
30–40	41	57	44	40
40–50	43	72	(30+)	50
50–60	43	66		(60)
70–	(50+)	(50+)		

FIG. 242.

MORTALITY—VARIOLA MINOR IN THE UNVACCINATED

The mortality from variola minor is exceedingly low. During the protracted outbreak in England it fluctuated between 0·17 and 0·43 per cent, and in the United States of America from 1927 to 1942 between 0·23 and 0·6 per cent. It is the practice in the United Kingdom to credit the death to smallpox if this is mentioned at all on the certificate. It would seem that the case mortality really due to variola minor is less than 0·1 per cent and even with poor social conditions a figure over 1·0 per cent suggests errors in diagnosis.

THE EFFECTS OF PREVIOUS SUCCESSFUL VACCINATION—MORBIDITY

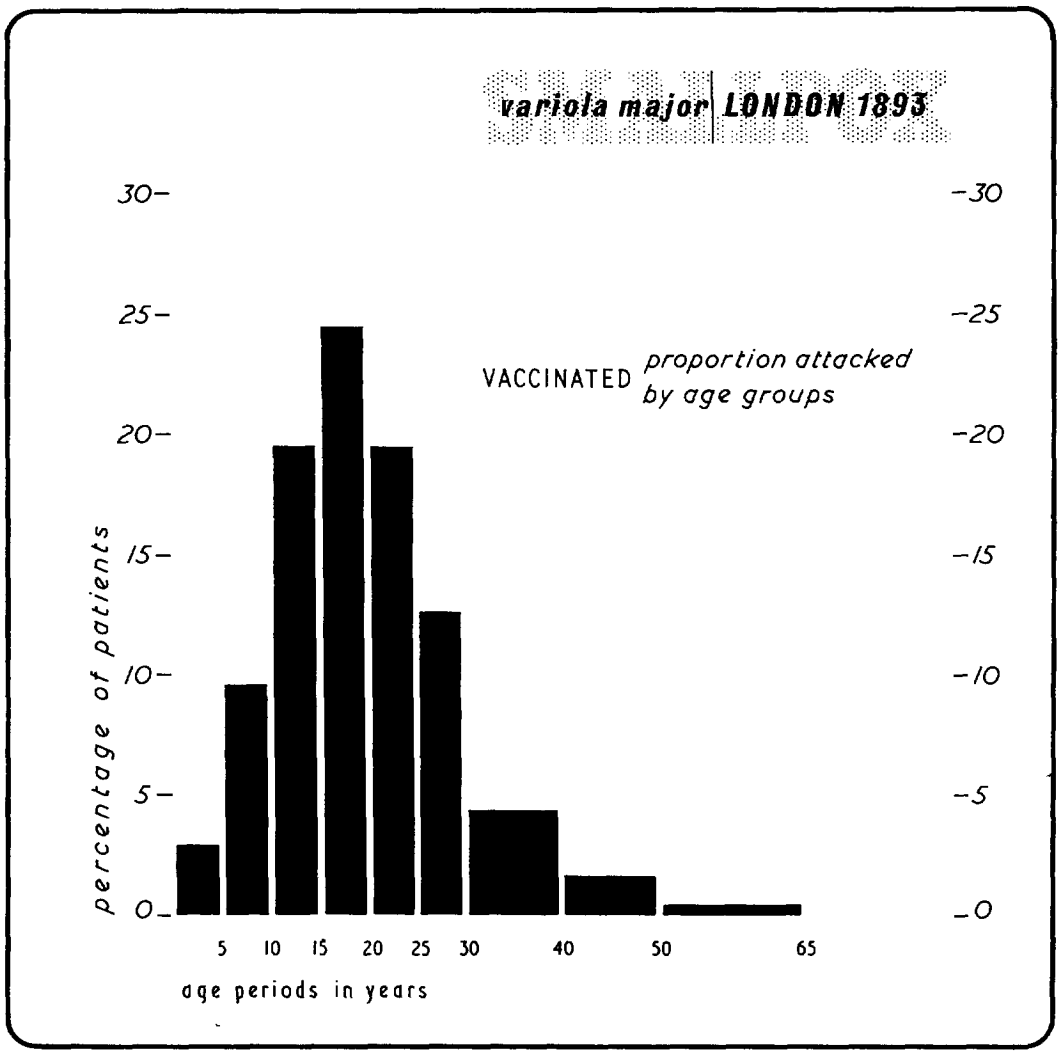
In most countries in the world, previous successful vaccination has in the majority of individuals been done in infancy, although in others, where vaccination is compulsory on school entrance, it has then been done at about the age of five. Sometimes primary vaccination has only been done on entry into the Services at the age of eighteen. What evidence we have as to the effect of previous successful vaccination is practically all related to primary vaccination performed in infancy. Due allowance must be made for those individuals or groups of individuals who have had successful primary vaccination at some later period in life.

The effect of previous successful primary vaccination in preventing attacks of smallpox is more difficult to assess than would appear at first sight. The difficulty is to obtain groups of individuals of the same age and sex who are exposed to smallpox under the same conditions. Comparisons made in the general population are frequently false, as the level of vaccination in different social classes is different, even in countries where vaccination is compulsory. Much of the information has come from the observation of the fate of vaccinated and unvaccinated persons in infected houses. Unfortunately, in some cases persons who were vaccinated during the incubation period are included in the vaccinated group, and in most of the earlier observations little attempt was made to verify whether the vaccination had or had not been successful, as indicated by a vaccinial scar. It was again further complicated by the bias of the investigator as to whether the scars were "good scars" or "poor scars" and the attitude of some to regard the single vaccination site as hardly a "successful vaccination".

First I will deal with the subject so dear to antivaccinationists, the apparent failure in individual cases of supposed vaccinal immunity to last more than a very short time, if at all. Stevenson (1944) quotes Coupland (1897) that in the Gloucester outbreak a child whose vaccination had been performed in three places twenty-two days before the attack of smallpox commenced, and who had three definite vaccinial sites covered with dark scabs, had a severe attack and died. There is always the possibility that the scabs were simple infection and not vaccinia, although this is an unlikely explanation. The most probable one is that vaccinial immunity did not develop, because of agammaglobinaemia or dysgammaglobinaemia. Cory (1898) records three cases of children who developed smallpox at the age of two or three years. They had been successfully vaccinated as infants, as evidenced by one, two and four scars respectively. Hanna (1913) reported seven modified smallpox cases in the age-group 2–5. Lemaire (1926) in Algiers, in a large outbreak, reported last successful vaccination fifteen to forty-five days in four cases, of which two died, three to six months in eight cases, of which six died, six to twelve months in four cases, of which three died, and one to two years in eight cases, of which five died. The very high mortality, taking the age into consideration, suggests no vaccinial immunity. Boulnois (1936) quoted a case where several members of a family developed mild attacks of smallpox forty-seven days after being vaccinated, and le Huludut (1936), reporting an outbreak in India, saw ten cases of smallpox successfully vaccinated twelve to thirty days before the attack, and one case vaccinated sixty days before. The severity is not mentioned, but it is observed that the results of vaccination were carefully watched at all stages. Two fatal cases of malignant smallpox occurred in subjects vaccinated twelve to fifteen days before. Morosov (1938) reported twenty-four cases of smallpox, two deaths, in those vaccinated successfully within twelve months, and thirteen with three deaths between one and two years. These cases had multiple insertions. I saw a case in Tripoli in 1946 of a very mild attack in a contact three months after a small but genuine primary vaccination.

There would appear to be two types of case, those where no immunity develops, in individuals who are possibly suffering from congenital or acquired agammaglobinaemia or dysgammaglobinaemia, and those in which some immunity develops, possibly fairly high at first but rapidly declining, and this gives rise to a mild and very modified attack. Although the pro-vaccinationists of the late nineteenth century were adamant that every person could be vaccinated and that the response ought to be the same in every person if the proper technique and care were used, I am sure that a small proportion of individuals naturally react to vaccination in a different way, producing a more superficial abortive and what the older

clinicians would call "imperfect" vaccination, no matter how it is done. Examination of material from many sources leads me to believe that in a community where smallpox is not endemic, compared with the unvaccinated, single-insertion primary vaccination within one year reduces the chance of any attack, including abortive and sine eruptione, to $\frac{1}{1000}$th,



Based on figures from Ricketts (1893)

FIG. 243.

within three years to $\frac{1}{200}$th, within ten years to $\frac{1}{8}$th, within twenty years to $\frac{1}{2}$, and has little if any effect in preventing infection after twenty years. In variola minor it is exceptional to get any clinical cases within five years of successful vaccination. The chance of clinical attack within ten years is about $\frac{1}{2000}$th of that in the unvaccinated. Thereafter it diminishes, but some

degree of immunity appears to be present for thirty years. I would suggest $\frac{1}{80}$th at twenty years, $\frac{1}{40}$th at thirty years and $\frac{1}{15}$th at forty years, diminishing further with time.

Where a population has been subjected to a fair amount of infant vaccination, the pattern of age of attack in variola major is obviously different. Examination of Fig. 243, for London

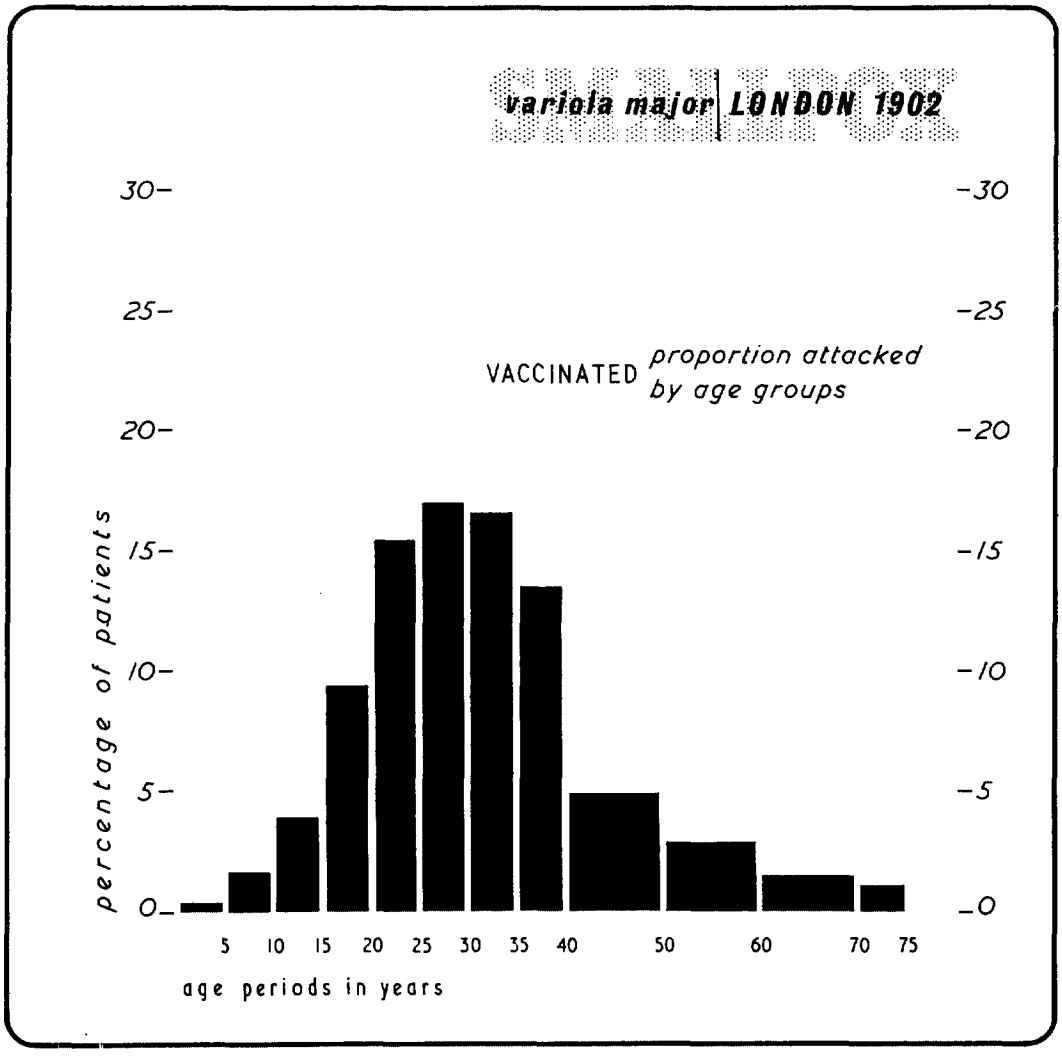


FIG. 244. Based on the histogram of Chalke (1929–30) and figures of Chalke (1958)

1893, shows a marked diminution of the attack rate under five, and from five to ten, and the peak is from fifteen to twenty, with a further decline in a similar manner to that in the unvaccinated. If, however, we examine Fig. 244, with similar proportional age specific attack rates for 1902, after an interval of under ten years, we find there has been alteration in the age-groups most affected, so that now the peak is between twenty-five and thirty, and a large

body of cases occurs between twenty and forty years of age, although the alteration in infant vaccination rates over this period is slight, and can have had no real effect. The peak has advanced about ten years, although the birth of these individuals would appear to be round the crucial years 1871–2, when smallpox was extremely prevalent. However, if we examine

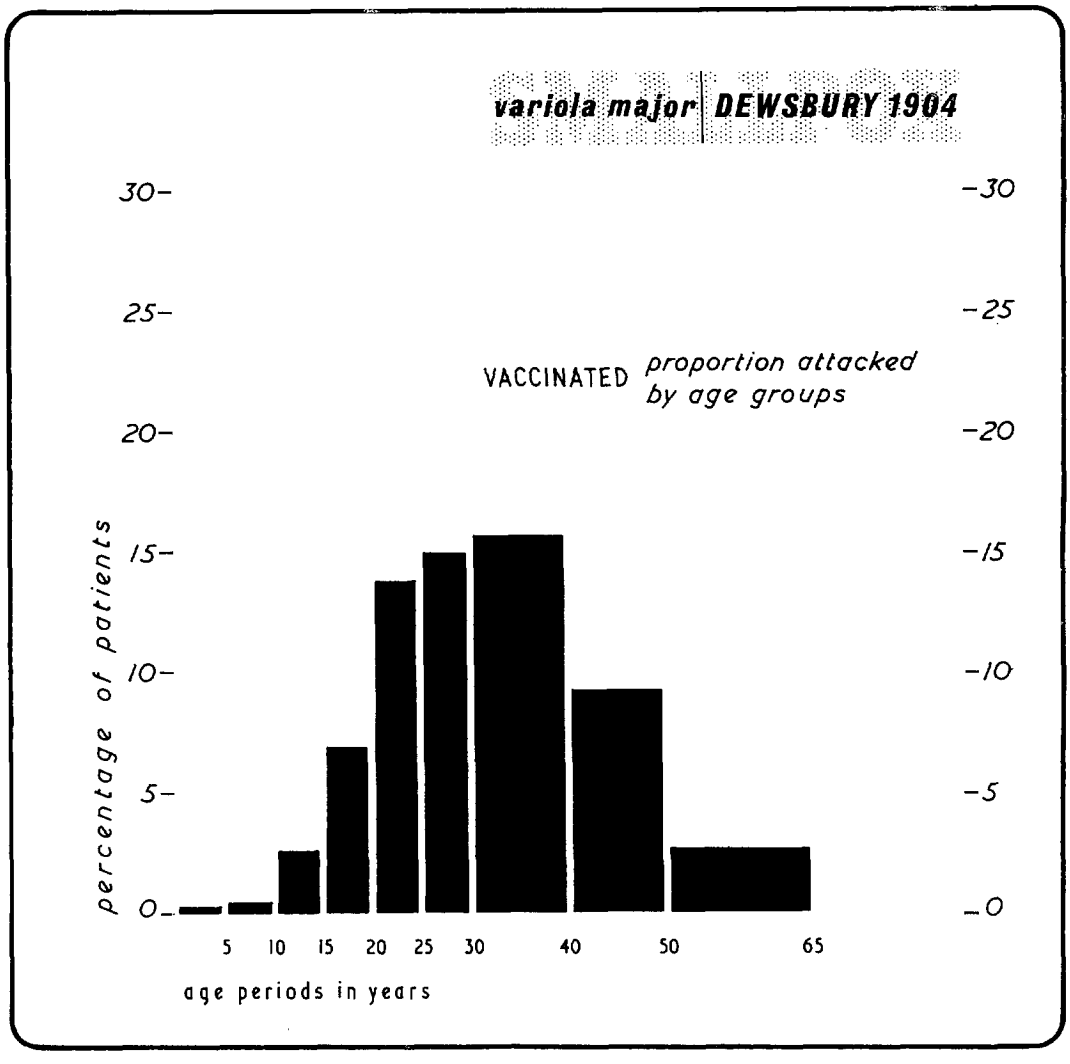
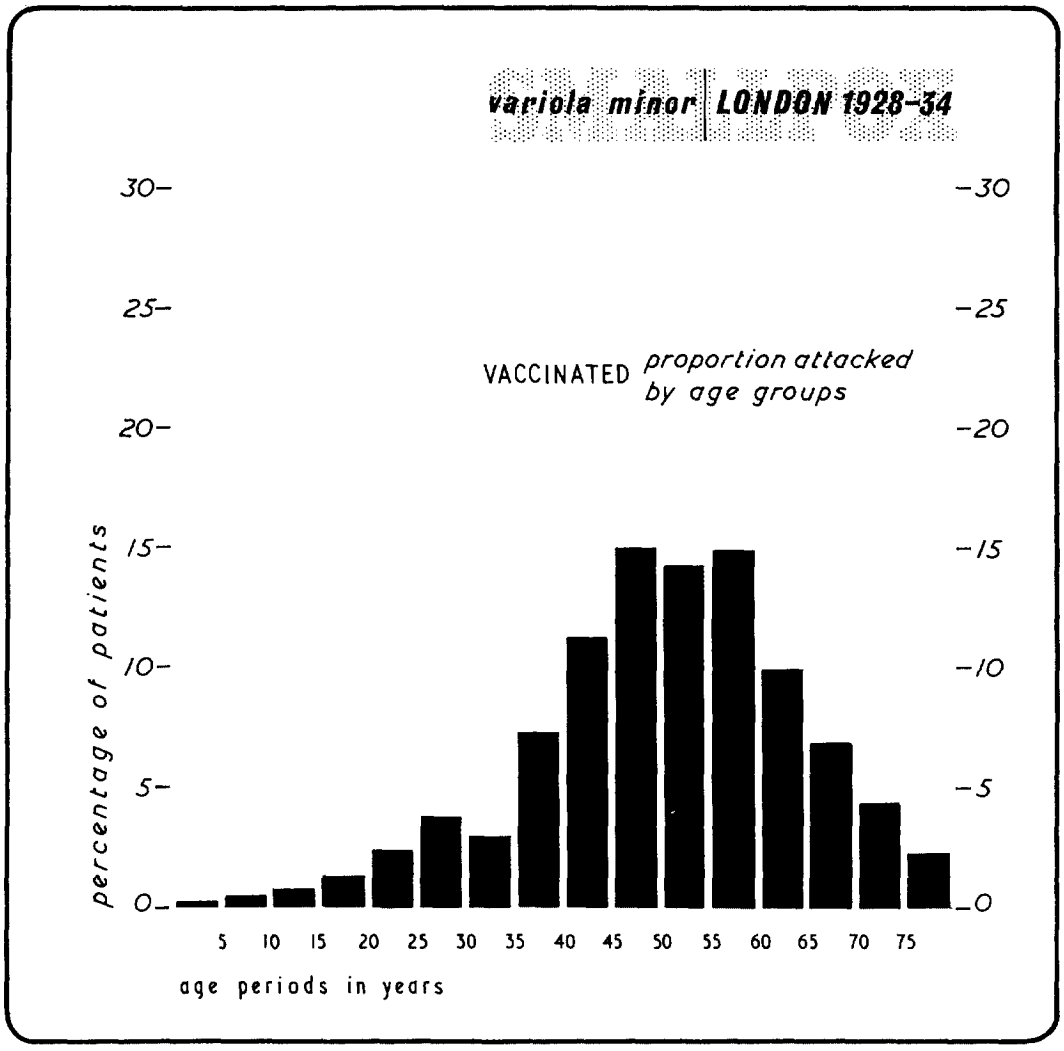


FIG. 245. Based on figures from Spencer Low (1905)

Fig. 245, it can be seen that in Dewsbury in 1904, two years later, the pattern of infection in the vaccinated was again different, with a maximum between thirty and forty, and a much larger proportion of patients in the age-group 40–50. This is probably due to sociological or occupational factors.

Figure 246 shows variola minor in the vaccinated in London between 1928 and 1934, with

proportional age specific attack rates. This gives a truer picture of the incidence in the older age-groups and also shows the age-groups 30–35 and 50–55, where the incidence is unexpectedly low. The age-group 30–35 would have been born somewhere between 1893 and 1904, and therefore could have received a smallpox boost from the tail-end of the outbreak in



Based on the histogram of Marsden (1936)

FIG. 246.

1893–4, or more likely from the outbreak in 1901–2. In the case of the 50–55 group, their dates of birth would be between 1873 and 1884, with a mean of about 1878. The stimulus here could have come from the peak in London in 1881, and possibly that of 1884–5. It looks as if those infants who are born and given infant vaccination some three to four years before a large-scale outbreak may receive some variolous stimulation which gives them an enhanced

immunity for the rest of their lives. If this is the explanation, it would seem that if the contact occurs very soon after infant vaccination or more than five years after, this effect is not observed.

The whole series of diagrams does I think show that the age pattern of infection in smallpox, both major and minor, in the unvaccinated and the successfully vaccinated, can produce many surprises, and we can only hazard a guess at their real meaning. A large series of variola minor in the vaccinated seems capable of detecting minor immunity changes in the herd that cannot be detected in any other way, and not seen in outbreaks of variola major, which appear only sensitive to gross changes in the herd immunity level. This is also borne out by the fact that in the 1902 outbreak of variola major, of 7,916 patients, 73 per cent were vaccinated at some time in the past, whereas in the 1924–34 outbreak of variola minor in a population containing a larger proportion of older people, of 13,686 patients only 13 per cent had been vaccinated at some time.

Although the histograms in Figs. 234, 243, 244 and 246 are based on age specific attack rates which compensates for some differences in the number at risk in each age group whereas the remaining diagrams are drawn from the crude proportion of deaths by age group, differences due to the method of presentation are very slight and do not affect the wide differences in the epidemic pattern. The more accurate method does show more correctly the proportion in the older age groups and enhances the features of Fig. 246.

ALTERATION OF SEVERITY

Many attempts have been made to prove the advantage of previous vaccination in altering the severity of attack. When vaccination has been performed within ten years, fulminating or malignant cases are extremely rare. The vast majority will be discrete or mild types 6 or 7. When vaccination is done within twenty years, a large proportion of the cases will be discrete but some malignant ones will occur, and occasionally fulminating cases are recorded. These appear to be due to personal idiosyncrasy in accelerated waning of immunity. Even in those cases with discrete attacks, there is usually evidence of vaccino-modification; the lesions are more superficial and the tendency to scarring, particularly on the face, will be much reduced. When it is more than twenty years since successful vaccination, an increasing proportion of fulminating, malignant and benign confluent cases occur without modification and as well as discrete attacks with vaccino-modification. Some discrete and mild attacks occur and their mildness credited to distant vaccination when there is no clinical evidence that this is so. At longer intervals than this, one may see discrete and mild attacks of smallpox even seventy years after primary vaccination, in which the rash suggests some vaccinial effect, but it must be remembered that most of these cases occur in individuals who not only had primary vaccination seventy years before, but who have passed at intervals in life through smallpox outbreaks. Their immunity may have been boosted from this source. I think it should be emphasized that most clinicians credit any mildness of a smallpox attack in a person as due to the effects of past vaccination, no matter how remote, oblivious of the large number of severe and fatal cases which can occur in a person who has been successfully vaccinated many years previously, and the natural occurrence of a fair proportion of milder cases in the unvaccinated. Assessment of severity, however, is full of bias, as the accounts of many outbreaks show. There has been a tendency in the past when confluent cases have occurred to get a surprising number of cases where the vaccinial state has been "unrecorded" and "unobserved", and undoubtedly the vaccinial scars may be so covered by rash as not to be seen. I think a considerable number of

fulminating and malignant cases in adults have been credited to the unvaccinated or doubtful vaccinated, when they probably have been successfully vaccinated in infancy. In children, claims to having been vaccinated, although no scar can be seen, are made by frightened parents, particularly when vaccination is compulsory and has been evaded.

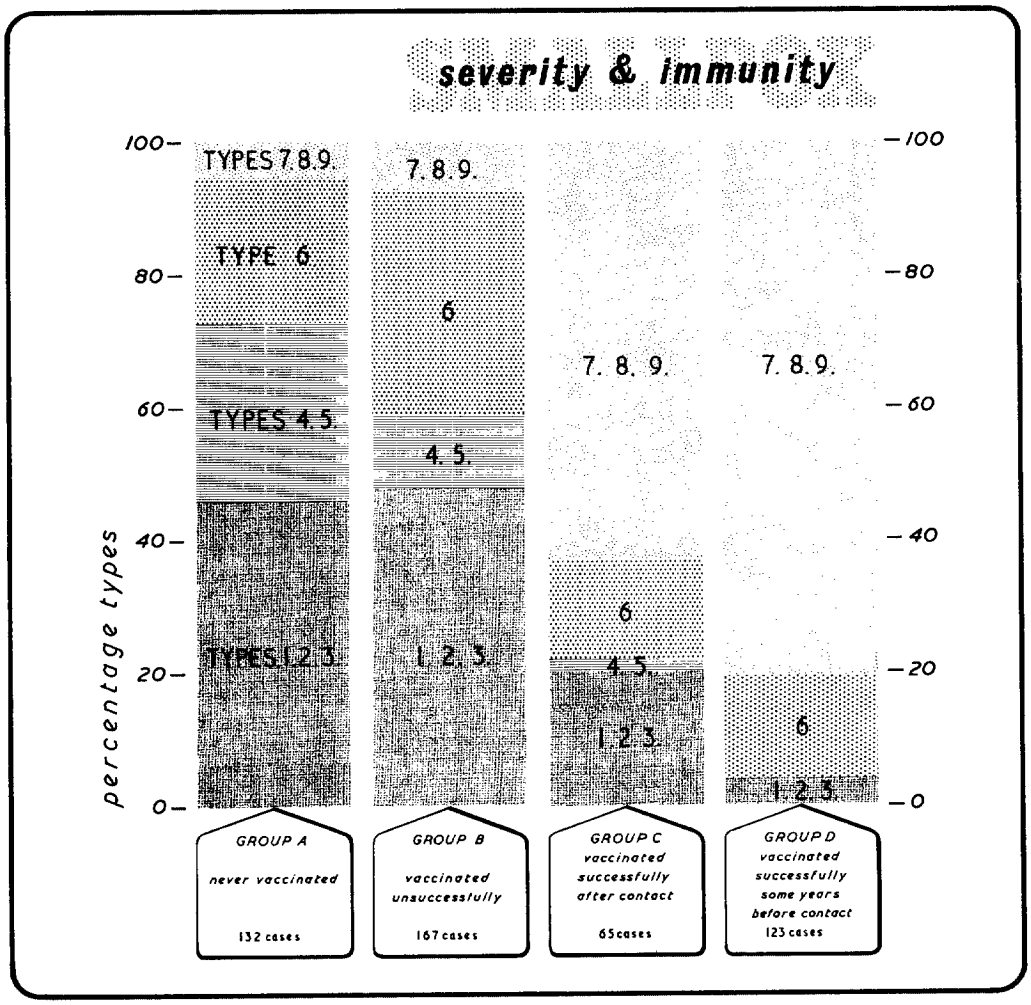


FIG. 247. Types of smallpox occurring per 100 cases in four immunologically different groups.

Figure 247 shows the variation in severity of variola major in Tripoli (1946). It shows that not only is the pattern of severity quite different in the vaccinated compared with the unvaccinated, but that there is a significant difference in the pattern of severity between the unvaccinated and those who were vaccinated previously, but whose vaccinations had failed to take. There were more malignant and discrete and less benign confluent and semi-confluent, suggesting that, as a group, some difference in susceptibility to smallpox is correlated with difficulty in growing vaccinia virus in the skin. This phenomenon may be a factor in the

apparent variation in clinical type, depending on the number and type of vaccinial scars (see p. 290).

The last column (Fig. 247) shows the severity spectrum in those previously successfully vaccinated. This would be different in a European population, due to a different age structure.

Vaccino-modification occurs readily in variola minor, but due to the naturally abortive character of the lesions, in many instances it is not possible to determine whether a successful vaccination many years previously has had any effect or not.

PREVENTION OF DEATHS

We are on very much firmer ground in assessing the effects of previous vaccination on the prevention of deaths from smallpox, as errors involved in clinical interpretation are so much less. In the Sheffield survey in 1887, the mortality amongst the vaccinated under five years was 0·05 per cent, whereas in the unvaccinated it was 42·9 per cent. In those aged 5–10, it was 2·1 per cent against 31·2 per cent; and in those aged 10–15, 4·4 per cent against 34·4 per cent.

It has been customary in many outbreaks to show the mortality under ten years of age, when the effects of infant vaccination are very considerable, and the mortality of those over ten years of age. Figure 248 shows this for a number of towns in England at the end of the nineteenth century, and England and Wales from 1927 to 1958. There is some variation in mortality in different areas, but this is probably partly due to variation in age of attack, which has already been shown to occur.

Mortality and vaccination state. Variola major: percentage mortality

Late nineteenth century

	Under 10 years		Over 10 years	
	Vaccinated in infancy	Unvaccinated	Vaccinated in infancy	Unvaccinated
Sheffield	7·9	67·6	28·3	53·6
Warrington	4·4	54·5	29·9	57·6
Derby	10·2	50·8	27·7	53·4
Leicester	2·5	35·3	22·6	50·0
Gloucester	8·8	46·3	32·2	50·0

1927–1958

	Under 20 years		Over 20 years	
	Vaccinated in infancy	Unvaccinated	Vaccinated in infancy	Unvaccinated
England and Wales	0	33	20	54

FIG. 248.

As already mentioned, owing to the existence of compulsory vaccination laws, I suspect that deaths in the vaccinated under ten years of age include some where there is a history of vaccination obtained from a statement from the parents, who because of feelings of guilt are very likely to say that the child has been vaccinated when it has not. At the end of the nineteenth century there also appears to have been a fair amount of poor vaccination, particularly by private practitioners, who had to rely on very uncertain and unsatisfactory supplies of

lymph. In the case of individuals over ten years of age, I think that in some instances cases were recorded as unvaccinated, when the history was not available, and because of the rash the vaccination scar could not be found. In most outbreaks a considerable number of cases are recorded as doubtful or not known. Even in London, between 1881 and 1900, at the height of the vaccination controversy, in over one-third of the deaths the vaccination state was not given.

The figures for England for variola major only between 1927 and 1958 to some extent bear this out. There were no deaths in the unvaccinated of nineteen years and under, although the numbers are admittedly rather small. Over the age of twenty, there is still an advantage to the vaccinated over the unvaccinated of about $2\frac{1}{2}$ to 1, and although the death-rates are high, this is partly due to the fact that a large proportion of the cases in these years occurred in the elderly.

Figures from some countries, particularly in the tropics, are not so satisfactory as this. An appreciable number of deaths occurred in Bombay in children under ten years of age who had been vaccinated (Thanawala, 1956), and the advantage of the vaccinated to the unvaccinated was only in the region of 2 to 1. It is often stated that the duration of immunity is shorter in tropical countries, and if this is true there is obviously room for a great deal of research to find out the reason why. It has I think in the past been too readily assumed that the failures are due to poor lymph, deteriorated as a result of climatic conditions, but in these days, with refrigeration, this cannot possibly be so in city populations.

There can be no question that a group of individuals who have been vaccinated successfully at any time in their lives will as a group experience a lower mortality from smallpox than those who have never been vaccinated, but it must be pointed out that to suggest that any individual who has been successfully vaccinated will automatically have *some* protection for the rest of his life is not borne out by the evidence.

In Pickford Marsden's (1936) series of 1,731 cases of variola minor occurring in those who had been vaccinated at some time previously, there were no deaths.

EFFECTS OF REVACCINATION

The effects of revaccination on liability to attack, alteration of severity or prevention of death can only be considered in relation to successful revaccination. The difficulties in deciding this are discussed in Chapter 10. Many successful revaccinations will leave no certain scar, and relying on the history alone will include unsuccessful revaccination. Marson (1866) felt that the immunity following revaccination was not as great as that following primary vaccination. I think this may well be so, as bearing in mind the smaller numbers of those at risk, cases and deaths occur in persons who have been revaccinated, some of whom have unequivocal evidence of scar. Statistical evidence from the nineteenth century is of little value, owing to the boosting effect of contact with variola virus in a predominantly older group. The mild attacks occurring in much-vaccinated troops and in foreign travellers in endemic areas do not lend any support to the view, still put forward today in some quarters, that it is usual for a person who has once been revaccinated to possess lifelong immunity. I would like to stress the wisdom of having the international certificate of vaccination valid for only three years.

EFFECTS OF A PREVIOUS ATTACK OF VARIOLA MAJOR

In general I think the immunity effect of an attack of variola major is about ten times that of primary vaccination. It would seem, therefore, that in most people this will give lifelong

immunity. There are, however, the exceptions, who lose their immunity more quickly, and therefore become susceptible to attack again. No satisfactory figures are available of liability to a second attack. The Sheffield figures suggest about 1 in 1,000, but what this would be in any other community is impossible to say.

When clinical infections do occur, they appear to be at both extremes of severity, the second attack being malignant and frequently fatal, or exceedingly mild and abortive, which I think suggests that two different immunity or susceptibility factors are operating in these two groups. The overall case mortality of second attacks is about 25 per cent, but this would be affected very considerably by the diagnosis of more of the very mild cases, which I think are misdiagnosed because of the patient's history.

Variola minor is most unlikely to occur after an attack of variola major.

EFFECTS OF A PREVIOUS ATTACK OF VARIOLA MINOR

I have no information, but would suspect that a previous attack of variola minor confers little more immunity than a primary vaccination against an attack of variola major. It probably protects against a second attack of variola minor to the same degree as variola major does to itself.

SUCCESSFUL VACCINATION IN THE INCUBATION PERIOD

Successful vaccination in the incubation period as a method of prevention of attack can only be assessed by taking two groups, both exposed under similar conditions, where one is vaccinated and the other is not. As it is obviously essential to vaccinate contacts immediately they become known, such an experiment is unlikely to be performed. The tendency in the past has been to always assume that any person who was successfully vaccinated in the incubation period and who did not contract smallpox must thereby automatically have been protected by the vaccination. There are many instances on record where persons have not been vaccinated and have escaped, although apparently in contact with infection, and those who have been vaccinated on the tenth or eleventh day of the presumptive incubation period, when in most cases we would expect no effect, have also had no attack. I think it is illogical to assume that the factor preventing infection would develop before the factor in immunity modifying the rash. Ricketts' (1908) dictum, and that of many of his contemporaries, was that in the main it would be accurate to say that successful vaccination done in the first seven days of a smallpox incubation period would wholly prevent the attack, but he added the warning that a patient might be vaccinated successfully as early as the fourteenth or even the fifteenth day before the rash and yet not escape the disease. Others have stated that the vaccination performed within the first three days would almost certainly prevent an attack, from the fourth to the sixth or seventh day would modify it, and after that would only add to the patient's miseries. It was even suggested by some health officers that once a successful vaccination was seen to take in a contact, there was no need to subject him to any form of quarantine, so satisfied were they that the successful vaccination would prevent the development of smallpox.

The exceptions were glossed over by most public health officers until the 1920's, when more caution was exercised, but as late as 1927 Leake stated: "Successful vaccination performed on the day of exposure will almost always give complete protection." In 1947 Bradley pointed out that there was no justification in assuming that protection would be obtained if vaccination was done within the first three days, but thought that Leake's statement was substantially true.

Further experience has shown that Leake's statement is misleading. In the Bilston outbreak in 1947 one person died from fulminating smallpox, having been successfully vaccinated twelve days before the onset of the disease, and a number of other cases had mild attacks, even when vaccinated thirteen days before the onset. In the outbreak in Yorkshire in 1953, four individuals contracted smallpox who were successfully vaccinated within a few hours of exposure.

In spite of this, we still continue to get statements in the textbooks that vaccination on the day of contact can be confidently expected to prevent attack.

Even allowing for some Victorian over-confidence, I do not think there can be any question that, fifty years ago, successful vaccination done during the early part of the presumptive incubation period would in the vast majority of cases prevent an attack, whereas today practically every report of an outbreak of variola major contains the statement by those with practical experience of the disease, that very early vaccination of some of the contacts did not give the protection expected from it.

Delay in diagnosis, particularly of the earliest cases, may often occur today, but there is no evidence that this did not happen fifty years ago, and in some of the recent instances the period of contact was known, was short and vaccination was carried out within a few hours. One possible cause of this change is the adoption of minor trauma techniques, instead of the old four or five large insertions. The other is that the present-day purification of lymph has excluded contaminants frequently present fifty years ago, or vaccinia virus has lost something of its antigenic properties. Both might have some effect, but statistical evaluation of the situation is impossible, as attack rates in comparable contacts are not available. The return to a more horrific technique for contacts, with three or four insertions, is in my opinion justified by recent experience, and might show where the fault lies. The preparation of a special vaccine for contacts containing hyaluronidase might be worth trying.

Alteration of severity of an attack of smallpox following successful vaccination in the incubation period is very much more difficult to measure, as the clinician is so likely to be biased in taking a mild attack as certain evidence of the effect of successful vaccination, and ignoring the fact that there may be no effect. It can, however, be stated that in general the earlier the vaccination is done in the incubation period the more likely is there to be some modification, and I think it will be generally agreed that successful vaccination within the first three days of the incubation period does tend to result in discrete, vaccino-modified attacks, with evidence of lesions more superficial as well as reduced number, and a definite reduction in facial scarring. As already mentioned, fatal cases may occur, even when multiple-insertion vaccination is done twelve days from the onset.

Variation in the response is common, even when vaccination of two or three contacts is done at the same time. In the outbreak in Yorkshire in 1953, two children, aged fifteen and seventeen, were vaccinated relatively late, on the seventh day of the presumed incubation period, both having had, as far as one could see, more or less the same degree of contact with the source case. One had a discrete attack with very slight evidence of any vaccino-modification and suffered considerable residual scarring, whereas the other had a mild attack, with much clinical evidence of vaccino-modification and no scarring. It is this chance factor which makes the effect very difficult to assess, but I think it is probably fair to say that at least 50 per cent of cases where successful vaccination has occurred in the first week will get some vaccino-modification and reduction of severity, whereas when done at a later period the number showing such modification is not likely to be over 20 per cent. Occasionally persons vaccinated quite

late show evidence of vaccino-modification in the eruption, particularly when the attack is otherwise mild.

The effect of vaccination in the incubation period on preventing death from smallpox can be assessed more accurately, and, to investigate the possibility that changing vaccination technique or materials has altered the development of immunity, I have surveyed the records of fatal cases of smallpox vaccinated in the incubation period, for Dewsbury, 1904 (Low, 1905), England and Wales, 1912–18 (Grant Nicol, 1959), Tripoli, 1946, and England and Wales, 1934–58 (Grant Nicol, 1959). In Dewsbury, 1904, and England and Wales, 1912–18, vaccination by multiple insertions was the rule, whereas, in Tripoli in 1946 and England and Wales, 1934–58, single insertions were much more common.

As the ages of those exposed to attack is likely to be different and social conditions vary in the four outbreaks, the death-rate in those vaccinated after contact has been expressed as a ratio of the deaths in the unvaccinated in each outbreak. Although persons may have been vaccinated at any time in the incubation period, it would seem that if anything those in the two later groups would be more likely to have been vaccinated earlier than in the Dewsbury, 1904, or England and Wales, 1912–18, groups. There is no significant difference in the ratio between the outbreak in Dewsbury in 1904 and England and Wales, 1912–18, or between Tripoli, 1946, and England and Wales, 1934–58. Taking these two pairs of groups, there is a statistically significant difference between the ratios. Where the vaccinations were done before 1920, the mortality of those vaccinated in the incubation period was slightly less than a quarter of the mortality of unvaccinated persons in the same outbreaks, whereas in the period after 1920 it would appear to be just less than one-half.

These figures would appear to substantiate the view of many clinicians that the protective effect of vaccination in the incubation period is less in preventing death today than it was fifty years ago, and is in conformity with the experience of being apparently less able to prevent attack, even when done on the day of contact.

In variola minor, the problem appears to be simpler. Both in the outbreak in Gloucester in 1923 and that in Rochdale in 1951–2, no cases of variola minor appeared to occur where vaccination had been done more than eight to nine days before the onset. In Marsden's (1936) series of variola minor between 1928 and 1934, out of the 1,083 cases following successful vaccination in the incubation period, only 5 would appear to have been done on the day of contact, 17 on the second day, and 89 on the third. This slightly exaggerates the risk as the interval was counted to the appearance of the focal rash which might well have been later than the third day after onset of illness. It would seem therefore in variola minor that the chance of preventing attack within the first three days is very considerable. The effects on modification of severity will be difficult to determine as the normal attack may in itself be so mild.

VACCINATION IN INFANCY AND REVACCINATION IN THE INCUBATION PERIOD

The next group to be considered are those who have been successfully vaccinated in infancy and revaccinated in the incubation period. This is an important group as it figures in the arguments in favour of infant vaccination.

A person successfully vaccinated in infancy will possess protection against infection, mitigation of severity and against death, depending largely on the interval of time since it was done, and personal factors of idiosyncrasy, which may reduce or increase these from the

norm. To this is added the effect of revaccination, instead of primary vaccination, in the incubation period. It is normally assumed that if a person is revaccinated, the vaccinial response will occur more quickly than in a primary vaccination, and therefore a person revaccinated in the incubation period should be much safer than a person who only has a primary vaccination then. Recent experience shows that when revaccination is done twenty or thirty years after the primary vaccination, its rate of development may be little, if any, different from that of primary vaccination. A second factor which complicates the practice is that failure to revaccinate such a contact successfully appears to be much commoner than failure to primary vaccinate a contact. Certainly the anxiety that occurs amongst contact medical officers and others, who have found their first revaccination fail, is a very common spectacle.

It is therefore necessary to appreciate that we have two factors operating together in assessing the value of revaccination to this group: (i) the acceleration that may occur if the revaccination is successful, and (ii) the reduced chance of getting a successful revaccination, due to a relatively insusceptible skin. The overall advantages to the group therefore may not be as great as appears at first sight. I have made a survey of variola major between 1946 and 1958 in England and Wales of those cases who were primarily vaccinated in infancy and successfully revaccinated in the incubation period, and those who were successfully vaccinated in infancy only, and those vaccinated in the incubation period only, and compared these with the unvaccinated of the same period. Unfortunately we are not able to measure the effects of prevention of attack or of alteration in severity, but only the crude effects of death or survival, although it would be very much better if one could take attacks, carefully recorded as to the severity, preferably on the classification that I have advocated. In Fig. 249 it can be seen that those primarily vaccinated in infancy and successfully revaccinated in the incubation period show no statistically significant advantage over those who have been vaccinated only in infancy, or over those who have received primary vaccination in the incubation period. The figures taken are for cases over twenty years of age. It is very desirable to extend observations of this kind, as the figures from England and Wales over the last few years have included a large proportion of cases of very advanced years in whom it has always been recognized that vaccination may be slower to develop and possibly not be so effective.

Variola major, England and Wales, 1946–1958. Death-rate over twenty years of age

Unvaccinated	Vaccinated in infancy	Primary vaccination in incubation period	Vaccinated in infancy and revaccinated in incubation period
54·8% (17/31)	20·6% (26/126)	27·7% (10/36)	27·2% (6/22)

Not significantly different on numbers involved, but each significantly different from rate in unvaccinated.

FIG. 249.

Once again, the quality of virus and the technique of vaccination might be called into question. I would stress the need for "horrific" techniques, even in the frail and elderly, if we are going to give them the maximum chance of protection when there is a real risk.

GAMMAGLOBULIN

In the last few years, high titre antivaccinial gammaglobulin has been prepared and used during the presumptive incubation period, to attempt to prevent an attack of smallpox. The method was used by Kempe *et al.* (1956) in India, and two attacks and one death occurred in fifty-six contacts who were vaccinated and given gammaglobulin, compared with eight attacks and three deaths in seventy-five controls, who were only vaccinated. There is no evidence, however, that the vaccinial or smallpox histories of the two groups were investigated, the latter an important point in a hyperendemic area, or that the two groups were even of similar age or sex, so that the effect cannot be judged from these much-quoted figures.

Pierce *et al.* (1958) reported its use in two cases and believed it modified attacks. The severity in both could have been due to natural variation, and not the use of gammaglobulin. In the Tottenham outbreak, Hogben *et al.* (1958) used this "successfully" on child contacts in a cubicle ward, but the degree of risk appears to have been low, and they were concurrently vaccinated by the multiple-insertion technique.

In view of the apparent failure of some incubation period vaccinations even when done early, at any rate in Europe at the present time, further experiments with gammaglobulin are fully justified. I would, however, appeal to those having the opportunity, to judge carefully treated and untreated groups that have been ascertained to be alike in age, sex, vaccination and smallpox experience, and, to those who use it on a few cases, to remember the wide variation of severity which can occur in natural smallpox. It would be tragic if the idea became prevalent that this was an approved method of prevention and *energetic* vaccination neglected. The first duty of anyone who diagnoses smallpox is to vaccinate the contacts vigorously. Then and only then should gammaglobulin be thought of and, in my opinion, given at about the eighth or ninth day of the presumptive incubation period, and not earlier.

INTERNATIONAL CONTROL

Under the International Sanitary Convention, smallpox is one of the five quarantine diseases. The regulations made in each country are based on the International Sanitary Regulations (W.H.O. Regulations, No. 2, which were adopted by the fourth World Health Assembly, and came into force in October 1952). Smallpox control measures rely on vaccination of persons coming from a smallpox area. Some countries, such as the United Kingdom, do not require vaccination certificates, even if the persons are flying direct from a country in which smallpox is endemic, others, such as Panama for example, apparently require vaccination certificates even when persons are coming from countries in which smallpox has not been present for twenty years. Many countries still require vaccination certificates when there is no risk. This is quite a different matter from advising passengers proceeding to various parts of the world to be vaccinated for their own benefit. Large numbers of unnecessary vaccinations are done for passengers on long sea voyages who only land for a few hours in countries where smallpox is absent.

The earlier international certificate of vaccination required the operator to certify the result of both primary vaccination and revaccination. Owing to the difficulty of reading revaccinations and the fact that in some genuinely immune persons the response may be so slight as to be negligible, in the past many documents were falsified simply to avoid putting down a negative response. A far more realistic attitude was adopted by the ninth World Health Assembly, 1956, only primary vaccination must be read and sufficient spaces are

provided on the record card for second attempts if a primary vaccination is at first unsuccessful. Revaccination is not read, a procedure which is scientifically unsatisfactory but administratively realistic. Although the certificates bear an approved stamp, this is only intended to show that the vaccinator is recognized by the health administration as qualified to perform the vaccination and sign the certificate. Any stamp prescribed by the health administration for this purpose is quite sufficient to render the certificate valid. In some ways this is an unfortunate state of affairs compared with yellow fever vaccination, where for quite different reasons a limited number of persons are specifically designated by the health administration as competent to give yellow fever inoculation. In those countries where practitioners have little experience of vaccination and revaccination, it is preferable for them to be done by officials of the health department. Some countries require certificates for persons of all ages, others allow exemption for children under three months of age. If the vaccinator is of the opinion that vaccination is contra-indicated on medical grounds, he should provide the person with written reasons underlying that opinion, which the health authority on arrival *may* take into account. Greater latitude should be shown to travellers from countries where there is no risk. Shipping companies appear over-anxious to get all their passengers vaccinated, possibly to save any administrative difficulties should the disease occur en route. Eventually it might be possible to reduce many of these requirements and to advise vaccination for individuals on assessment of risk. Instead of many thousands of perfunctory, and often unsatisfactory, revaccinations being done, travellers to definite endemic areas would be done well, with three insertions, and read by a competent and interested doctor.

The World Health Organization Epidemiological Bureau's broadcasts by radio of up-to-the minute information on the occurrence of smallpox, particularly on the international sea and air highways, allows sea and airport medical officers to give special attention to travellers who are possible risks.

It is difficult to see why the United Kingdom does not require at least a valid vaccination certificate for those persons who are coming by sea or air from India, Pakistan, Burma, Nigeria and other places which are important reservoirs of smallpox. Macgregor (1942) pointed out that the danger of introduction of ship-borne smallpox into the United Kingdom was very great at that time, and that more should be done to protect those on board, and so minimize the risk to Britain. However, even if valid vaccination certificates were asked for, this would not absolve the medical officers on board ship from the responsibility of making accurate diagnoses. In many instances, however, when the diagnosis is known before the ship arrives in Great Britain the immediate vaccination of contacts on board and the discharge of passengers is the normal procedure. The only protection is the hope that vaccination, even when done relatively late, may prevent an attack of smallpox in the contact, or that the contact, having been given a warning card, will show this to a general practitioner, and the secondary cases of smallpox can then at least be controlled. Information is passed on to the medical officer of health for the area of the address that the contact gives, and his department is put to considerable trouble to keep the contacts under surveillance, should the addresses be accurate, which is not always the case. Marsden (1942) makes the point that further thought should be given to the question of quarantining ships. He points out that events following the *Tuscania* in Glasgow in April 1929, and the *Cathay* in the Port of London in March 1938, suggest that as a ship at sea is a closed community where conditions are almost ideal for containing the outbreak, and at a time when the country is free from smallpox, a strong case can

be made out for enforcing quarantine of the ship, such as is done in a number of other countries in the world. One would strongly support this, and add that perhaps the classic example is the case of the *Mooltan*, where there was late diagnosis and late vaccination, and on arrival at a United Kingdom port the contacts had only some four or five days of the quarantine period left. They were released from the ship on Saturday, and by the Tuesday the first cases of smallpox were occurring in the contacts, who were allowed to freely travel throughout the length and breadth of the country. Fortunately the outbreak was controlled, but an immense amount of public health work was done, which, however, could not be separately costed and charged to smallpox control. On the other hand, if the ship had been maintained in quarantine from the Saturday until the Wednesday or Thursday of the following week, all the cases could have been diagnosed without any risk to the population of England and Wales at all. A frantic outcry is usually made of the great importance of not holding up a ship, of the difficulty of maintaining a ship in quarantine for this period, quite oblivious of the fact that if the ship breaks down at sea it may arrive in port four or five days late; it has ample supplies of food which can always be replenished. The plea that the cost to the shipping company will be enormous if the ship is held up looks rather silly, for when a dock strike occurs, fifty or a hundred ships may be rendered immobile for a fortnight, and the shipping companies don't seem to go bankrupt.

In the case of travellers by air, the majority will enter a country during the incubation period, and therefore no examination of passengers will give us any practical measure of control. Reliance must be made on vaccination certificates to reduce the chances of infected persons entering, and many countries demand vaccination certificates for passengers coming by air and not for those coming by sea. We must, however, rely finally on the general practitioner regarding any person who has a febrile attack within sixteen days of arriving in the country as a possible case and observing it with very great care. In 1951 I suggested that notification of pyrexia "within sixteen days of landing" in travellers from certain specified countries might be a practical way of ensuring that these cases were not missed.

The World Health Organization is encouraging the freeing of international travel from unnecessary inoculation procedures. Its handbook, *Vaccination Certificate Requirements for International Travel*, should be in the hands of every medical officer of health who should make available and, if necessary, explain the requirements to general practitioners.

HERD IMMUNITY

If smallpox spreads uncontrolled in a non-immune community, there will be many clinical attacks, some sub-clinical infections, and a few individuals will appear refractory to infection. The disease will die out and the group appear to be completely immune, but if transferred to another area where smallpox is epidemic, it is probable that some who had passed through the previous outbreak unscathed would be attacked.

If Jenner had been right, and infant vaccination gave lifelong immunity, then we would have no problem today, but duration of immunity to prevent attack is very variable and relatively short. The three-year period of the international certificate only represents about one-twentieth of the average life-span.

Production of a high degree of herd immunity necessitates vaccination and revaccination at short intervals. In armies exposed to high risk, annual revaccination may be advisable. A three-year interval may appear quite sufficient, but administrative rather than immunological

reasons should determine the best interval. The crucial point to consider if the risk is high is the possible effect on immunity of double the proposed spacing between revaccinations. For example, the declining immunity which is sufficient at three years to prevent successful revaccination may not be sufficient at five and a half years to prevent smallpox infection, just before a further revaccination is due. In hospitals, where staff-moves often occur at the end of three years, the danger of vaccination being forgotten makes it better to impose a two-year interval. It is better to err on the side of too frequent revaccination of these important groups, rather than the reverse. In armies, where the personnel are under complete control, revaccination intervals may vary from annual in areas of high endemicity to every five years in areas where the disease is a rarity.

Experience shows, however, that when an army is operating in an area with a high risk of infection, an occasional very modified case may occur, Edwardes (1887), who examined the work of the German commission of 1884, observed that however carefully a group were vaccinated and revaccinated, some cases and even some deaths from smallpox did occur, especially if the group was brought into contact with a population in which smallpox was very prevalent. I think it should therefore be made quite clear that, although in practice we can produce groups who are practically completely immune, it is impossible to guarantee that a very large body of men, such as an army or a country, can really be completely immune. Cases of smallpox probably occur more frequently than appear in the records, due to difficulties of diagnosis, and the absence of spread would allow it to pass unnoticed. From the practical point of view smallpox in such a group of men is, to them, less of a nuisance than the common cold. Cases that are discovered can be treated within the group with a minimum of inconvenience, although enough infection may be present in the body or clothing of such persons to constitute a threat to a civilian population. The outbreak of smallpox in Italy at the close of the war was probably due to smallpox introduced and spread in this way; a large proportion of the patients were women.

To obtain a relatively immune herd in a civilian population requires a procedure akin to that practised in armies, but it has to be modified to something more practicable. Vaccination could be done in infancy, on entry to school about the fifth or sixth year, at age 12, 21, and from then on at about ten-year intervals at, say, 30, 40, 50, 65, possibly coinciding with the retiring age. This would give six or seven revaccinations spread throughout life. If importation of smallpox into the area were relatively infrequent, then one would have to be very unlucky to get any fatal cases with this scheme, and even diagnosable ones would be very few. On the other hand, if infection was frequently introduced, those individuals whose immunity wanes more rapidly than most would eventually be found out and severe cases and deaths would occur, although the chance of any real spread would be very slight. One cannot imagine many populations in the world who would knowingly subject themselves to the inconvenience and undoubted risks of vaccinial complications multiplied six or seven times. Taking England and Wales as an example, revaccination on a ten-year basis would require between four and five million per year (Griffith, 1959). Put on a life risk basis, primary vaccination in infancy and revaccination five or six times gives a risk of death of about thirty per million. Even if revaccination at these fairly short intervals would reduce the complications of revaccination, the risk would still appear to be in the region of twenty per million, without taking into account the residual effects of non-fatal encephalitis. Duncan Forbes (1938), criticizing an article by Butterworth, stated: "Even if Dr. Butterworth could have universal vaccination

repeated in every member of the population at suitable intervals, would he think it worthwhile, seeing that at least variola major is easily controlled by the administrative methods described, combined with vaccination of staff and contacts. If we were also given power to

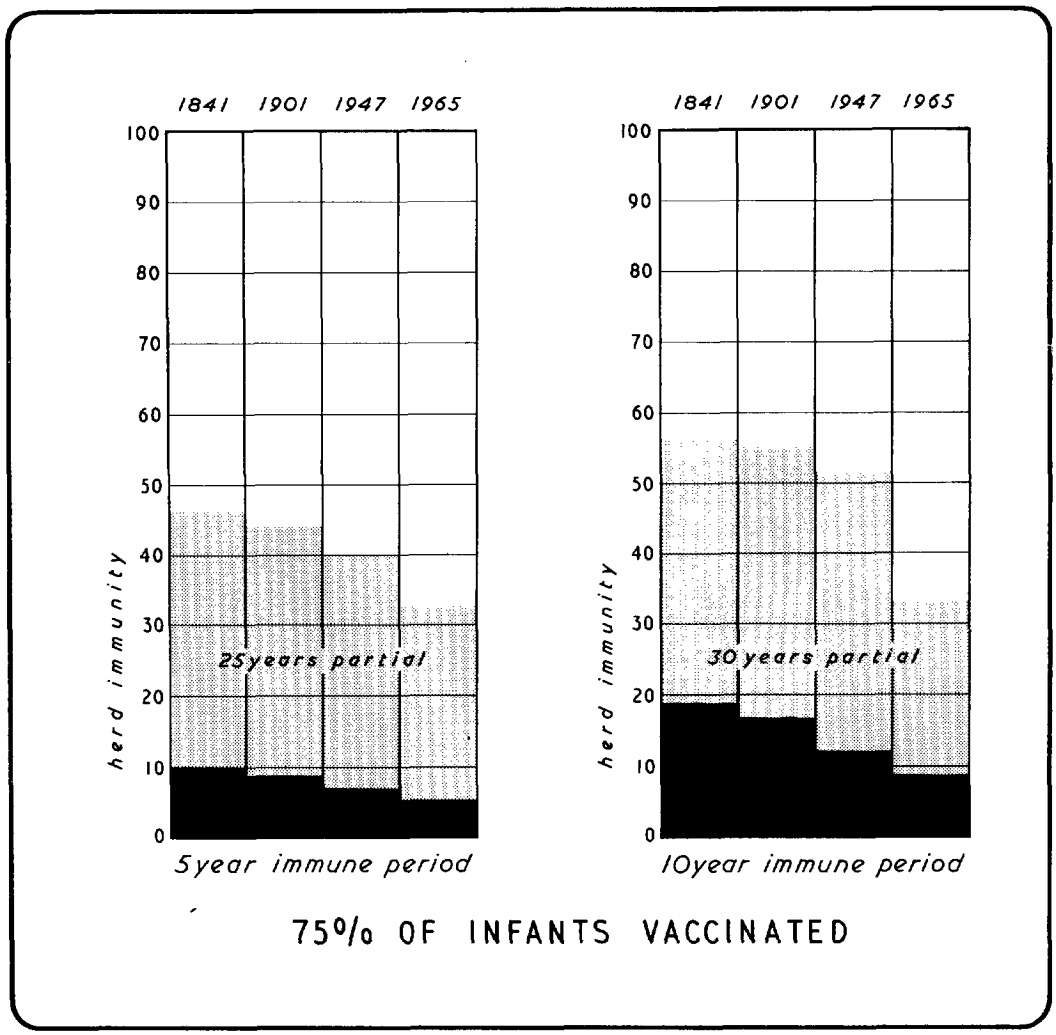


FIG. 250. Herd immunity and infant vaccination.

control the movement of tramp contacts, to keep in better touch with immigrants from infected ships, our means of stopping the spread of disease would be complete." After twenty years, this statement is even truer.

As already discussed, in the early days of vaccination smallpox was predominantly a disease of children under ten, and often limited to children under five, adults being immune as a result of clinical or sub-clinical attack. Nothing appeared simpler than to vaccinate infants, and so

produce an immune herd. However, once the infants were rendered immune by vaccination, the variolous stimulus to the adults was removed and their immunity started to wane.

It has often been assumed, therefore, that infant vaccination produces a large degree of herd immunity, but an important point in considering this is not only the duration of immunity, but the proportion of infants and younger children to the older age-groups.

In the diagrams in Fig. 250, the effects of infant vaccination on the herd immunity of the population of England and Wales are given for 1841, 1901 and 1947, and for the predicted population for 1965. These are taken from a paper published in 1951(*a*).

The number of infants vaccinated is taken as 75 per cent of the births, which is a good average for the period, and not far short of the maximum acceptance rate ever achieved in England and Wales. If the duration of absolute immunity, protection against attack, is taken as five years, and partial immunity, protection against death from smallpox, a further twenty-five years, the percentage of immunes and partial immunes in the herd due to infant vaccination is as shown in the figure. If it is thought that this does not credit vaccination with as much protection as it possibly may have had, the second diagram shows the herd immunity, assuming that infant vaccination gave absolute protection for ten years, and partial immunity for a further thirty years, a state of affairs which applies to variola minor rather than variola major. It is apparent that the immune state of the herd in 1841, due to infant vaccination alone, would not be very high, but to this we may add the immunity produced by some adult vaccination done in the 1820's, and the probability that at least 6–10 per cent of the population had had smallpox. Even with this addition to the immunity, large outbreaks of smallpox occurred: 16,000 deaths in 1838, and 10,000 in 1840.

Due to the much larger proportion of older people in the population, we can see that in 1947, and even more so by 1965, the proportion of immunes produced by just the same proportion of infants vaccinated would be only just over half that of 1841. Even if 100 per cent of the infants were vaccinated, the herd immunity in England and Wales in the immediate future would not be 10 per cent. Figure 251 shows the herd immunity due to infant vaccination in 1947 and 1965, based on 40 per cent in the former year, and 20 per cent in the latter, when it can be seen that the level is surprisingly low.

Although the average rate in England and Wales is now about 40 per cent, there is very great variation in different areas, from 2 per cent in some to over 75 per cent in others. The location of outbreaks of variola major over the last fifty years has not been related to the proportion of infants vaccinated in different areas, which is understandable when the small effect of this on herd immunity is appreciated. "The distribution of variola minor in England and Wales has certainly not been determined by the local acceptance of infantile vaccination" (Ministry of Health, 1931*a*), where prevention of attack certainly lasts longer.

It is sometimes claimed that vaccination done in the Services must have a large effect on the population, but Fig. 251 shows the effect on herd immunity of the vaccination of National Service entrants, when military service was compulsory in the United Kingdom. Figure 252 gives an estimate of the total herd immunity due to infant vaccination, vaccination in the Services during the war, 1939–45, and vaccination done during the variola minor outbreak in 1920–34, the latter possibly too high, from which it can be seen that in 1947 the total complete immunity in the population was just under 20 per cent, but by 1965, when much of this will have been lost, the total immunity, assuming 20 per cent of infants are vaccinated, would be under 5 per cent.

These estimates of herd immunity due to infant vaccination alone were commented upon in the annual report of the Chief Medical Officer of the Ministry of Health for 1950. "Although at first there may appear to be much to support this view, the decision to abandon altogether a valuable prophylactic measure, even one that is admittedly increasingly neglected, ought

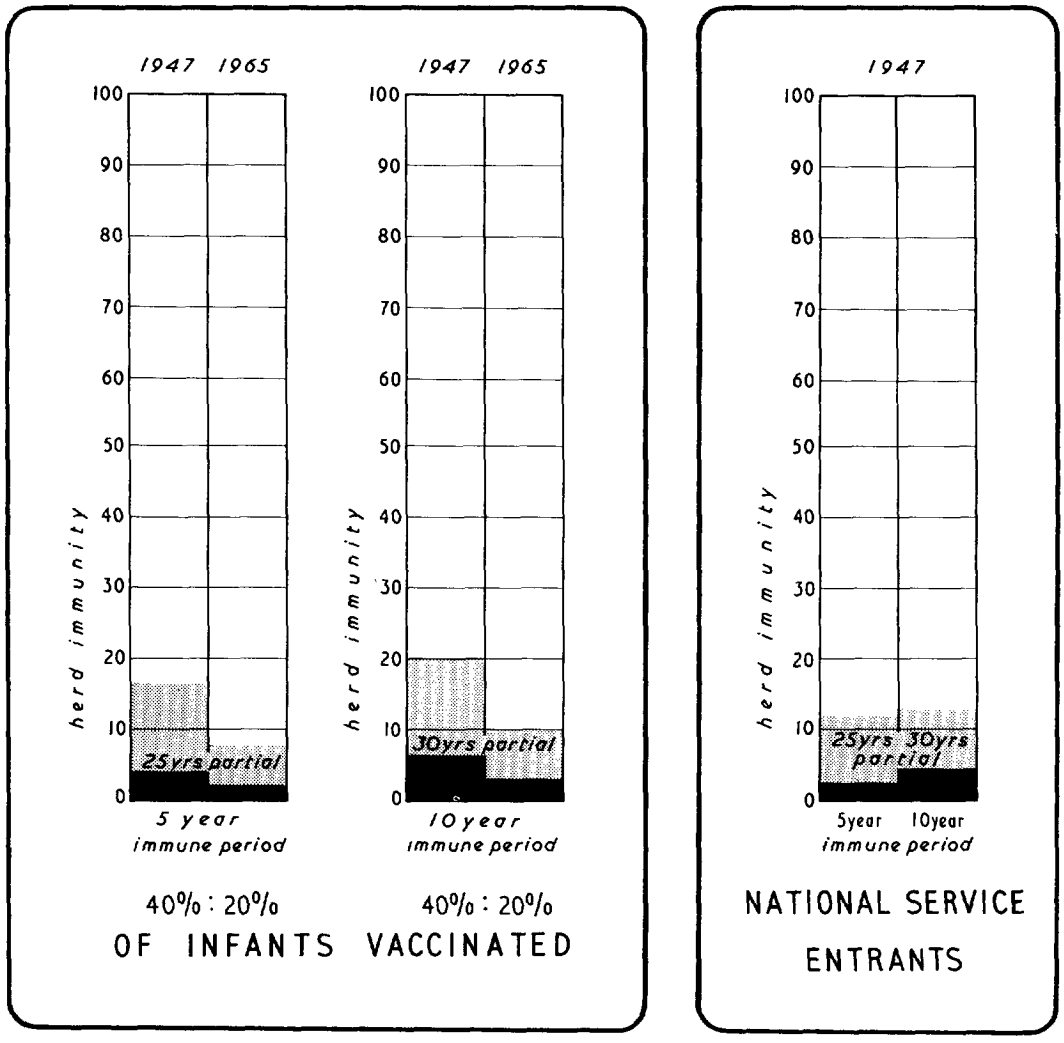


FIG. 251. Herd immunity; vaccination rates and effect of National Service.

not to be taken lightly or in haste. It is moreover doubtful whether even with a disease like smallpox, which has immense potentialities for the destruction of the individual and the disruption of the community, any prophylactic measure, how little it may contribute for the time being to the prevention of local outbreaks, ought to be entirely discarded."

I would certainly agree with the need for great care and thought, and with the principle that every little help in preventing smallpox is worth having, but this little help must be

balanced against the administrative or personal inconveniences and the risks of vaccinating all infants, to which might be added the increased liability to missed cases.

There is often, however, confusion in assessing the benefits to the individual and those to the community. Undoubtedly we have no right to prevent an individual obtaining even

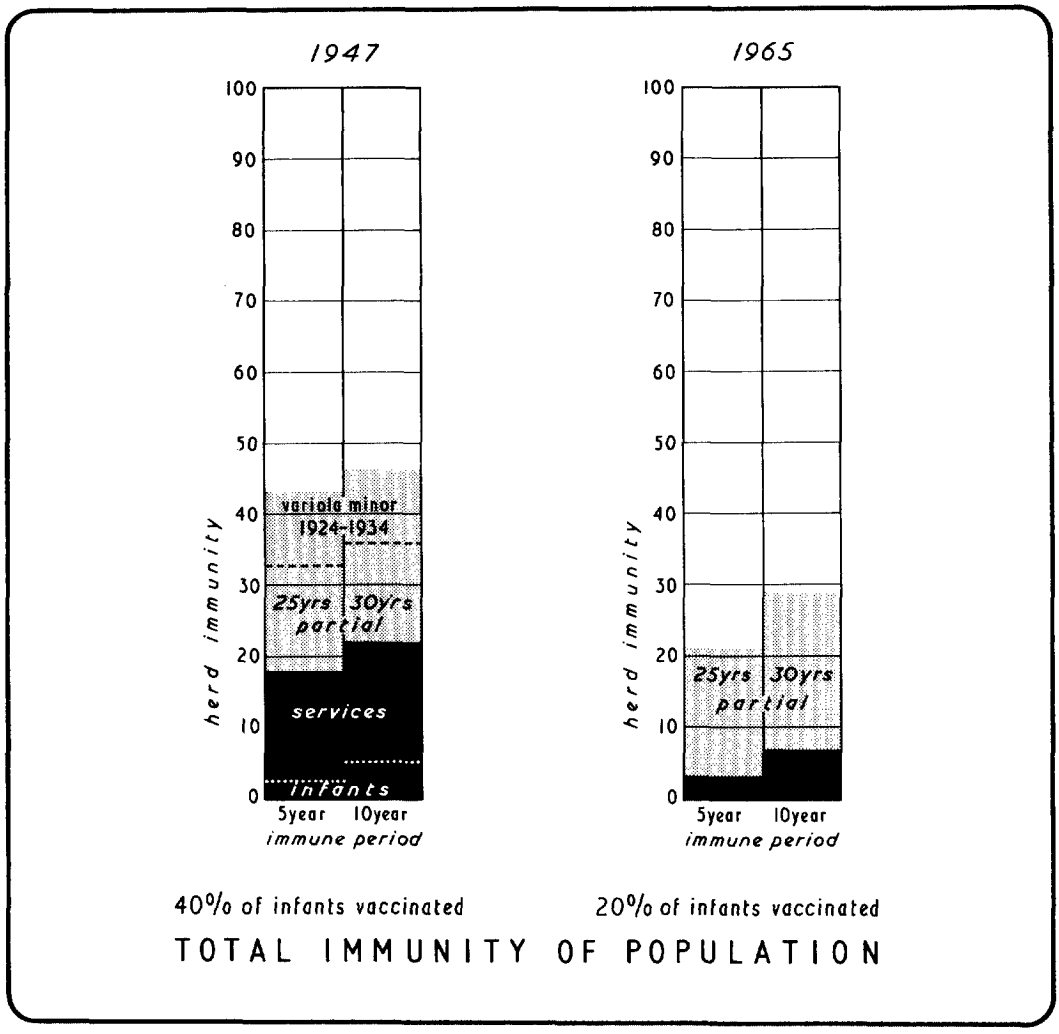


FIG. 252

some temporary protection against attack, and more lasting benefit against severe attack or death, should he desire it, but to some extent infant vaccination alone is antisocial, giving rise to missed cases which increase the risk of smallpox to others. Those who advocate infant vaccination should ensure that they can persuade these individuals to be revaccinated at intervals throughout life. The population would then be strictly divided into complete

immunes and wholly susceptibles, and not affect one another. Although the benefits to individuals may be considerable, from the community point of view we have to justify a number of deaths per year directly due to infant vaccination, when we honestly cannot say that this amount of vaccination, this 10 per cent of immunes at any one time, would have any material effect on the spread of smallpox in a community with similar social structure and medical services to that of the United Kingdom. If New Zealand had strongly advocated infant vaccination during the last forty years and the incidence of complications had been the same as in the United Kingdom, 20 infants would have died from complications and a number of others would have been handicapped by the sequelae of encephalitis. This loss would doubtless have been claimed by some as a small price to pay for "security" but New Zealand has an almost unvaccinated child population and has had no smallpox for the last forty years.

Lack of appreciation of the limited herd immunity obtained is further illustrated in relation to vaccination in schools. The Ministry of Health states: "Incidentally the amount of revaccination at school age which the primary vaccination of only a quarter of the infant population makes safe, would, if thoroughly done, make a further useful contribution to the immunity of the population as a whole." If this procedure were carried out, the total immunity would still be less than 10 per cent. This faith in the idea that small amounts of immunity in the herd will really affect smallpox spread has produced the extraordinary situation of the Ministry of Health advocating infant vaccination and revaccination on children entering school, but for the usual reasons quietly discouraging primary vaccination at school age. This policy must be most confusing to even a reasonably intelligent public. The height of folly was perhaps reached in a letter sent to local health authorities, not written I am glad to say by a medical officer, dated 9 July 1956, in which it was stated: "For adequate protection of the population against the epidemic spread of smallpox, at least 75 per cent of infants should be vaccinated." One suspects that the figure 75 per cent was assumed to be applicable as it had previously been used in diphtheria immunization campaigns, but I need hardly say that if 100 per cent of the infants were successfully vaccinated this in itself would not prevent the epidemic spread of smallpox in the United Kingdom at the present time. In Sheffield in 1887–8, an outbreak of smallpox occurred with 7001 cases and 653 deaths although 97·9 per cent of the total population and *96·1 per cent of the occupants of invaded houses were vaccinated.*

The advantage that those vaccinated in infancy possess as a group in reduction in severity of attacks and prevention of death has already been discussed. It need not be emphasized that in the individual, duration of immunity may be so short that an attack may be severe, and death ensue. When the risk of infection is high, some immunity is valuable to a large number of individuals and to the State; an outbreak may have a low mortality instead of a high one. But if the risk of smallpox in a country is low with sporadic importations with a few deaths before the disease is controlled, then the deaths from smallpox are likely to be less than the deaths from total infant vaccination. To the layman, however, the determining factor is an emotional one so ably stated by Hough in 1737, concerning variolation. "For parents are tender and fearful, not without hope that their children may escape this disease, or have it favourably, whereas in the way of art, should it prove fatal they would never forgive themselves."

In some countries infant vaccination is compulsory and revaccination is done when the child enters school at the age of five years. School entry is prohibited unless a revaccination certificate is presented. Even assuming that all these revaccinations are done effectively, what sort of

immunity will the herd possess? There is no evidence that a person who has been successfully revaccinated at five years possesses any more immunity than the individual who has had a primary vaccination at five years. Therefore this procedure will add approximately five years' immunity to the population at risk. If the population was a primitive one, with high death-rate from many causes, and an expectation of life at birth of about thirty years, a fairly high degree of immunity to attack would occur, and the partial immunity might be sufficient to allow a few modified cases and for the disease to die out, although it is in this type of community, where living conditions are primitive, that case-to-case transfer is maximal.

Primary vaccinations may not be done in infancy, but as a requirement for entrance to school at about the age of five years. This would produce a similar immunological picture to the last, except that one would have the child population under five completely susceptible. This might not be as serious as might appear at first sight, as modern experience of smallpox suggests that the maximum incidence and the mode of transmission is frequently in the age-group 10–30. On the other hand, those infants that were attacked would have a high mortality.

In some countries infant vaccination is compulsory and revaccination at the age of eleven or twelve, when the child is at school. This is the law in France. The accounts of recent outbreaks in France do not suggest that these two measures in themselves or the further revaccination of the military call-up at twenty-one (males only) is producing an immune herd, sufficient to protect France against smallpox. It would appear that although it is compulsory, a fair amount of evasion occurs, and this leads to a false sense of security which can be disastrous.

The figures given by Woodward and Feemster (1933) are often quoted as proving that those areas of the United States which have compulsory vaccination legislation have a low incidence of smallpox, and those with no laws or prohibition of compulsion have high rates, and that this demonstrates the value of vaccination in preventing smallpox. It was pointed out by Paul (1952) that there is a significant difference in the rates of smallpox in those States where there are no laws, and where compulsion is prohibited, and he suggests that factors other than vaccination rates are different. I feel that this is likely; sociological differences are many and the smallpox referred to is variola minor, not major. Experience in London between 1928 and 1934 showed that amongst a section of the population many would prefer the fairly small risk of an attack of variola minor to the fairly certain discomfort of a three- or four-insertion vaccination. Perhaps cause and effect are the other way round.

Maxcy (1956) writes: "There is only one way to prevent the epidemic spread of smallpox in a community, and that is by maintaining at all times a high degree of immunity through routine vaccination of all infants, and revaccination of young children on entering school. The entire population should be revaccinated when the disease appears in its severe form." This appears to have been current American opinion for some time and determined action in the outbreak in New York (Weinstein, 1947). I need hardly say that this appears to be a policy of despair for any community with well-organized medical and public health services and a socially conscious and responsible population.

VACCINIAL COMPLICATIONS

Apart from the difficulties of obtaining and maintaining herd immunity, we are confronted with the very real problem of vaccinial complications. These are described as clinical rarities in the chapter on vaccination, and indeed they are in the professional lives of most clinicians.

Their infrequency is such that they have no practical importance in the vaccination of Class 1 or 2 contacts in smallpox control, but they have to be considered in random or mass vaccination, more particularly in any schemes of routine infant, school-child or special group vaccination, when large numbers are involved.

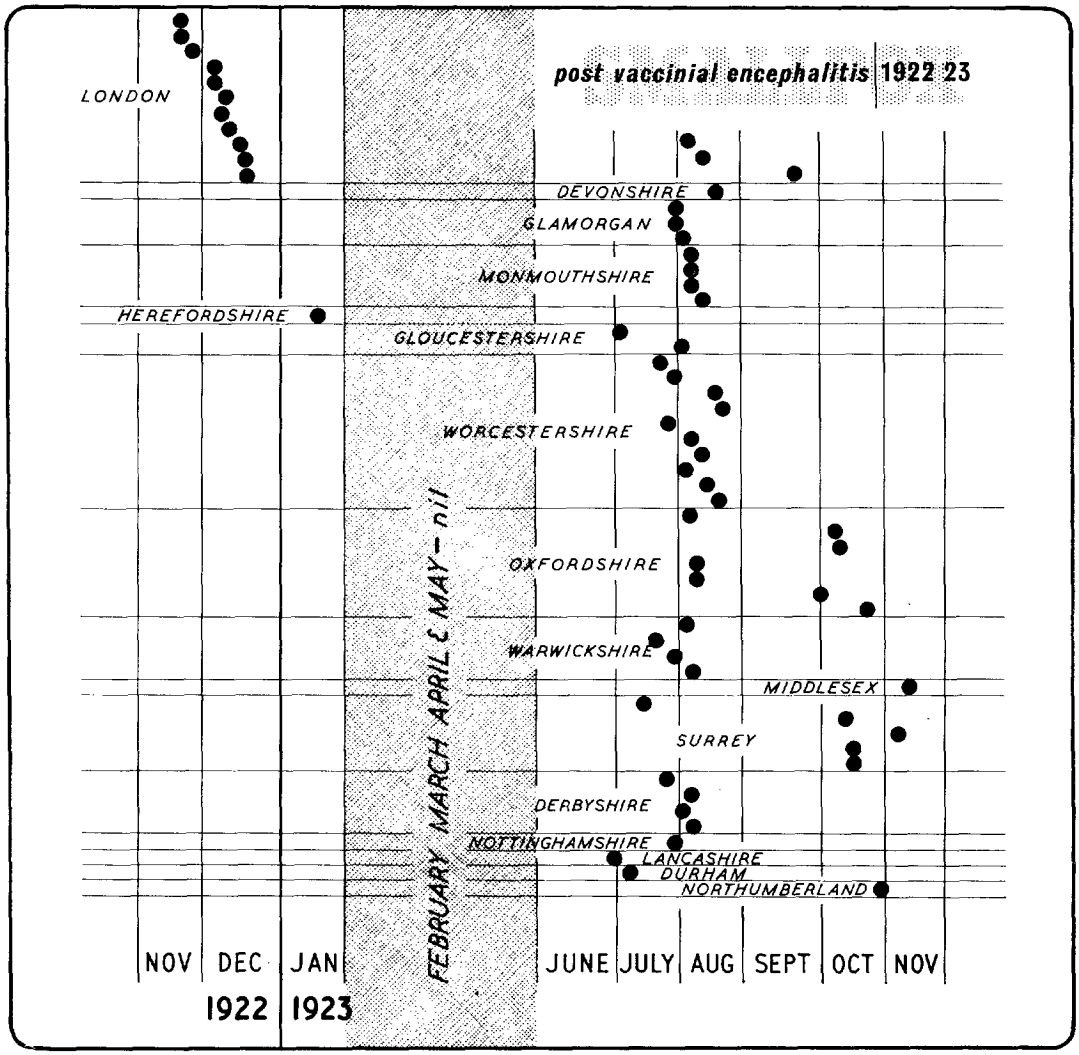


FIG. 253.

I have already referred to the optimistic statements made of the rarity of vaccinial injuries in the nineteenth century, but we still have people blind to reality: "If these simple precautions are adhered to, vaccination can be said to be free of risk to the health of the child" (Ministry of Health, 1924, Report No. 8); "With proper precautions, the individual risk is now nil" (Maxcy, 1956); "There is virtually no danger from smallpox vaccination, if proper precautions

are taken" (Metcalfe Brown, 1959). Although these writers *may* have made these statements relative to the great value of successful vaccination against a real smallpox risk, my complaint is that they imply that any risk is entirely due to unskilful vaccination. This is just not true. Even with first-class lymph, conscientious vaccination, no neglect by the patient or his family,

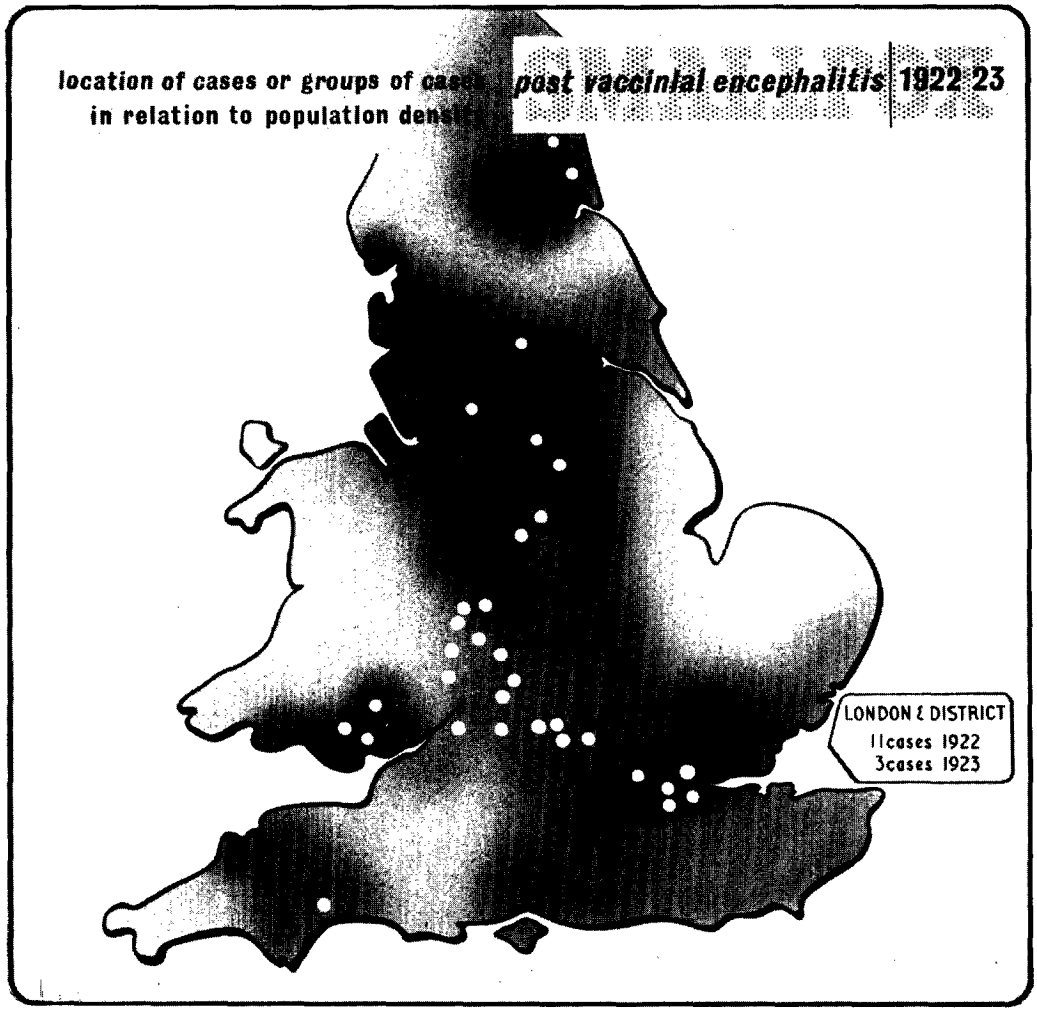


FIG. 254.

important complications do occur. In the present state of our knowledge there is no evidence that the complications discussed below, with the possible exception of some cases of generalized vaccinia, could be avoided. The history clinical features and sequelae are discussed in chapter 7.

The first and most important is post-vaccinial encephalitis. Although in many countries it is claimed that the disease does not occur, hardly a year goes by without the "first case" being discovered in some country. From my own personal experience in fourteen countries in the Western Pacific region and South-East Asia, I feel these cases do occur, but are not disclosed

by private practitioners, particularly in countries where vaccination is compulsory. On the other hand, there can be no doubt that the incidence in certain countries, particularly Holland, England and Germany, has been very much higher. Why this should be so is one of the epidemiological mysteries.

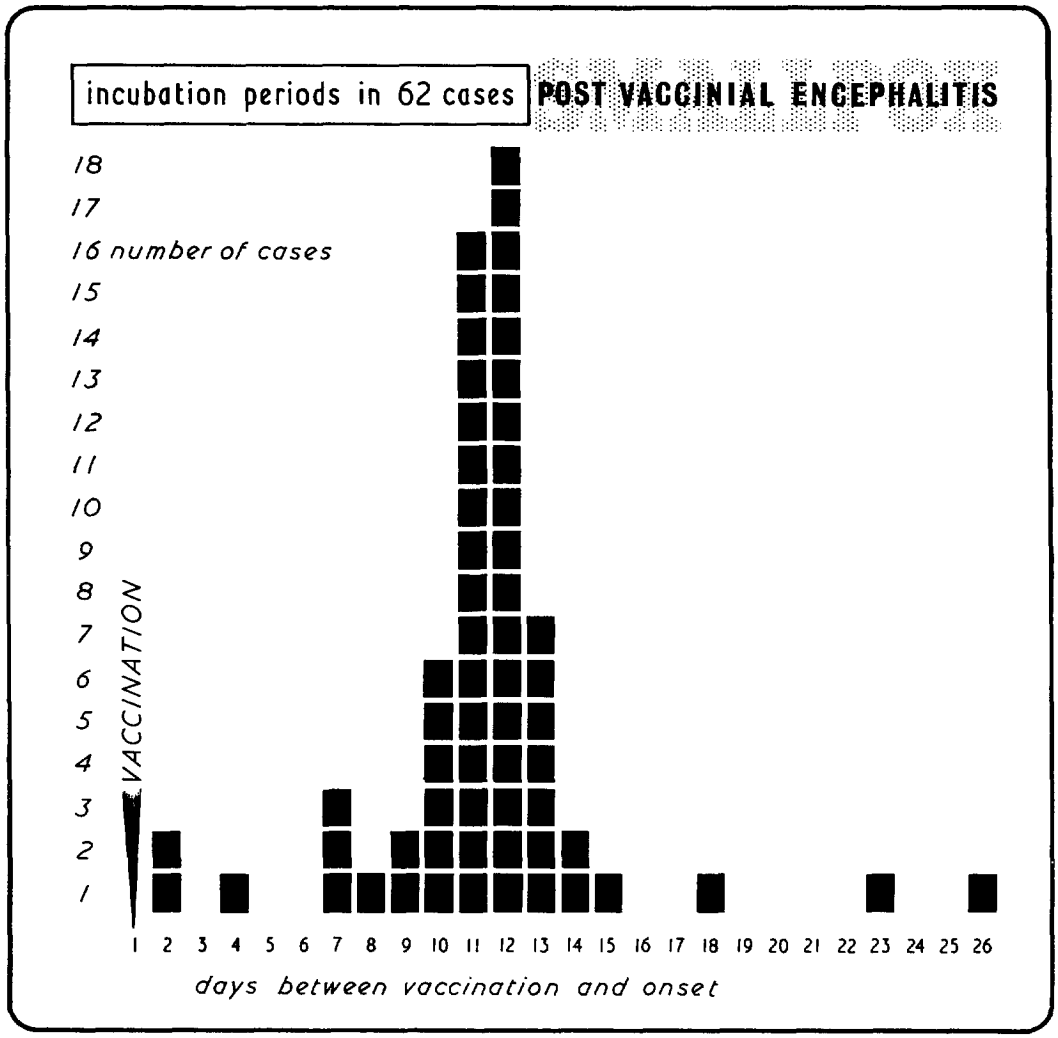


FIG. 255.

The occurrence of cases of post-vaccinial encephalitis between 1922 and 1923, in England and Wales, is shown in Fig. 253. This and Figs. 254–256 are based on information given in the Rolleston Committee's report of 1928. The peculiarity of geographical distribution is shown in the map in Fig. 254. As can be seen, the cases occur in two groups, with an interval of six months in which no cases were recorded. The first group of cases occurred in London, and the remainder were scattered throughout England and Wales. Vaccination was being

done fairly widely, due to the prevalence of variola minor. There was no direct relationship between the incidence of cases and the number of vaccinations being performed, or of the presence or absence of smallpox in a particular area. There were two instances of encephalitis in two persons in the same family, and in Derbyshire four cases occurred within ten days.

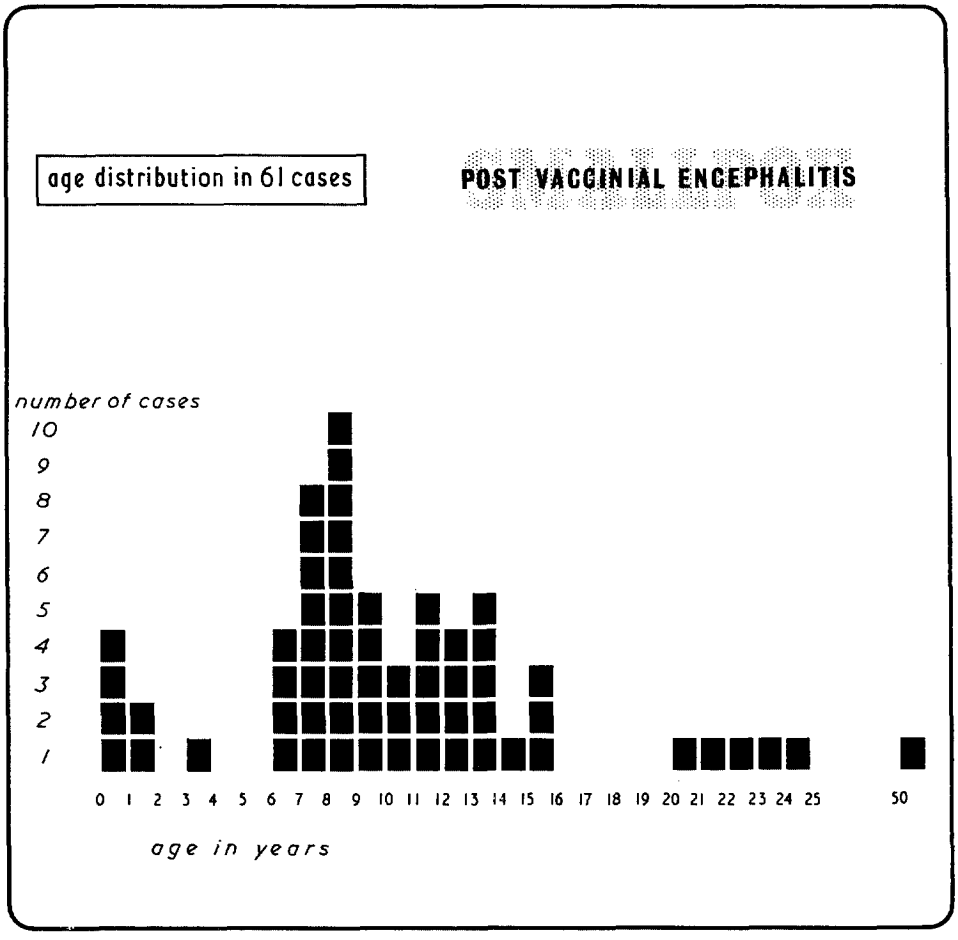


FIG. 256.

Cases occurred almost simultaneously in countries widely separated. There was no evidence of possible spread of infection from one place to another, except in three cases in Gloucestershire, three in Birmingham and four at Stourbridge.

Perhaps the most important piece of factual evidence is the incubation period. Figure 255 shows this, and suggests that true post-vaccinial encephalitis tends to occur between the ninth and fourteenth days. It seems possible that some of the cases recorded either in the first two or three days after vaccination or some eighteen to twenty-six days might be due to some other virus infection of the central nervous system. There was an excess of female cases in the proportion of two to one in the cases reported by Rolleston (1928) but in Conybeare's series (1948),

although a large number of service vaccinations gave a preponderance of male cases in the adolescent group, in those under fifteen years of age there was no sex difference.

Figure 256 shows the age distribution, and it is noticed that the bulk of cases fell on children between the ages of six and sixteen. Because of this, much attention has been paid to the apparent susceptibility of the school-child to post-vaccinial encephalitis, compared with younger children or with adults. The Committee noted that because of the prevalence of variola minor, a large number of primary vaccinations were being carried out in school-children, but stated that it is possible that primary vaccination of children of school age occurred on a similar or even larger scale during the smallpox epidemic in 1901–2 when post-vaccinial encephalitis was not recorded. This seems unlikely as the infant vaccination rate was then 70 per cent, compared with 40 per cent in the later outbreak. The problem was of very great public health interest, because vaccination was being urged for the prevention of variola minor, a disease with a low mortality, and the public were becoming resistant to vaccination due to the publicity given to events such as the happenings in Bristol. Six cases of post-vaccinial encephalitis occurred within an area of one square mile in the centre of Bristol, and three further cases occurred a short distance away. Only about nine thousand vaccinations had been done in the relevant period.

The figures produced by Van den Berg (1947) are often quoted as proving the danger of primary vaccination during school age.

His table (Fig. 257) shows that all the cases in the outbreak occurred in children of later school age, 8 to 16. With the small numbers involved in other age groups, cases would not be expected in the 0–1, 17–25 or 26 plus age groups but it is not highly improbable (P = 0·065) for no case to occur in the 2–7 age group.

Noord Brabant

Total number of inhabitants	113,271
Total number of vaccinations	16,750

Age-group	Number of vaccinations	Cases of encephalitis
0–1 year	300	—
2–7 years	1,988	—
8–16 years	13,325	23
17–25 years	890	—
Above 26 years	247	—

(Van den Berg, 1947)

FIG. 257.

Incidence has varied greatly partly due to some unknown causative factor and partly due to variation in the medical and lay interest in the disease at various times. As diagnosis is entirely clinical in the non-fatal cases, there is opportunity for both under and over diagnosis. Often in the fatal cases "typical" post mortem findings are not always present and there is a tendency to discount this type of case as not being post-vaccinial encephalitis, but if a person has died from a disease with clinical signs that would fit the diagnosis, within an accepted time following vaccination and there is no other cause of death, it seems wrong to completely exonerate the vaccination. The acid test is whether the person would probably be still alive if vaccination had not been performed.

In Hamburg, for the period 1939 to 1958, Seelemann (1960) found the incidence was one in 10,805 primary vaccination under four years of age with the case mortality of 38 per cent but one in 2,226 over four years of age with an unusually low case mortality of 8 per cent. On this experience the chance of dying from post-vaccinial encephalitis would, however, appear to be the same at all ages.

In Sweden, the largest number of cases has been in the age group 5–8 (Heinertz, 1947–8) but no information is given of the numbers vaccinated at each age. The age at which primary vaccination is done whether in infancy or on entering school has tended to give the appearance of many cases at a particular age but rarely are figures available for the number of vaccinations done by age group.

The incidence of encephalitis in mass vaccination campaigns, which include primary and re-vaccination at any age, varies considerably. Glasgow (Anderson and McKenzie, 1942) had one in 70,000, Edinburgh (Clark, 1944) one in 20,000, Fife (Fyfe and Fleming, 1943) one in 8,300. In New York (Muckenfuss, 1948) had one in 150,000, but in Gloucester and Worcester in 1923 the rate was one in 800, whilst in small towns in Holland it has been as low as one case of encephalitis in every 63 vaccinations.

Case mortality is generally about 40 per cent being as high as 75 per cent under the age of one year and between 20 and 30 per cent at other ages. So much depends on whether mild cases are diagnosed and included.

Perhaps the two most common mis-statements made, are, first that post vaccinial encephalitis is very rare in infancy and second, that it is rare and not fatal after re-vaccination. In Conybeare's (1948) series of 222 cases of which 110 died, 10 per cent were under two years of age but they accounted for 20 per cent of the deaths. Unfortunately no figures are available for the amount of vaccination done, and hence the rates, but the figures from Griffith's Table (Fig. 258) show that the incidence at age 0–1 is about the same as in the reputed danger period of 5–14 and it carries a higher mortality. The comparison of Conybeare's figures for England and Wales for 1927 to 1946 with Griffith's for England, Wales, Scotland and Ireland for 1951 to 1958 suggests that there has possibly been a change in the age incidence with a proportionate reduction at ages 5–14 and an increase in the age group 0–5 probably most in the age group 0–1.

In Conybeare's series, sixteen cases of encephalitis, of which six were fatal followed revaccination but in thirty-six cases the previous vaccinial state was not known. In Griffith's series the incidence following revaccination, almost certainly an understatement, is eleven per million at ages 5–14 and seven per million at age 15 plus. The mortality of two per million at 15 plus is higher than Conybeare's estimate of one per million.

How far these figures apply to other countries, or even to Great Britain in the future, is impossible to predict.

In the 1928 Report an attempt was made to prevent post-vaccinial encephalitis by modification of vaccination technique in spite of the fact that there was no evidence to incriminate any particular batch of lymph, method of vaccination or pre or post vaccination treatment and the situation is the same today. It is generally considered inadvisable to vaccinate concurrently with other inoculations if this can be avoided but there is no scientific proof that this really affects the incidence of encephalitis.

The other complication of importance is generalized vaccinia. Although in infants this can be partly prevented by not vaccinating infants suffering from eczema, a number of cases occur in adults, where there is only a remote or no history of previous eczema. Occasionally

cases of pyaemia also occur. Although many official statistics, because of procedural rule, exaggerate the importance of vaccination as a cause of death or of morbidity, there are also other cases, particularly those not fatal, that are not recorded. In this very difficult field we can only take the figures as we find them.

It is often stated that vaccination is best done in infancy, as at this time it is virtually devoid of complications. Griffith (1959*a*, *b*) has obtained the figures for complications for England and

Complications of vaccination. England and Wales, Scotland and Northern Ireland (part), 1951–1958

	Ages in years							
	0–1		1–4		5–14		15–	
Primary vaccinations	2,343,908		538,529		246,189		377,145	
Re-vaccinations	6,241		39,811		182,358		1,005,502	
	P.V.	R.V.	P.V.	R.V.	P.V.	R.V.	P.V.	R.V.
Cases of:								
Generalized vaccinia	119	0	14	0	7	4	29	8
Post-vaccinial encephalitis	36	0	1	0	4	2	10	7
Deaths from:								
Generalized vaccinia	11	0	0	0	0	0	0	0
Post-vaccinial encephalitis	21	0	0	0	0	0	2	2
Other complications	4	0	1	0	0	0	0	1
Rates per million: vaccinated or revaccinated								
Incidence:								
Generalized vaccinia	50·8	0	26·0	0	28·4	21·9	76·9	8·0
Post-vaccinial encephalitis	15·4	0	1·9	0	16·3	11·0	26·5	7·0
Mortality:								
Generalized vaccinia	4·7	0	0	0	0	0	0	0
Post-vaccinial encephalitis	9·0	0	0	0	0	0	5·3	2·0
Other complications	1·7	0	1·9	0	0	0	0	1·0
Total mortality	15·4	0	1·9	0	0	0	5·3	3·0

FIG. 258.

Wales, Scotland and Northern Ireland from 1951 to 1958 (Fig. 258). Although local health authorities are obliged to send the Minister details of complications of vaccination that come to their notice, it is not legally incumbent on medical practitioners to notify these, and it would seem if anything that the morbidity figures are an understatement of what really occurs. The incidence and mortality rates of both primary and revaccination at different ages are worthy of close study.

Arguments are advanced in favour of infant vaccination, not as a method of preventing infants from contracting smallpox, but as a method of preventing adults from contracting vaccinial complications when they require to be vaccinated for travel or military service. It

should be noted (Fig. 259) that, adding the risk of primary vaccination in infancy and that of revaccination over fifteen together, the incidence of generalized vaccinia is slightly less than that of primary vaccination at fifteen-plus alone, and the incidence of post-vaccinial encephalitis appears to be about the same, a view similar to the estimates made by Conybeare (1948) for the latter condition. When we turn to mortality, however, the total mortality of primary vaccination done at fifteen-plus from generalized vaccinia, post-vaccinial encephalitis and other complications would appear to be 5·3 per million, whereas the combined mortality risk from primary vaccination in infancy and revaccination at fifteen-plus would appear to be 18·4 per million, a very significant difference. The point made by Griffith was that the age-group 1–4

Complications of vaccination and revaccination singly and in combination at different ages

	P.V. at 15+	P.V. in infancy and R.V. at 15+	P.V. 1–4 and R.V. at 15+	P.V. at 1–4 only	P.V. at 0–1 only
Incidence of:					
Generalized vaccinia	76·9	58·8	34·0	26·0	50·8
Post-vaccinial encephalitis	26·5	22·4	8·9	1·9	15·4
per million vaccinated					
Mortality:					
General vaccinia	0	4·7	0	0	4·7
Post-vaccinial encephalitis	5·3	11·0	2·0	0	9·0
Other complications	0	2·7	2·9	1·9	1·7
Total mortality per million	5·3	18·4	4·9	1·9	15·4

FIG. 259.

appeared to be very much better for primary vaccination than that of 0–1. Primary at 1–4 plus revaccination at 15 gives generalized vaccinia 34, and post-vaccinial encephalitis 8·9, a considerable advantage over primary vaccination at fifteen. Comparing mortality from generalized vaccinia, post-vaccinial encephalitis and other complications, the combined risk would appear to be 4·9 per million, which is about the same as that from primary vaccination at fifteen-plus. It would seem, therefore, that on the figures given the incidence of complications for those vaccinated between the ages of one and four and revaccinated at fifteen-plus is definitely less, although the fatality would appear to be about the same. Most clinicians would, I think, agree that inconvenience to the mother and to the child will probably be greater if routine vaccination is done between one and four than if it is done between 0 and 1, but one small advantage is that the older the child, the smaller will be the ultimate scar size in the adult. In areas where the risk of smallpox is appreciable vaccination in infancy is essential.

Although the argument in favour of infant vaccination is so often given "that for one reason or another a substantial number of residents in this country will find it desirable to be vaccinated on some occasion during their lives", examination of Griffith's figures shows that during the eight years from 1951 to 1958, during which there were a number of outbreaks of smallpox, the total number of individuals over the age of fifteen who found it necessary to be vaccinated or revaccinated was 1·3 million, roughly 175,000, or 1 in 280 persons per year.

Taking the expectation of life at fifteen as about fifty years, less than one person in five will require to be vaccinated at some period of their lives if the risk continued the same.

The likelihood of vaccination or revaccination in adult life for travel purposes can be assessed by subtracting the 300,000 vaccinations which were done in this age-group during the outbreaks in Brighton, Todmorden and Rochdale, but does not exclude those done in small outbreaks in Liverpool and London, during this period. This leaves about a million vaccinations, probably less, done between these years, giving the chance of any person over the age of fifteen requiring vaccination or revaccination for travel purposes during their lifetime of about 1 in 8. When one bears in mind that some countries still require valid vaccination certificates, quite unnecessarily, it would appear that in the future those who require vaccination for travel to an area of smallpox risk are unlikely to be more than one in ten of the population, and these will be very unequally divided geographically or by social class. One should therefore consider whether it is necessary to vaccinate ten infants or young children, so that one adult may have a revaccination for travel purposes rather than a primary one.

Contrary to popular opinion, it would appear from Griffith's figures that infant vaccination has no advantage—in fact some disadvantage for prospective adult travellers; but routine vaccination in the age group 1–4 would have an advantage in lower incidence of complications although not of mortality, if one in three of the adult population eventually required vaccination certificates for travel purposes. This appears to be the position regarding safety but we should not ignore minor discomfort as this is not unimportant to the man in the street. Undoubtedly vaccination in infancy and early childhood does spare many adults the discomfort and malaise association with primary vaccination, but its evil reputation, is, I feel, partly due to many doctors making too large an inoculation. In the elderly, primary vaccination in infancy may not spare them from quite severe local and general reactions from what is technically a revaccination.

The assumption that a person once vaccinated in infancy is always at an advantage in preventing an attack if revaccinated in the incubation period compared with those primarily vaccinated in the incubation period is often used as an argument in favour of infant vaccination. The problem has been discussed earlier in this chapter where it can be seen that the advantage can not be demonstrated. This may be partly due to the increasing age interval since primary vaccination in smallpox contacts in outbreaks in the United Kingdom in the last twenty years, and may also be related to vaccination technique, or avidity of current smallpox vaccines. From a practical point of view it is of little weight in the argument in favour of infant vaccination in non-endemic areas where the risk of post-vaccinial encephalitis and other complications is appreciable.

The problem again emphasizes the importance of assessment of risk. Whereas in places like Liverpool or Glasgow, and other ports trading with endemic areas, in the families of those who are directly connected with the port, infant vaccination and revaccination is a very desirable thing, but to suggest that the same pattern should be required for the whole of the country is failing to appreciate widely different risks. We need a better understanding by the general practitioner who is going to advise his patient. If the family live in a locality where there is risk, or if the social class of the patient is such that vaccination is likely to be required later in life, then this is a stronger argument for doing primary vaccination at some time when the risk of complications is minimal. There is a very great need for accurate and honest collection of statistics relating to these complications, but unfortunately there is considerable and under-

standable reluctance on the part of the medical profession to report these in the medical journals, as these now provide far too much material for the lay press, where a true appreciation of the complex problem of relative risk can never be presented.

SMALLPOX ERADICATION

Smallpox eradication has been exercising people's minds since Jenner's discovery over 150 years ago, and yet it is still such an important disease in some countries.

All public health control measures aim at eradicating the disease either from a locality or from a country. In some, such as variola minor in the U.S.A. and in Britain, infection died out rather than was controlled, and this has probably occurred in outbreaks of variola major, although our control efforts are usually much more successful.

Smallpox can be kept going in a country with as few as twenty-six cases a year, and possibly also with virus on clothing, but persistence of infection is probably slight and could be eliminated by exposure to the sun. No chronic carrier state exists and no animal reservoir, so that "simultaneous" vaccination of the population of the present world endemic areas would eliminate the disease once and for all.

The World Health Organization has been interested in this problem since 1952. In 1954 I carried out a survey of smallpox control methods in the Western Pacific region of W.H.O., and suggested methods, particularly by a policy of attrition, by which smallpox could finally be eliminated from this region. The problem, however, is not so much a medical one as one of organization, requiring stable governments and social conditions for this to be carried out.

The problem of world smallpox eradication is discussed in the report of the Director General of W.H.O., 28 April 1959. Europe has no problems as the small outbreaks can be controlled by ring vaccination. In the Americas, the United States is free from smallpox, and South American countries have embarked on large-scale vaccination projects, principally using house-to-house vaccination, so as to cover the entire population. Smallpox still exists in Central and West Africa, and the considerable movement of people, particularly for the Mecca pilgrimage, contributes to the spread from west to east. The major problem is South-East Asia, particularly India and Burma. It is usually assumed that the persistence of smallpox is due to a failure of vaccine, as many of these towns have trained vaccinators. In some instances large numbers of cases occur within a mile of the vaccine institute producing perfectly satisfactory glycerinated lymph, showing that there is much more to the problem than the supply of a thermo-stable lymph. Undoubtedly the use of dried vaccine would have great advantages in the vaccination of people in the more inaccessible areas, but smallpox is still a problem in the major cities.

The W.H.O. report states: "It is generally agreed that eradication of smallpox from an endemic area can be accomplished by successfully vaccinating or revaccinating 80 per cent of the population within a period of four to five years." W.H.O. appears to be committed to the idea that obtaining herd immunity is the only way of controlling smallpox. I cannot see why the 80 per cent figure was chosen, and it is obviously not valid under all conditions. If more study were given to the foci of smallpox, it might be possible to eradicate the disease from an area by vaccinating a far smaller proportion of the total population. Even if 80 per cent of the population were vaccinated under four to five years, they would certainly not remain immune, and if still in contact with other endemic areas there is a strong possibility of many missed cases and small foci continuing for many years. In the light of the remarks of Fabre (1948) and

of Thanawala (1956, 1959), of the appreciable number of deaths from smallpox in Indian children under ten who had been successfully vaccinated in infancy, one wonders what duration of immunity will be obtained with dried lymph under these circumstances, a fact which is still unknown. It would seem that if really intensive and efficient vaccination and revaccination were done in the large towns, this would stop the major reservoirs of infection. Those areas which are so inaccessible for the supply of glycerinated smallpox vaccine are probably also fairly inaccessible to the movement of smallpox both in and out of the area. A barrier of immunes in the right place is more effective than attempting to produce a herd immunity, when there may be opposition from the population. The average number of vaccinations done by each vaccinator in mixed type of country is between sixty and eighty per day. The cost is about ten cents per vaccination, but in a country like India the total cost of vaccinating the population would be thirty-nine million American dollars. In my opinion money could be better used in providing basic public health services, training good medical officers, all-purpose public health nurses and sanitary inspectors, and in this way gradually discovering the foci of infection, working across country and eliminating the disease as elsewhere by attrition. At the same time, a great deal of other useful public health work, the control of many other infectious diseases, could be instituted. There is too great a tendency to continue the old policy of large numbers of poorly paid and ignorant vaccinators producing satisfactory statistics of vaccination, but who are inadequately trained and supervised. A smaller number of *really well-paid* staff should be employed in multi-purpose public health, thus attracting some of the best medical or auxiliary workers, and barriers of really immune people could easily be obtained where they are wanted at a minimum expense and inconvenience to all concerned. The control of smallpox in a country is not, and never has been, solely a matter of vaccination, or the production of a thermo-stable smallpox vaccine, but there appear to be some who oversimplify the problem.

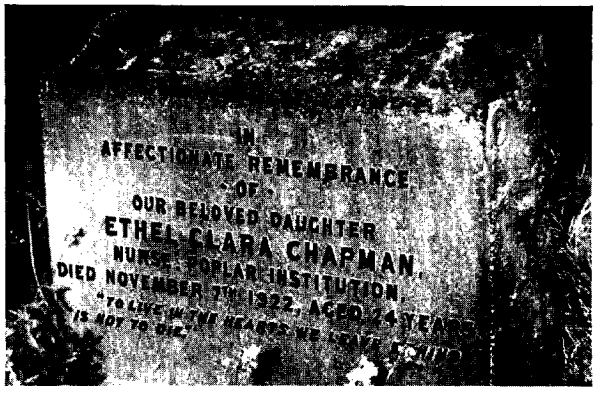


FIG. 260. Smallpox claims the unvaccinated nurse.

CHAPTER 15 | *The Smallpox Hospital*

The earliest use of hospitals for infectious disease was for the accommodation of persons suffering from leprosy, a name used to include a number of skin diseases. These lazarettos were established extensively from the eighth century onwards, and have occasionally been commemorated in place-names, such as Burton Lazars in Leicestershire. Their purpose was largely to remove individuals thought to be suffering from infectious disease from the public view. When plagues became common in England, pest-houses were set up, usually temporary buildings on the outskirts of the town. However, many epidemics were regarded as visitations from God, and not as being infectious, and many pest-houses were used for treatment rather than for isolation. Even Sydenham did not regard smallpox as infectious. An isolation hospital appears to have been set up in Cambridge in 1574, but the first proper hospital for infectious disease control appears to have been used by Haygarth in Chester in 1784. Although other towns followed, cases of fever were admitted to other types of hospital. The proportion of patients who could be admitted to hospital would be very small. The London smallpox hospital had been established in 1745, but primarily as an inoculation hospital, and only secondarily for the treatment of smallpox. The London fever hospital was established in 1802.

The first Public Health Act in 1848 contained nothing to authorize local boards of health to establish hospitals for infectious disease. Entire reliance was placed on sanitary reform as the main preventive measure. Lack of interest in isolation is shown by the fact that an Act for the prevention of cholera in 1832 and an Act in 1846 for the more speedy removal of certain nuisances allowed the Privy Council to provide for contagious and epidemic disease, but no hospital appears, however, to have been established under either Act, nor in fact were any orders issued under them. Under Section 10 of the Nuisances and Removable Diseases and Prevention Act, 1848, the General Board of Health was empowered to issue directions and

regulations to provide for medical aid for people suffering from contagious or infectious disease. Apparently no means of isolation were provided under the statute, and none were provided under the Diseases Prevention Act of 1855. In 1842 the opinion of many hospital physicians in London was against separate fever wards or fever hospitals and favoured mixing the fever patients with others, as, when concentrated in fever wards, they were most dangerous to the staff. In 1860, of eleven of the London general hospitals, eight admitted a limited number of fever cases. Many types of fever, particularly typhus, typhoid and scarlet fever, were treated without reference to different modes of infection. After about 1861 typhus cases tended to be separately treated, but the arrangement frequently broke down. Smallpox was generally not treated, as it was regarded as more infectious than others, but cases were knowingly admitted from time to time, as early records of London teaching hospitals show. By 1863, in their report to the Privy Council, Bristowe and Holmes strongly advocated that fevers should be kept in separate wards, and recognized that smallpox particularly should not be admitted to a general hospital, because of the risk of infection to other cases. John Simon, however, regarded a hospital's most important function to be the removal of cases of infectious disease from the community, so as to reduce the chance of spread.

Prior to 1866, therefore, it was exceptional for patients with smallpox to be treated other than at home, and reference to them running the streets in their delirium is frequent. Apart from the few special admissions referred to, the only place to which a person suffering from smallpox could be admitted was a workhouse infirmary, where the conditions were deplorable. Progress, however, was slow; under the 1866 Act authorities could provide hospitals, or could combine for providing accommodation for those "suffering from any dangerous, contagious or infectious disorder without proper lodging and accommodation, or lodged in a room occupied by more than one family, or being on board any ship or vessel". It was not until the Public Health Act, 1875 consolidated these provisions and allowed local authorities to provide hospitals, that medical and public health needs were considered, so that both paupers and non-paupers could be admitted to such hospitals, and persons in common lodging-houses could be removed in order to prevent the spread of infection. The Poor Law Act of 1879 initiated the transfer of workhouse infectious hospitals to rural sanitary authorities. However, an inquiry from the Local Government Board showed that only 296 out of a total of 1,593 sanitary authorities possessed any means of isolation of infectious disease. In a great many instances the provision of accommodation was only in name and not in fact. This prompted the investigation of Dr. Thorne Thorne, who stated in the Local Government Board report for 1880–1 that most of the hospitals were "the outcome of panic resulting either from the actual prevalence of some epidemic, or the anticipated invasion of some infectious disease". In the vast majority of cases the disease which had led to the provision of hospitals was smallpox. Even in the 1880's some of the smallpox hospitals had been satisfactory and continued and developed into general infectious-disease hospitals. Others had never received a patient with smallpox. Many were of a temporary nature; only a few, such as Huddersfield and Salford, were provided with permanent buildings. The almost universal practice of providing temporary buildings hampered the development and use of permanent buildings. Where a district already had a hospital in existence, it had a very much greater chance of controlling an outbreak of smallpox than one which had to start to provide accommodation in the middle of an epidemic.

Due to the intense parochialism of the time, patients were very reluctant to be moved from

out of the district in which they lived. There was almost complete failure of the arrangements made by sanitary authorities in the neighbourhoods of Bradford, Leeds, Manchester and Middlesbrough to use the infectious-disease hospitals in these towns for cases from the surrounding boroughs. In Todmorden, where the hospital was within a mile of the town, the journey was so circuitous and difficult that few patients undertook it. Many of the temporary hospitals were built of wood and with the primitive type of heating by open fires in the severe winters of 1880 and 1881 the temperatures near the beds did not rise above 32° F. In some of the hospitals it was not uncommon for water to freeze near the beds of patients. Straw mattresses on beds of oat chaff were commonly used, being burnt from time to time, and were not likely to attract many patients.

FIG. 261. Smallpox hospital, Birmingham, 1893.

Although most hospitals for infectious disease were primarily for the pauper class of patient, even before 1880 Folkestone had provided a small detached hospital, including private apartments for the reception of a "superior class of person". The use of such hospitals was considerably hampered by the lack of compulsory notification, although Leicester and Warrington had commenced this in 1875, and by 1880 the number included Blackpool, Derby, Huddersfield, Norwich and Nottingham. A fee of two shillings and sixpence, a considerable sum at this time, was paid for each notification. Although powers existed under the 1875 Act for compulsory removal to hospital, even in 1880 it was shown that such a procedure was very rare. When taken, it was largely for the benefit of the individual concerned, rather than for the protection of the community. In 1880 the Medical Officer of Health of Oldham, in an early example of health education, threw open to public inspection for a week a new infectious-disease hospital, during which time about 13,000 of the town's inhabitants came to see it, and

"were loud in their praise of the comfort and accommodation it was calculated to afford", with the result that refusal to allow admission, particularly of children, rarely occurred.

By 1882 increasing emphasis was placed on the provision of smallpox hospitals as a preventive measure. General practitioners, however, were anxious that fee-paying patients should not go into hospital, and this probably hindered notification where this was applicable. In some of the hospitals, however, in Bradford and in Rochdale, patients were treated by their own doctors while in hospital. In some instances the local sanitary authority admitted non-pauper patients to its hospitals, and the paupers still continued to be admitted to the isolation section of the Poor Law institution.

About this time attention was also given to the problem of conveyance of patients to hospital. The Local Government Board issued memoranda on the design of horse-drawn vehicles. It also stressed the necessity for the person in charge to be fully trusted to look after the patients en route, in view of the frequent necessity of drivers of ambulances to stop at local hostelries to resuscitate themselves, if not the horses.

By the end of the century it was increasingly recognized that infant vaccination alone was not the complete remedy, but by 1895 only about a third of the sanitary authorities were providing infectious-disease hospitals. Small wonder that smallpox was not under very effective control. Gradual amalgamation of sanitary areas for fever hospital purposes occurred, but as late as 1935 it was a common thing to see through the length and breadth of England small tumbledown buildings, with barely discernible lettering showing that they were some local authority's smallpox hospital. Many had been built in the last panic of 1902, but had never had a single smallpox patient.

These historical notes on the smallpox hospital would be very incomplete without some reference to how the problem was dealt with in London (Caiger, 1924–5). Although many of the larger provincial cities had provided for notification of infectious disease by special Acts of Parliament, these powers were absent in London, with a population of over three million, until 1889. Medical officers of health only received information about the presence of smallpox in their areas from being told of the cases in the workhouse hospital, and information from the death registers.

In the original Act of 1889, notification was not required for patients in the some 130 hospitals which were situated in London at the time, but the Public Health Act (London), 1891, remedied most of the earlier defects.

Prior to 1867, smallpox in London was handled in much the same way as other diseases, and most of the cases would be nursed at home. There was but one hospital, the private smallpox hospital at Highgate. The Sanitary Act of 1866 enabled sanitary authorities in London to provide infectious-disease hospitals, or arrange for existing hospitals to receive their cases, and although the provisions were made to apply to any paupers or non-paupers without proper accommodation, it was not obligatory, and only three of the authorities did anything. On the other hand, the Guardians of the Poor in every union were obliged to provide medical treatment for paupers, whatever disease they might be suffering from. It was because of the difficulties of trying to treat infectious disease in the ordinary workhouse hospital that the Metropolitan Asylums Board was created to deal with smallpox, fever and the care of imbeciles. The first act of the newly formed board was to provide accommodation for smallpox, although there were no figures of incidence from which to estimate needs. Three sites were acquired, one in north-east London at Homerton, one in south-west London at Stockwell, and the

other in the north-west at Hampstead. At Homerton and Stockwell, a permanent hospital was built to include 100 beds for smallpox.

As was to be expected, there was some opposition from the local residents in these areas, who objected to a smallpox hospital in their midst. The epidemic of 1870–2 put the M.A.B. to a severe test. The hospitals were still unfinished, and a temporary hospital at Hampstead was used. The Islington old workhouse was transferred to the Board and used for smallpox, and the hospitals at Homerton and Stockwell were obliged to accommodate both smallpox and fever patients. Cases were put in beds in hospital corridors, and tents were erected in the hospital grounds, and later the hospital ship *Dreadnaught* was brought into use and moored off Greenwich. It was estimated that during the epidemic about 16,000 cases were admitted to the Board's hospitals, but this was only about one-third of the number of cases in London as a whole, and therefore made relatively little impact on the reservoir of infection in the

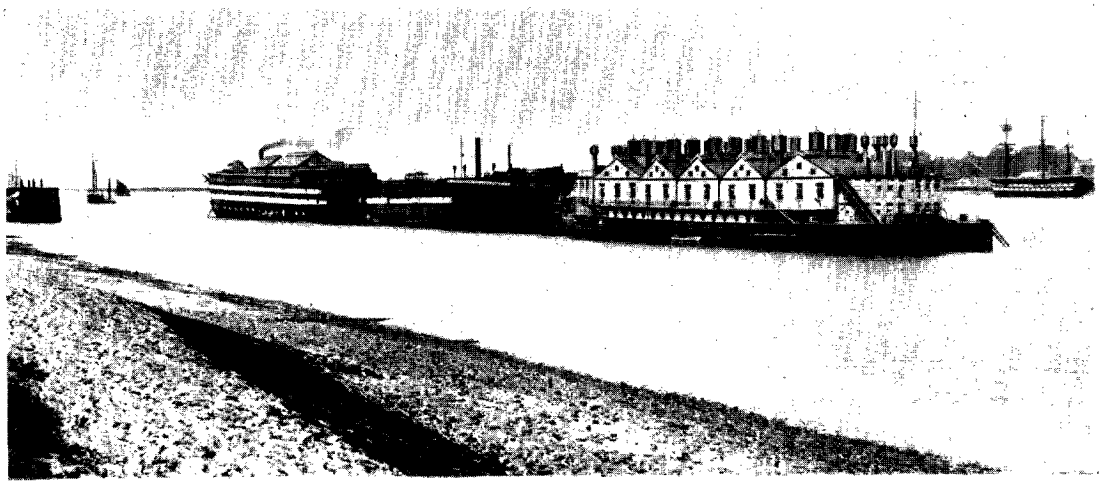


FIG. 262. The *Atlas*, *Endymion* and *Castalia*, floating smallpox hospital at Long Reach, about 1900.

metropolis. There was considerable opposition, particularly at Hampstead, but the Parliamentary Committee, which carried out an enquiry, recommended no interference, but suggested that the reserve sites at Fulham and Deptford might have administrative offices completed, so that when the need arose these places might receive cases that would otherwise be sent to Hampstead. This was done. Following the epidemic of 1870–72, there was virtually no smallpox until 1876. Cases were then admitted to Stockwell hospital and later to Homerton, and finally the Hampstead hospital was again used for smallpox. However, the disease increased rapidly, and it was proposed to take the Westminster union schools at Battersea and use them as a smallpox hospital, but the guardians refused to give them up, owing to strong local opposition, and the plan had to be abandoned. Temporary huts were put in the grounds of all three hospitals but the demand for accommodation was more than could be provided, and in Limehouse a private factory was used as a temporary hospital by the Board. The absence of sufficient hospital accommodation resulted in whole streets being marked off with plague flags as infected areas.

Once again, the residents around the Hampstead hospital complained bitterly, and a lawsuit was taken against the Board, which resulted in the closing of the hospital to smallpox cases. This having been done, at the next outbreak in 1880–81 the Fulham residents formed an association to prevent the use of this hospital for smallpox, and were successful in obtaining an injunction which restrained the Board from receiving patients into the hospital from any distance beyond a radius of one mile, a move which meant practically closing it. To compensate for the loss of the Fulham and Hampstead hospitals, the Board resorted to a practice which was carried out in other parts of England, that of providing floating accommodation, so as to be more secure from the risks of legal action. Two hospital ships, the *Atlas* and *Endymion*, were moored in the Thames off Deptford, and a camp for convalescents was established at Darenth, near Dartford. The camp at Darenth was canvas, and erected in the grounds of the Board's school for imbeciles. As many as 650 patients could be accommodated at one time, and were transported from the ships by road in the Board's four-in-hand horsed vehicles, the distance

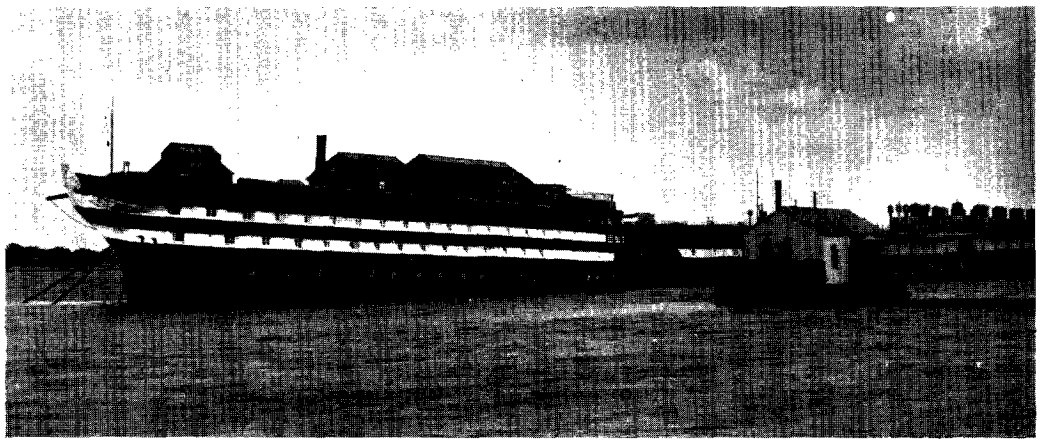


FIG. 263. The *Atlas*, part of the floating hospital at Long Reach, Dartford.

of eighteen miles being covered in three hours. The possibility of infection from convalescent patients was probably less than popularly supposed, although on more than one occasion the drivers invited patients to join them in refreshments at numerous hostelries *en route*, completely contrary to the Board's instructions. It is related how one was so drunk that he fell off the driver's box on arriving at Dartford and broke his leg. At the end of the epidemic the two ships, the *Atlas* and the *Endymion*, which had been lent by the Admiralty, were purchased. The Board was in a difficult position; the hospitals at Hampstead and Fulham were closed to smallpox, and it seemed that those at Stockwell, Deptford and Homerton were only accepted on sufferance in the neighbourhood in which they were, and at any time in an epidemic might suffer the same fate. Although the Board only had powers for reception and treatment of pauper smallpox cases, it had gradually become the central hospital authority for all cases, and was continuously being cajoled to provide hospital accommodation for patients, nine-tenths of whom were not paupers. Patients were normally admitted by the relieving officer, but during the height of an epidemic they were often admitted without statutory authorization.

Caiger (1924–5) stated that the Board, because of the protection shown to its successfully

revaccinated staff, had urged the more efficient administration of the vaccination law as a means by which the recurrence of epidemics could be prevented, but in practice the vaccination laws only applied to infants, and an increasing proportion of smallpox patients admitted to hospital had been legally vaccinated.

The Royal Commission in 1881 was set up to investigate the peculiar arrangements in London, and the Disease Prevention Metropolis Act of 1883 enabled the admission of any person to any of the Board's hospitals, without it being considered parochial relief. The report of Sir William Power (1884) on the effects of the Fulham hospital on the incidence of the disease in the area surrounding it, and the very general view at the time of the possibility of aerial spread, or at any rate the ill-effects of smallpox hospitals in densely populated areas, led

FIG. 264. *Matron's sitting room on the ships.*

to the idea of placing smallpox hospitals in isolated areas. The hospital ships *Atlas* and *Endymion* were moved seventeen miles down-river to a position off Dartford, at Long Reach, and a third vessel, the *Castalia*, of double-hulled construction, originally designed by Sir Henry Bessemer for the Channel crossing, was purchased and converted into a floating administrative building. Other buildings were provided on land opposite the ships, and the policy was laid down to have a small number of beds for smallpox at the London hospitals for those cases which, on medical grounds, could not be moved to Dartford, and for three reception wharves in London and five hospital steamers or ambulances to transfer the cases to the hospital ships. In 1893, the river ambulances covered 28,000 miles and conveyed over 10,000 patients. At first only convalescent patients or those suffering from relatively mild attacks were moved to the ships, all the admissions coming through one or other of the London hospitals, but in 1884 for the first time certain cases were sent direct from their homes to the wharves, and by 1885 all cases

FIG. 265. Smallpox ward on the ships, about 1900.

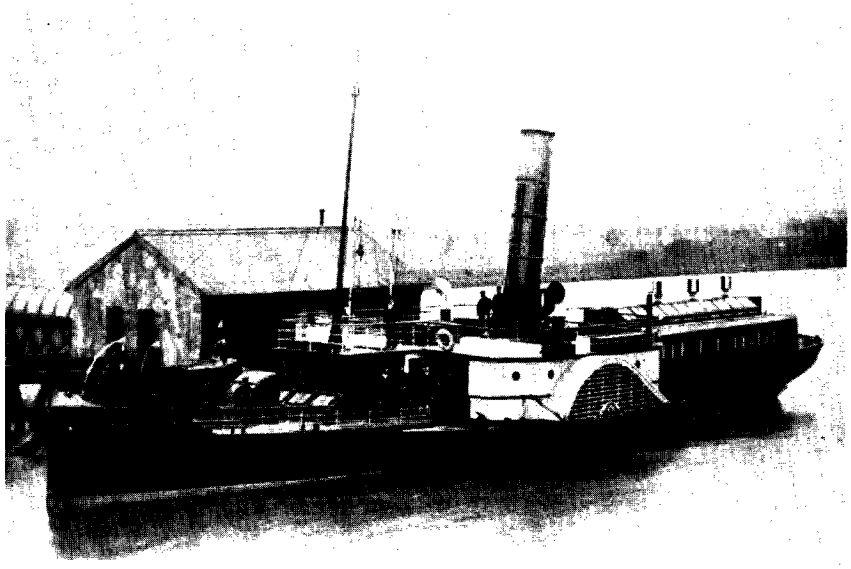


FIG. 266. River ambulance.

were dealt with in this way. The receiving wards at the London hospitals were then discontinued. Convalescent camps at Darenth were again established to take the convalescent patients from the ships during the epidemic of 1884–5, and these were kept until 1890, when a

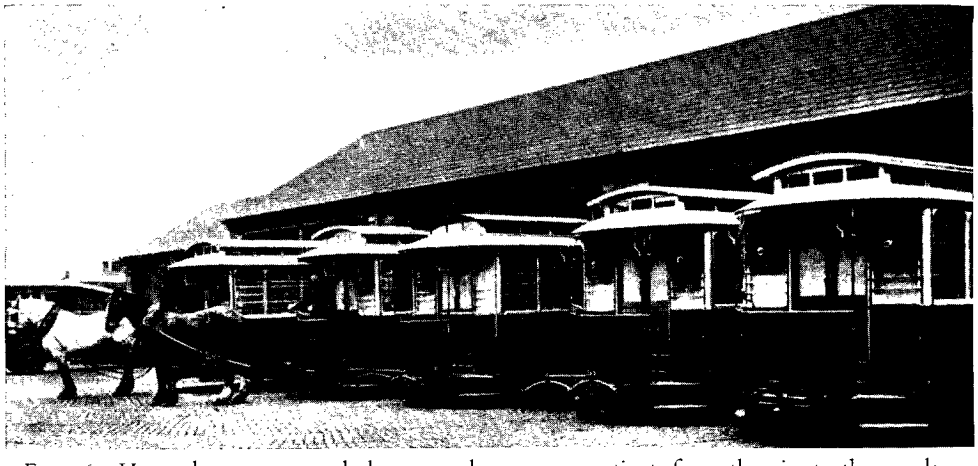


FIG. 267. Horse-drawn tram ambulances used to convey patients from the pier to the wards.

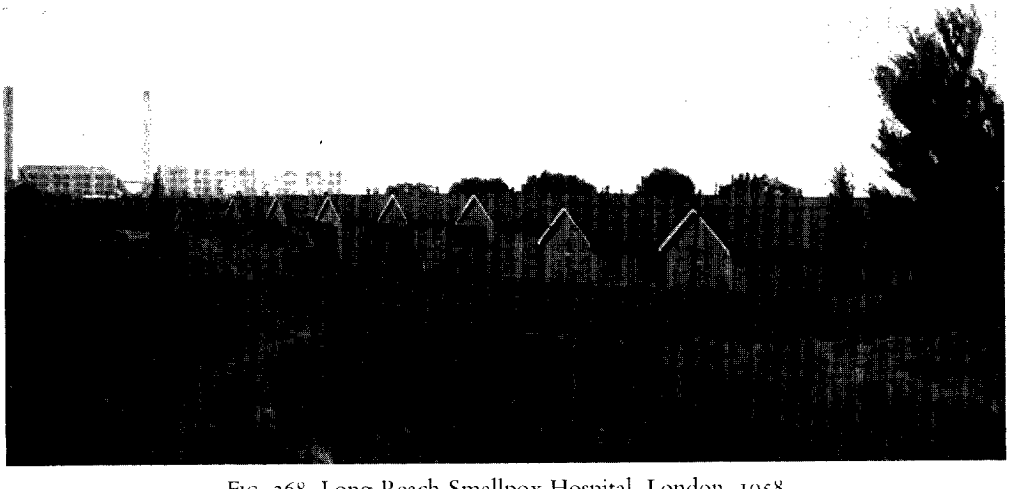


FIG. 268. Long Reach Smallpox Hospital, London, 1958.

hospital of 150 beds was provided, later known as Gore Farm Lower Hospital. A permanent hospital of 600 beds was built, known as Gore Farm Upper Hospital. In 1893–4, there were 300 beds for acute cases in the ships, and 800 for convalescent cases on shore. Eleven hundred beds for smallpox was less than the 2,700 suggested by the Royal Commission. Ten years later a permanent hospital, Joyce Green Hospital, with 940 beds, was opened. In 1901–2, the last great epidemic of variola major occurred in London. A temporary hospital of 300 beds

was erected immediately at Long Reach, and later an additional temporary hospital, the Orchard Hospital of 800 beds, and an extension to 850 at Gore Farm Lower Hospital, bringing the total number of smallpox beds available at one time to about 3,200. Although the epidemic of 1901–2 was a large one, accommodation was not strained, and some was not brought into use at all. The ships (Figs. 262–265), which had been in use for twenty years and had received 20,000 patients, were now considered unsuitable because of their age and the danger of fire, although they were provided with electric light, and in 1904 they were dispensed with. Joyce Green, Long Reach, and Orchard hospitals, having a total of about 2,000 beds, were regarded as the normal accommodation for smallpox for London. The ambulance steamer service still continued, and patients were brought by this to the small pier at Long Reach, and conveyed from there to the ward block by horse ambulances, and later by horse-drawn tramcars (Fig. 267). By 1910 the position was reassessed. The accommodation not being required for smallpox was used for scarlet fever, and these patients were also conveyed to Long Reach by river ambulance. The permanent smallpox accommodation at Long Reach was then reduced to a total of 350 beds. The situation remained much the same until the next test, the handling of variola minor, when between 1928 and 1934 some 13,686 cases were admitted. The situation at present (1961) is that London possesses at Long Reach a complete 50-bed smallpox hospital entirely self-contained, with its own kitchens, laundry, mortuary and ancillary services, and with a small admission section which is continuously staffed with a nurse and porter on a caretaker basis, so that it is always available for the reception of a smallpox patient.

SMALLPOX OBSERVATION UNITS

The problem of having to open the smallpox hospital on a clinical diagnosis often made under difficulties in the patient's home or in a general hospital, and which ultimately proves to be wrong, has impressed on many the value of having observation accommodation for one patient when there is considerable doubt whether the case is smallpox or not. Although this sounds easy, it is surprisingly difficult to provide single-room isolation accommodation clear of other patients, in the ordinary general or fever hospital, and, unless this is so, whenever a patient is admitted as a doubtful smallpox it is necessary to vaccinate nearby patients and staff, and it is difficult to know where to draw the line and allow a reasonable margin of safety. Due to the frequent occurrence of chance infection in persons who have had no known contact with the patient, most hospital administrators are very chary of this procedure. Although it has been advocated for variola minor due to the lesser infectious potential, we cannot tell at once whether the doubtful case is major or minor.

An alternative arrangement is to provide a small house in the grounds of a hospital, well isolated, with one room for the patient, two for the nursing staff, with self-contained kitchen and other facilities sufficient to last independently for five or six days at the most, when the diagnosis should have been established. Personally, I feel there is much to commend in this plan, but if it necessitates new buildings, at a number of general or infectious-disease hospitals, the initial cost and the maintenance has to be balanced against the cost of opening a single small smallpox hospital serving a much larger area.

When the query smallpox case turns out to be a false alarm, everybody is anxious to avoid opening the smallpox unit in the future, but if the query smallpox case has been admitted to a side room or an inadequately isolated part of an infectious or general hospital, and turns

out to be a case of smallpox, many administrative complications arise which could otherwise have been avoided. The medico-legal repercussions of the spread of infection have led many hospital administrators to feel that the *ad hoc* smallpox hospital, even if it is a white elephant for a great many years, may in the long run be the cheapest way. It is obvious that a final decision on these matters can only be taken by those aware of the problems of any particular locality. Apart from the question of buildings, of overwhelming importance is the vaccination state, discipline, loyalty and supervision of the medical, nursing, domestic and ancillary staff.

In some parts of the world, particularly where smallpox is endemic, the smallpox ward is frequently a ward or even part of a ward in a general hospital. The chances of infection being spread from this source are certainly very great, but notification is very incomplete, making it impossible to assess the danger. Although it is often stated that under these circumstances the hospital gives rise to no trouble, I am quite certain that this is almost always an unsatisfactory arrangement. The only circumstance in which I would admit smallpox to a general hospital is to a military one on active service, where one should be fairly certain of a high level of immunity of both patients and staff, but even here cubicle nursing should be practised if possible.

PROVISION OF SMALLPOX HOSPITALS

The smallpox hospital should be sufficiently close to the major population at risk, and in the past this has often been close to a major port. This is likely to be of less value in the future. With the increase in air traffic, patients may be disseminated widely in a country, as they are more likely to enter during the incubation period of the disease. The hospital should be at the centre of road communication for a large area of the country, and if this can be arranged, very few smallpox hospitals are required for quite a densely populated country. This is best expressed not in terms of distances, but in terms of time. Smallpox patients travel well, and with modern, efficient public health departments able to control smallpox by expanding ring vaccination and contact surveillance, it is perfectly practicable to maintain a single smallpox hospital for an area within four to five hours' road journey by modern ambulance. There is no public health danger in taking patients long distances in this way. In countries where smallpox is endemic, or where control of the disease is unlikely to be so effective in the early stages, facilities for hospitalization will need to be more extensive, but it must be emphasized that as far as is practicable money should be spent on public health preventive measures, rather than in assuming that the smallpox hospital will control the disease, particularly when diagnosed late. Road conditions may be bad in the winter months, as occurred during the Brighton outbreak (Cramb, 1951), so that the hospital administrator must also keep in mind the possibility under exceptional circumstances of using alternative accommodation, but it should be emphasized that in those countries in which smallpox is not endemic, but where it may be introduced from time to time, it is essential to plan a hospital arrangement which is primarily economical and reasonably practical, although it has been pointed out that due to the "loathesome, dangerous and disfiguring nature" of the disease, public opinion will sanction more drastic measures and greater expenditure than for ordinary infectious disease.

The siting of a smallpox hospital is more important than most, as it has been found from experience that secondary cases occur when the hospital is closely surrounded by houses. The cause of this spread was the subject of an immense amount of controversy about the end of

the last century, particularly after the opinions were given by Power and others, and the reports of the Royal Commission of 1882 and the Local Government Board reports of 1884 and 1885, that infection was probably conveyed by aerial spread. Hospitals containing a large number of acute cases appeared to give rise to infection in the surrounding population, but not hospitals that were full of convalescent patients, those in the relatively late scabbing stage of the disease. This is a view in keeping with the idea that the smallpox patient discharges the most infectious material during the initial and early eruptive state, and the environment and particularly the clothing is contaminated with respiratory virus, forming invisible infectious dust, rather than the more obvious scabs.

It is surprising how well the evidence of aerial spread could be made to fit certain outbreaks. Smallpox occurred in nearby houses shortly after the admission of early cases, the occurrence of smallpox in the path of the prevailing wind, the experience at Purfleet (Thresh, 1902), with the apparent transfer of infection across the river, a distance of nearly half a mile, from the floating river hospital. When concentric circles were drawn around the hospital on a map at quarter-mile distances, it could frequently be shown that the intensity of infection was progressively less the further away from the hospital. The pattern, however, did not always fit, and Hope (1905), in Liverpool, showed that when a smallpox outbreak occurred in a town, an increased incidence occurred around a hospital if it was not admitting smallpox at all. The idea, however, is by no means dead. In 1946, in the outbreak in Hong Kong, it was thought that the smallpox hospital, situated in the middle of the city, appeared to give rise to secondary cases on the leeward side, and more noticeably on the crests of successive rings of hills. In a recent outbreak in Cheshire, in 1958, a small boy, living 400 yards from the smallpox hospital, was infected, and opinions were expressed by some that this again was an example of aerial spread. It was even suggested that the infection might have been conveyed from the hospital by a cat, doubtless a Cheshire one, but on a critical date the boy had had his hair cut at a barber's shop in close proximity to the smallpox hospital.

It is almost certain that the safeguards against the communication of hospital staff, particularly porters and others, with the outside world, is far less secure than most medical superintendents of smallpox hospitals imagine. It is very unlikely that questioning staff ever brings to light some of the irregularities of practice which have occurred, and which could account for spread of infection. Victorian inflexibility, and the incarceration of nurses in smallpox hospitals for many weeks at a time, is also likely to have encouraged acts contrary to the rules. It is often forgotten that areas around hospitals tend to be populated by the lower social classes who always have a higher incidence of smallpox. The words of McVail (1893) are still apt: "The practical conclusion of this whole question may be said to have already been arrived at. The smallpox hospitals are not now erected in the midst of towns, and those already in existence are being more and more sparingly used. Accidents incident to the system of hospital treatment of smallpox within populous districts must be said to be inevitable, so that the only remedy under the one theory and under the other is the removal of such institutions to a distance from populous places."

Chapin (1910) wrote: "The evidence in favour of aerial transference of smallpox is so slight that it should never influence a municipality in the selection of a hospital site." He was, however, writing during a period of high endemicity of variola minor and many would support him if we were only dealing with this disease. The experience of de Jong (1956) suggests that even variola minor cannot be isolated so easily in an infectious-disease unit of a general hospital.

Most public health officers would feel happier if variola major was nursed as far away as practicable from susceptible people.

The original conditions laid down by the Local Government Board, and continued by the Ministry of Health (England and Wales) are as follows: "First the hospital must not have within a quarter of a mile of it either a hospital, whether for infectious disease or not, or a workhouse or any similar establishment, or a population of as many as 200 persons. The site must not have within half a mile of it as many as 600 persons, whether in institutions or in dwelling houses. A smallpox hospital must not be used at one and the same time for the reception of smallpox and any other disease."

FIG. 269. Aerial spread!

These principles, although laid down so many years ago, are really quite sensible, but they need not be adhered to exactly. In Edinburgh, for example, in 1942 a small number of smallpox cases were successfully nursed in a ward block adjacent to a general fever unit. The distances have no magic properties of their own, and the number of persons are not absolute, but they do indicate that the smaller the number of people in close proximity to the smallpox hospital, the less the risk of anyone being infected, and in particular the greater the chance of keeping them under observation, and seeing that their vaccinial immunity has been properly maintained.

In the United Kingdom, the deeply rooted opposition of the public is not likely to be easily changed, whatever scientific observations are made in the future.

Although we are unlikely to see riots, which once occurred in Stroud, feeling was strong in Bebington, Cheshire in 1958, against the continuance of the smallpox hospital, once very

isolated and now surrounded by houses. The prime mover in the agitation was a retired sanitary inspector.

Public health action is not above criticism. The notice board fixed on a public road in Yorkshire in 1953 (Fig. 269) is not calculated to allay the community's fears of aerial or mystic spread.

SMALLPOX ACCOMMODATION

The ideal arrangement for a first-line smallpox hospital is to have a building providing about eight to ten beds. If in cubicles, possibly six or eight might suffice. If an old building is available, two large rooms or wards, for separation of the sexes, would be satisfactory. Normal sanitary facilities are required, and at least one bathroom. If water supplies are limited, showers would suffice. Quite a large steam disinfector is required, capable of doing bedding and utensils of various kinds, with a "clean" and "dirty" side, and a destructor is necessary for soiled dressings and disposable containers.

A proper mortuary is rather a luxury, although deaths are likely to occur in a first-line unit. A small room in the disinfection block should be available for encoffining the body.

A caretaker's house is essential, with sufficient accommodation adjacent to provide changing-rooms and washing and bathing facilities for visiting staff, ambulance drivers and others leaving the hospital after duty. Sleeping accommodation for two or three nurses can be provided here, but perhaps is better adjacent to the wards, as they can remain "infected" while on duty. If this is difficult to arrange, it is better to keep the number of staff in the unit as small as possible, and let them work long and unorthodox hours, to be recompensed by cash bonuses and leave privileges after the outbreak is over. With particularly reliable staff, it may be safe and practicable for them to be non-resident, living in the nearest parent hospital, preferably with some degree of segregation.

It is better not to have extensive kitchens, laundry or other facilities on this site, as this not only increases overall expense, but increases the number of individuals who will be coming into contact with the first and possibly only cases admitted to the unit. The feeding and laundry services can be provided by a larger institution, separate, and preferably about half a mile away, but there is no difficulty if this institution is considerably further away, provided that suitable containers are available for the transport of cooked food.

The first-line smallpox unit is normally not staffed, but should be kept in a state of preparedness by the resident caretaker, so that it can be opened at approximately three hours' notice. It should be surrounded by an unclimbable fence at least six or seven feet high, and a gate that can be locked so that unauthorized persons cannot enter. The provision of good fencing is very costly today, unless of the steel link type. This degree of security to exclude unwanted visitors and the unauthorized discharge of patients may appear rather extraordinary in this modern age, but the absconding smallpox patient is quite a problem in some countries. Delirious patients have been known to run out of hospital and give rise to infection in houses they have gone to. In spite of the character of the disease, it is surprising how people will attempt to get in touch with patients. It cannot be overemphasized that the purpose of the smallpox hospital is to retain infection, and to avoid at all costs the introduction of non-immune persons.

Where the primary unit is far away from the other hospital, and the parent hospital is only capable of supplying cooking and laundry facilities and not additional beds, it is obviously

advisable to have sufficient land alongside the first-line unit for the erection of temporary buildings should these be required. Today, with such advances in the design of temporary buildings it should be practicable to erect these at very short notice, and use them subsequently for other purposes. In countries where these are not obtainable, tented wards may be used. If these are placed on previously prepared concrete or asphalt foundations, they can be quite satisfactory in practice. Schools and factories or even aerodrome hangars, such as used in Gloucester in 1923, can be adapted in an emergency (Fig. 270). Temporary cooking, laundry and disinfecting facilities can be provided from civilian or army sources.

The diagram in Fig. 271 gives the principles which should be followed in controlling infection in a small primary smallpox unit. It is purely diagrammatic, as in most instances some available accommodation will be adapted as cheaply as possible.

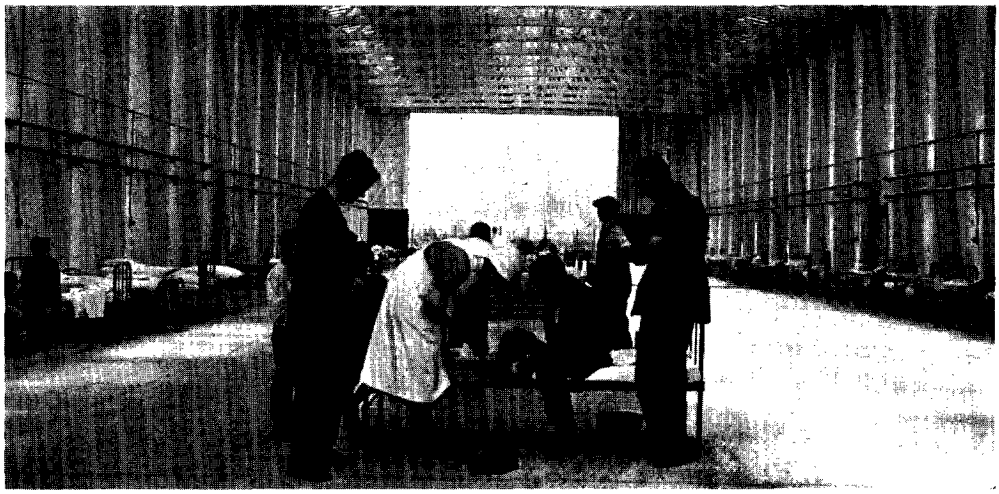


FIG. 270. Temporary smallpox hospital in an aeroplane hangar at Gloucester, 1923.

FACILITIES: WARD DESIGN

Cubicles are ideal for all patients, but it is particularly desirable to have at least one side room for the very severe case that will die. Heating and lighting should be adequate by ordinary hospital standards. Good ventilation is necessary as the smell of the smallpox patients can be quite offensive. In the early days great attention was paid to sterilizing the air from smallpox hospitals (Barry, 1893), but this is quite unnecessary, although virus can be detected in the dust from wards, and doubtless can get blown small distances from the hospital. Patients are usually not allowed to send out letters, because of the difficulties of disinfecting them, and it is better to have a telephone available in or near the ward, so that patients may speak to their relatives. There is a lot to be said for having at least one telephone on a long extension lead, so that this can be taken to the bedside of patients who are seriously ill, and this may obviate visiting. As already mentioned in the chapter on treatment, many of the patients will be feeling quite well, although they will be kept in hospital for at least four weeks, until all scabs have disappeared. It is necessary to keep them amused, and radio and television sets are a very great help in keeping the patient in contact with the outside world. Card games and

occupational therapy like rug-making are also very useful, as the rugs made can be easily steam disinfected subsequently.

It is obviously undesirable for waste water from baths or showers to be discharged untreated into streams, particularly as in some countries these may be used for drinking or washing, but

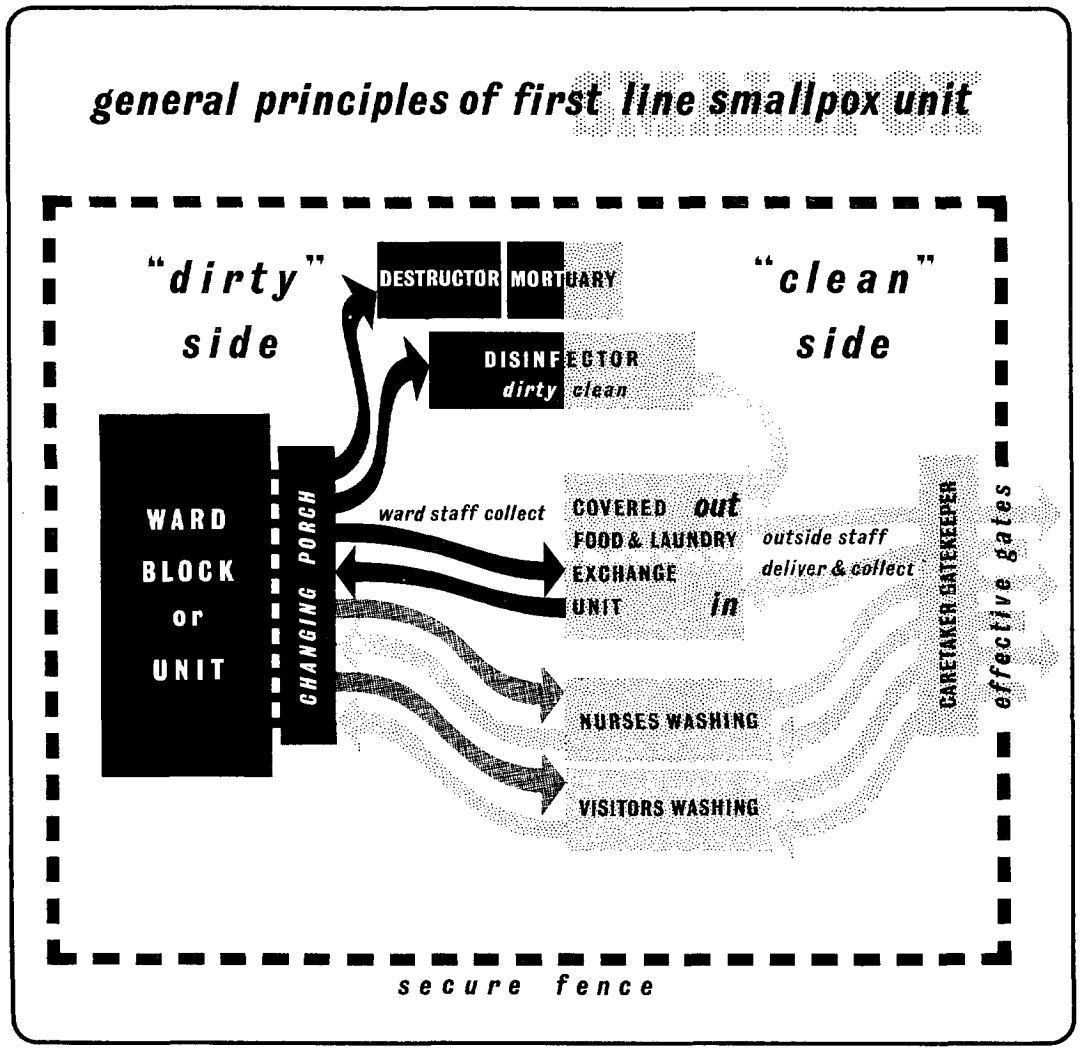


FIG. 271. Principles of smallpox hospital design for a simple immediate unit of 6–12 beds, dependent on major hospital for food and laundry services.

there would be no danger to public health from the admission of this kind of effluent into public sewers, where adequate sewage purification occurs. Although Bradford Fever Hospital in 1892 disinfected the sewage from its smallpox pavilion, I am not aware that any laboratory work has been done to confirm or refute the possibility of smallpox virus being present in sewage effluent.

In countries where flies are a nuisance, complete fly-proofing of windows and doors is essential, as there is a very real possibility of the transfer of virus picked up by these insects from the skin or clothing of a patient, and transferred to the nares or the conjunctiva of others. The discharge of bathwater into streams might also allow mechanical transfer of the virus, if these are also fly-breeding areas.

STAFF DUTIES

In the past it has frequently been the practice to call for volunteer nurses, and incarcerate them in the smallpox hospital for many weeks, sometimes months, until the last case has been treated, when they are then set free. Clark (1944) stated that in Edinburgh picked nursing staff remained in the smallpox unit for the whole time from October to the middle of December. In contrast to this, medical staff and visitors frequently come to smallpox hospitals, and after wearing a small amount of protective clothing, go on their way without any very vigorous disinfection procedure. It might be argued that what is satisfactory for the doctors in visiting should also be satisfactory for the nurse, but in practice this is not always so. Zur (1948) related how nursing and other staff in an American hospital in Germany were allowed to go home each day, and this gave rise to secondary cases amongst their relatives. So much depends on the type of supervision and the standard of nursing staff. Although today it would seem unnecessary and undesirable to attempt to keep nursing staff incarcerated in the smallpox unit for long periods of time, the long period in contact with smallpox patients, in contrast to the relatively short time of visitors, particularly of medical visitors, does make the chance of their carrying virus on their skin somewhat greater, but one would think that a bath, washing of the hair and a complete change of clothing is sufficient. Due to the undesirable effects, particularly on permanently waved hair, of repeated washing under somewhat difficult circumstances, it may be preferable for the nursing staff to remain in the smallpox hospital, possibly three to four days at a time, working longer hours than normal and then taking cumulative time off at the end of this period. It is most important for the medical officer in charge to thoroughly explain to all his staff, nursing, domestic and other, the mode of infection in smallpox, and the possibility of chance infection being carried from the hospital. In the past the policy of incarceration of nursing staff has encouraged the violation of the rules. Even the most ardent volunteer nurse in a smallpox hospital will cool off after some two to three weeks of seeing just the same ward.

In the case of the doctor visitors, their wives and families and immediate close contacts are nearly always vaccinated when an outbreak occurs, but the relatives and friends of the nursing staff are much less likely to be, and therefore may form a path for the transfer of infection from the hospital. As it is possible that virus can be passively carried in the nose or throat, which we cannot disinfect before leaving hospital, continuity in our barrier of immunes should be ensured by arranging for the vaccination of close friends or relatives of nurses before visiting occurs. The final policy on this matter is best decided by the hospital medical officer in charge of smallpox, after close consultation with the medical officer of health or medical officers of health of the areas in which the nurses are likely to go when off duty.

CLOTHING

The staff on duty can wear clothing and footwear appropriate to infectious disease nursing. All clothing is removed for disinfection when bathing before leaving hospital, and footwear can be

left on the "dirty" side of the change-room. In the case of medical staff who may not be resident, and visitors who require entrance, the problem of clothing is slightly more complicated. A room should be set aside for visitors to change their clothing, and this is best attached to the porter's lodge at the entrance.

Outer clothing should be removed and ordinary hospital-type gowns, closely fitting to the neck and done up down the back, are suitable to cover the ordinary everyday clothing. There seems to be some difference of opinion over the advisability or not of wearing Wellington boots, so as to avoid contaminating the shoes, which might pick up infected dust, although how long they would remain infectious is another matter. The smallpox virus can undoubtedly be recovered from the floor of smallpox wards and it would therefore seem advisable for visitors to wear Wellington boots, although it should be noted that these are normally returned to the robing room and are not disinfected before being used again. In general it is rather impracticable to have a sufficient supply of these to provide a clean pair for every visitor. If the visitor thoroughly washes his hands after removing the boots the danger would appear to be extremely small.

The question of headgear is also another controversial point. The normal staff will wear any appropriate headgear, although in the case of females this will not cover the hair, but in any case this will be washed before they leave the hospital. It is particularly desirable that the staff can appear as attractive as possible, as this is some small stimulus to the patients. In the case of visitors, there is considerable variation in practice; in some smallpox hospitals small circular hats, similar to those used in operating theatres, are worn, perched somewhat precariously on the visitor's head, and are obviously inadequate protection from dust settling in the hair, but the danger from this is likely to be small and impossible to assess. The alternative is to cover the visitor with an all-over hat and mask, just leaving the eyes peering through a slit, which is somewhat unnerving to the already very apprehensive patient. The wearing of separate masks seems undesirable, as they are notoriously inefficient in preventing infection. In some hospitals, nurses wear rubber gloves but this is quite unnecessary and suggests that the patients are unclean.

The intelligent visitor to a smallpox hospital makes sure that his own family and close contacts are themselves protected by recent vaccination or revaccination. Examination of the records of a number of outbreaks suggests that cases of mysterious origin in other hospitals, or sometimes in bedridden patients in their homes, may really be due to the careless doctor. Pyrexial attacks, or even a few spots in such professional contacts, are not likely to be admitted. As smallpox is a rarity, it is most desirable to allow as many doctors as possible to see cases, particularly medical officers of health and others directly concerned. It would, however, seem that medical visitors are sometimes too casual in their attitude to this problem.

The procedure for visitors should be as follows, but it must be remembered that it is the public health, not the hospital, authority which is primarily concerned with preventing the transfer of infection to the community, and the conditions of admission and protective and disinfective procedures should be approved by the local medical officer of health.

Only those should be admitted who have been successfully vaccinated or revaccinated to the satisfaction of the doctor in charge of the unit. He should have complete authority to demand the revaccination on the spot of any person about whom he has the slightest doubt, or to refuse admission. On entering the lodge the visitor should remove the outer clothing and any headgear and shoes, and put on the gown, Wellington boots and hat provided. He

can then walk out of the lodge across to the smallpox ward, enter and examine the patients and carry out any other duties. On leaving the smallpox unit he will remove his gown and headgear, and these can be placed in a suitable receptacle in the ward porch. The Wellington boots can be removed here and these can be cleaned with antiseptic solution. The visitor may put on his shoes, which he has previously deposited on the outdoor step, but in practice there seems little disadvantage in his walking back to the porter's lodge in the boots, to be removed and kept there. In a small smallpox unit it is probably better to cut down on the number of staff to the barest minimum, which means that labour will not be available for continually rewashing the boots, than to increase the number of staff, and run into a number of administrative and practical difficulties because of this. On arrival at the changing-room, the visitor can remove the Wellington boots, put them in a corner, thoroughly wash his hands, face and, if necessary, his hair, although the latter is rarely done, and he is then fit to leave the hospital and be no danger to his immediate contacts. It does not seem possible to devise an absolutely infallible system, and it is important to appreciate that a reasonable compromise has to be evolved. Minor variations can undoubtedly be made to suit local circumstances, and it is important to appreciate that with the ordinary casual visitor who is only in the smallpox ward for a short time, the chance of picking up appreciable quantities of virus is small, and probably that on the mucous membrane of the respiratory tract is the most dangerous, and yet we cannot effect any control over this. It is for this reason that more reliance should be placed on the immunity state of the immediate, particularly family, contacts of visitors to a smallpox hospital. The principal visitors are likely to be doctors, administrative officers of one kind or another, tradesmen for repairs and ministers of the Church. The medical officer in charge should co-operate, through the medical officers of health, so that the families of any of these visitors can be satisfactorily vaccinated or revaccinated, preferably *before* the visit is made.

VISITORS TO PATIENTS

Visitors to patients in smallpox hospitals are discouraged, and often prohibited, even to patients who are dying. This seems a hard restriction, as obviously the relatives could carry out the procedure which was suitable for doctor visitors, and their immunity state as contacts would doubtless have already been dealt with. On the other hand, the condition of the patient is often so frightening to those not used to smallpox, that perhaps it is really more humane to deny them access, or at any rate to go to considerable length to discourage them. It is obviously desirable for mothers to visit young children, although by far the best scheme is to admit them with the child.

Apart from the adverse psychological effect of visiting, it should be pointed out that in most parts of the world the general public strongly support no visiting of smallpox and are likely to ostracize relatives of smallpox patients if it is known that they visit them. Weighing up the problem as a whole, I think it is preferable to have no visiting in smallpox hospitals, and to make provision by long-lead telephones for patients to keep in contact with their relatives as much as possible.

Normally nothing leaves the smallpox hospital that has not been disinfected. An exception is pathological specimens. Instructions for the collection and despatch of these is given in Chapter 4.

ADMISSION AND DISCHARGE OF PATIENTS

In most countries the admission of smallpox patients to hospital will rest with the medical officer of health, as he is concerned with confirmation of diagnosis and the necessity of the patient being admitted to some special place of isolation. What is very important is to emphasize to hospital medical officers the great importance of bringing in the medical officer of health to see a case already in a general hospital if there is the slightest suspicion that it could be smallpox.

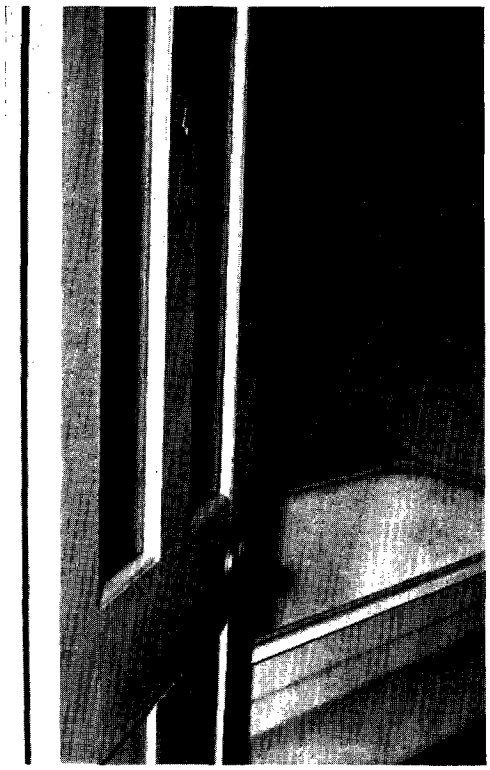


FIG. 272. Bathroom for disinfection of patients or staff. Bath is fixed across the room, dividing it into "clean" and infected sides with separate doors on each side.

Of considerable importance is also the discharge of patients from a smallpox hospital or isolation accommodation in a general hospital. No patient, convalescent, smallpox contact or unconfirmed case should be discharged without the concurrence of the medical officer of health of the area in which the person lives. Failure to do this may result in patients being sent home quite unprepared for the reception they may well have at the hands of their neighbours, and also without even the normal necessities of life. The outbreak in Todmorden in 1953 demonstrated how patients discharged from hospital could be ostracized and they may require a fair amount of welfare attention from the medical officer of health and his staff. Where an unconfirmed case has been discharged after a few days, although other contacts in the area may still be under surveillance, it is important that the medical officer of health informs the neighbours and the press that the person is entirely free from infection.

Prior to discharge from the smallpox hospital, patients are given a complete bath, including washing the hair, and dress on the clean side of the bathroom in clothing which has been brought from an uninfected home (Fig. 272).

DISINFECTION OF AMBULANCES

Ambulances will normally be disinfected at the smallpox hospital, and this may be done by one of two methods suggested by the Ministry of Health, England and Wales, namely (*a*) the use of a spray consisting of 2½ lb. carbolic soap, 1½ pints white cyllin and 2½ gallons water; or (*b*) by the formalin solution method, using 2 ounces formalin to 1 gallon water, and leave sealed for one hour. The ambulance crews will normally carry out this work and subsequently will bath and put on clean clothing kept in the smallpox hospital lodge ready for this purpose. The whole procedure takes about two and a half hours. Although the ambulance has been disinfected, it is normally better practice during an outbreak to keep one ambulance and sufficient well-vaccinated crews for this work only. If the area covers a number of ambulance authorities, arrangements can usually be made for only one to carry out this service, the other authorities paying for it at an agreed rate.

It has already been mentioned that a proper mortuary is probably somewhat extravagant for a small 10–12-bed smallpox hospital, although deaths are likely to occur there. Viewing the body is usually not permitted and this spares the relatives a very harrowing experience, although in a new mortuary recently provided at Long Reach, Dartford, the accommodation is most elaborate, and includes facilities for viewing the body through a glass screen. The scientific need for post-mortem examination is, however, very great, to give opportunity for modern pathological techniques to be applied, but there seems no reason why these cannot be done under somewhat improvised conditions without the risk of spread of infection.

PROCEDURE ON OPENING SMALLPOX HOSPITAL

Immediately a case of smallpox is diagnosed, the hospital authority's senior medical administrator must be informed, and he must give instructions for the immediate or first-line smallpox unit to be opened. The person to communicate with first is the caretaker of the hospital. In spite of the expense, it is important that telephone communication is maintained at the caretaker's house of the immediate smallpox unit. It should be part of his terms of contract that he must at all times leave a suitable message of his whereabouts at the secondary hospital. This is one of the difficult matters to enforce, as it may not be required for many years. Unfortunately only too often by the chance of fate the first case of smallpox is diagnosed at a weekend, when in many countries the public health and hospital services are not their most efficient. The caretaker must open up the wards, and turn on the heating if required, which in the case of a small unit is preferably by electricity. The next step is to inform the medical officer who is directly responsible for running the hospital clinically and, even more important, for the security of the smallpox unit. A suitable person should be nominated from year to year, and he should make it his responsibility to inspect all facilities from time to time so that he knows what is expected of him. Often, when a unit of this type is opened, it is discovered that some sanitary facilities are inoperative, and repairs are required, or telephones require maintenance. All kinds of artisans appear on the scene, and unless recently revaccinated may greatly increase the chance of disseminating infection and of bringing repercussions on the hospital authority.

Smallpox units must really be in isolation from the moment patients are admitted. Security must be maintained, and in an antibiotic age the old ritual of control of infection worked out in the infectious-disease hospitals is having to be learned all over again. Unless one medical officer is made responsible for the security, loopholes of all kinds will appear. It should be made an absolute rule that no person, whatever his rank, should be allowed into the smallpox hospital without a written consent given by the one medical officer who has been appointed in charge. In this way the responsibility is completely fixed. This written authority must be shown to the gatekeeper who would not otherwise allow entry to the hospital. All persons other than patients should sign the visiting book kept in the entrance lodge every time they enter. It is important to see that the gatekeeper is competent for this job, and this may be difficult as he will probably have been the caretaker for many years without his services being required. It may be worthwhile to draft in an intelligent young clerk from the health department or hospital authority to take over these duties.

The nursing officer, or other person whose concern is the nursing staff, should call on the nurses who are for smallpox duty, whose immunity has been specially maintained, and they

should report straight to the hospital. The number of staff required for the first patient will be very small, but should put into effect a well-organized plan which has been thought out beforehand and has even been rehearsed by the admission on occasion of a doubtful chickenpox or some other disease. It is the practice of Marsden at the River Hospital at Long Reach to keep his staff constantly prepared and trained by this method and there is a great deal to be said for it. Mistakes made in the administration of a smallpox hospital may be extremely costly, politically, economically and in human life. Whatever their vaccination record all personnel should be revaccinated—three insertions—on arrival at the gatekeeper's lodge.

When the immediate unit is open, there is time to consider the next move. It is vitally important that there is close liaison with the medical officer of health if he is employed by a different authority, and it is important, as is discussed in greater detail later, that the hospital medical officer busies himself with the treatment of patients and rigid control of infection and leaves the contact with the press and with the public to the medical officer of health of the district in which the smallpox cases are occurring.

Smallpox spreads in an orderly manner, and a competent medical officer of health should be able to predict to some extent when the next cases will occur, so that the hospital authority can plan ahead if and when the second-line unit will be required. In this way the secondary unit can, if necessary, be evacuated and prepared with the minimum of inconvenience. Where medical services are not well organized, where there is ineffective notification or co-operation from the local population, then it will often be necessary to plan ahead accordingly. The secondary smallpox hospital can be any 50–100-bed unit, preferably the parent hospital of the first-line unit, normally handling tuberculosis, chronic sick or other class of patients who can be sent home or transferred to other hospitals at a few days' notice. It should preferably be in some fairly isolated position and provide complete accommodation for patients and staff under conditions of maximum security.

COST OF SMALLPOX HOSPITAL

It is difficult to get the actual cost of smallpox hospitals because conditions vary so much. Williamson (1953) states that at the smallpox hospital at Oakwell, both the immediate unit and the geriatric unit subsequently taken over, cost £3,850, or £5 16*s*. 4*d*. per patient per day. However, after the last patient was discharged a considerable time was taken in disinfecting the hospital and the total cost until reinstated for its previous geriatric purpose was £5,730, or a cost of £8 13*s*. 1*d*. per patient per day. The average patient therefore costs about £280 to treat. This does not include the cost of painting and other works which might be undertaken in reinstating the unit. On the other hand, some of this might have been required for routine maintenance purposes.

When smallpox occurs in a general hospital, or if a hospital has to be cleared of other patients for this purpose, the loss of the use of many beds for general purposes may be the equivalent of quite a large sum. In Halifax this was about £2,500 (Eastwood, 1955).

SMALLPOX IN A GENERAL HOSPITAL

In those countries with efficient welfare medical services, there is an increasing tendency for acutely ill patients to be admitted to hospital, with the result that the diagnosis of smallpox is

more likely to be first made in a patient admitted to a general or fever hospital. This has occurred in many outbreaks in Britain and France in the last twenty years.

Eastwood (1955) describes in some detail his experiences in handling the administrative problems after smallpox had been introduced into a general ward, and I am reproducing much of his paper on this subject, as it illustrates how difficulties arose and were overcome. I have made comments (in brackets), some appreciated by Eastwood himself. It is easy to be wise after the event, and some of the "mistakes" were on the safe side.

On 12 March 1953, a patient was admitted to the Halifax General Hospital at 10.05 with

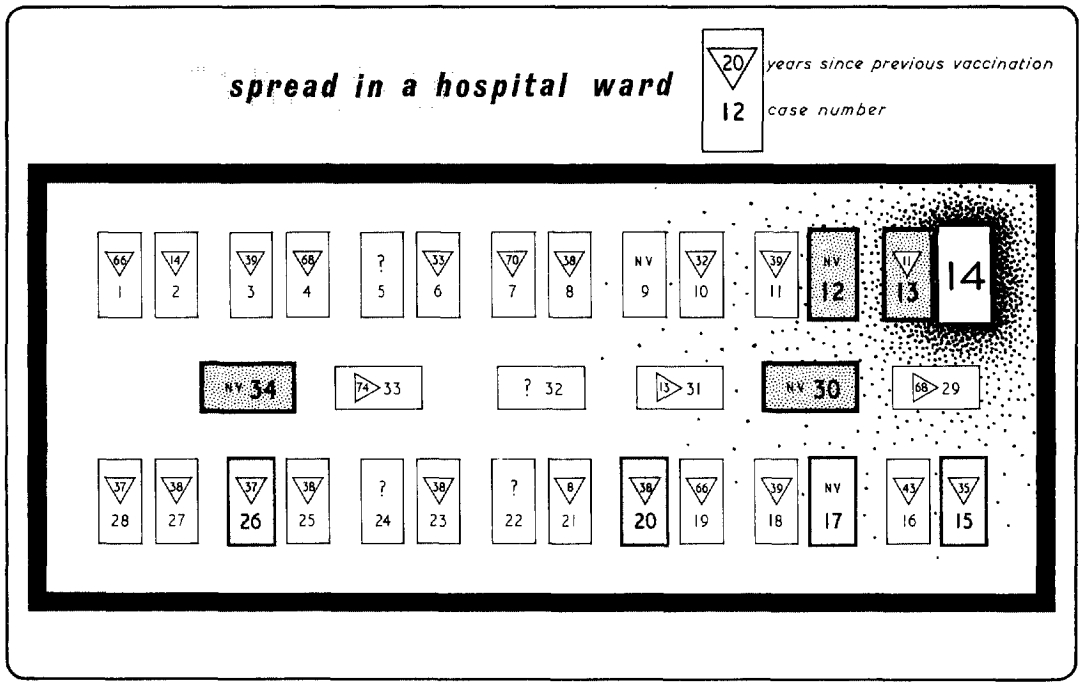


FIG. 273. Infected ward in the Halifax Hospital.
14: smallpox patient admitted as generalised herpes simplex. All patients vaccinated after contact.
12, 13, 30, 34 contracted smallpox. 15, 17, 20, 26 had pyrexial attacks within 14 days of contact.

a diagnosis of generalized herpes simplex. He had been seen the previous day in his home by a consultant dermatologist at the request of a general practitioner. On admission the patient was put to bed in bed 14, at the far end of the ward [see Fig. 273] by two nurses. Four other members of the ward staff assisted in the general work, and two other nurses assisted the medical staff at a later examination. A boy (bed 17) fetched the patient an orange drink and handed it to him. During the afternoon I saw this patient and was able to diagnose with confidence benign confluent smallpox. The medical officer of health for the area was informed. "All traffic to and from the ward was immediately controlled. All personnel were listed and instructed to remain in the ward. Other members of the nursing staff on duty during the day were sought and requested to report for vaccination. A supply of vaccine was obtained and warning given to the laboratory that a further supply might be required. With the exception

of the obstetric unit, which was the major unit for the area, no further emergency cases were admitted to the hospital.

"The smallpox case was removed to the smallpox hospital at 6.15 on the day of admission, by which time he had been in the ward for eight hours and ten minutes. After being placed on a stretcher by the matron and assistant matron, who wore caps, gowns and masks, he was wheeled through the ward to the waiting ambulance staff, and conveyed down the lift to the basement, then through a side entrance to the ambulance. The mattress, mackintosh sheet and cover from the bed were rolled up and dispatched by a reliable and frequently vaccinated porter to be burnt. [Not necessary, as sterilization would be effective.] Bed curtains and screen covers around the bed, caps, masks and gowns, together with towels used by the staff, were placed in bags in preparation for autoclaving. [These articles should be placed "gently" on the bedding and thoroughly sprayed with water to reduce dust, placed in containers at the bedside and removed.] This material was conveyed down the fire escape from the ward into the hospital grounds. A spoon and urinal used by the patient were boiled for an hour, and then destroyed. [The latter procedure is unnecessary, as they were boiled.] The bedstead, locker and screen frames were washed down with strong lysol solution. A cloakroom was set up at the entrance to the ward, and all staff removed coats or caps and aprons before passing into a second room to put on caps, masks and gowns. On leaving the ward, these were put into a special container, the hands then being washed in Dettol solution.

"The vaccinial histories of the patients in the ward were recorded. Information regarding possible contacts was sought, particular attention being paid to those members of the ambulance and hospital staff who had attended to the patient prior to his admission into the ward. The situation was then explained to all patients. They were told that they would shortly be offered vaccination, being strongly advised to accept it, both for their own sakes and for that of others. All patients in the ward agreed to vaccination. It was pointed out that vaccination following exposure to smallpox might not prevent the disease but would certainly modify its course, and result in a milder attack. Vaccination of patients and staff in Ward 12, the affected ward, was commenced and completed by late evening the same day. A single linear scratch insertion was made on the left upper arm, and when dry this was covered with a plain gauze dressing. [Three insertions would have been a better procedure, and there was no need for any dressing.]

"Thirty-three patients in the ward were directly exposed to the risk of smallpox, in a hospital containing in all some 330 adults and 89 children, and giving full out-patient services. The procedure to be followed was discussed with the medical officer of health, and it was resolved to attempt to localize the infection to Ward 12, and retain the inmates for the normal period of observation. A barrier and notice forbidding entry of unauthorized persons was placed at the ward entrance. Food was sent in marked containers to the lift landing, prior to it being conveyed by the ward staff there to the kitchen. Vessels containing bulk food were washed after use. Facilities for the sterilization of such large vessels were not available on the ward. They were then returned to the lift landing for collection. In the hospital kitchen these containers [potentially infectious] were kept separate from those used by the remainder of the hospital. [The hospital kitchen was running some small risk from washed and not sterilized returns. In St. Ann's, Tottenham (Hogben *et al.*, 1958), disposable food containers were used and nothing sent back to the kitchen.] Refuse, soiled dressings and similar material was not allowed to accumulate, but was conveyed down the fire escape to the grounds and burnt daily.

Soiled linen was placed in bags and conveyed by the same route for autoclaving, after which it was dispatched to the hospital laundry in the normal fashion. Returned mattresses and pillows were handled as far as the lift landing, and there left till dealt with by the linen checkers. The transport of this material was the responsibility of a reliable porter who had been successfully vaccinated on the second day of the outbreak. [No guarantee he would not be infected—illustrates the need for staff to be vaccinated *before* an outbreak.] Dressings and medicines were sent up to the ward as required. Returnable containers were placed in a bowl and sterilized. With the exception of patients' correspondence, which was placed in a sealed tin and exposed to strong formalin vapour for twelve hours [Penetration of the envelope would probably not occur], no documents were allowed to leave the ward. Paper money was sterilized in a similar manner to letters, coins were immersed in a strong lysol solution for twelve hours [see Chapter on disinfection].

"It was recognized that boredom would be one of the main obstacles to maintaining an effective voluntary quarantine. Extra packs of cards, games, books, a piano and other amenities were obtained. Owing to the very short notice in which quarantine had been put into operation, some patients became short of money and a temporary loan was arranged to tide them over this difficulty. In the normal course of events some of the patients in the ward would have been discharged; as a result of their staying in hospital, several of them were in difficulty over loss of national insurance benefit. The local office of the Ministry of National Insurance acted with commendable speed and dispatched a supply of certificates. Completion of the certificates ensured that the patient would not lose benefit by voluntarily submitting to isolation.

"Every effort was made to ensure the maintenance of a good ward spirit. Authoritative information on the progress of the outbreak was given each evening by the epidemic officer or some other member of the medical staff. Difficulties of a personal nature arising as a result of the quarantine were dealt with. In one case only was the quarantine broken, and this was by an extremely difficult patient, who despite the advice of the medical staff and against the wishes of his family insisted on being discharged. [A television set would have been an additional amenity, and the use of a long telephone lead extension would be of value in maintaining contact with patients' relatives or even their business interests. In many countries, but not England and Wales, legal powers exist for retaining such a contact who could be a considerable danger.]

"The control-of-infection committee, consisting of senior medical and nursing staff and the medical officer of health, considered the best way of dealing and implementing control. It was not considered necessary to apply strict isolation measures to any other ward. Hospital visiting was curtailed, but on the whole the routine in the remainder of the wards was altered as little as possible. The public were informed of the restrictions through the local press, and medical practitioners by circular letter. Relatives of the dangerously ill were admitted to the hospital on the production of a note signed by the ward sister. Before being admitted to the ward, they were offered vaccination. If they accepted, it was carried out at once, and they were then escorted by a porter to the ward required. No difficulty was met as a result of relatives refusing vaccination.

"Each patient in the hospital was given a form requesting the name and address of any person who had visited them on 12 March, the day the smallpox patient was admitted. This was to enable the medical officer of health to keep such persons under supervision and advise

their vaccination. On the whole, visitors co-operated wholeheartedly, but some difficulty was met in persuading the relatives of certain private patients that the regulations were intended to apply throughout the whole hospital. It was decided that it was the duty of the medical officer of health, or his deputy, to keep the press informed of progress. All matters of publicity relating to the hospital or the communal spread of infection were referred to him. The hospital staff were requested to refer inquiries directly to him and not be drawn into making statements. The local press co-operated readily and were most helpful in giving publicity to official announcements. The national press, with one or two exceptions, continued to block the telephone lines to the hospitals with leading questions. [It is desirable in the first press release of the medical officer of health to state that no information will be given to the press by the hospital.] Lectures were given by the medical officer of health to the staff on the diagnosis of smallpox and the various aspects of vaccination. Bulletins signed by him were displayed in prominent positions throughout the hospital. In circumstances such as this an authentic source of information should always be readily available. It was found that non-resident nurses were suffering embarrassment when travelling in identifiable outdoor uniform to the hospital on public transport. Permission was granted for them to travel in civilian clothes, and a special cloakroom was provided to enable them to change prior to going on duty. If any member of the staff had to be suspended from duty as a result of the outbreak, he or she received full pay during the period of suspension. This rule was applied in the case of a number of cadet nurses, and also the male orderly, the latter being removed to isolation as a suspect case. One member of the kitchen staff was suspended as a result of his refusal to submit to vaccination, and was transferred to other duties at another hospital in the group. To prevent apprehension on the part of the clerical staff employed at the local offices of the Ministry of National Insurance and the G.P.O., certificates and all letters from the hospital were dispatched in bulk, after having been exposed to formalin vapour overnight. Certain members of the clergy attended the hospital and were vaccinated. A list of these priests was available, should their services be required. They were admitted to any ward in the hospital. In the isolation ward the priests observed the same precautions as the medical staff.

"A careful check was kept on the employees of outside undertakings, for example local gas and water board men, employed on work within the hospital grounds. Each was approached and offered vaccination. If evidence of recent successful vaccination could not be produced, and vaccination was refused, then the person was not allowed to continue working at the hospital. It is this group of personnel that are most readily forgotten. [It would be better if all outside workmen reported to the secretary's or steward's office before commencing any new work, firms engaged being notified of this.]

"Many members of the auxiliary staff had already arranged their holidays, some having laid down a deposit. Advice was sought from the epidemic officer on his daily round as to whether the holiday should be cancelled. Each case was considered on its merit. In the case of successfully vaccinated persons rating as Class 3 contacts there could be little danger. Class 1 and 2 contacts were, however, advised to remain under supervision. So far as could be determined no financial loss was suffered as a result of these instructions."

Eastwood rightly stresses the importance of co-operation at all stages. The senior administrative medical officer of the regional board has the important duty of giving the medical officers at hospitals in the region up to date in information concerning the progress of the outbreak. This can be usually achieved by the issue of regional memoranda to every hospital

in the area. This does much to allay rumour as to the progress of infection. The medical officer of health, however, has the primary responsibility for the protection of the public against the spread of infection, but he cannot be expected to carry out executive action within the hospital. It is for this purpose that the general hospital must have an epidemic medical officer working through a "control-of-infection committee". Eastwood enumerated his duties as follows: (1) to carry out close liaison between the hospital and the M.O.H.; (2) to see the M.O.H. daily and report the state of the hospital; (3) to ensure that the M.O.H.'s recommendations are carried out; (4) to examine all suspect cases in the hospital; (5) examination and treatment of cases admitted to isolation accommodation or observation; (6) the daily checking of all resident and non-resident hospital personnel; (7) to provide immediate advice on matters of current difficulty.

The daily examination of patients in the wards was carried out by the medical officer normally in charge of the ward, but all patients with a pyrexia had to be reported to the epidemic officer. The organization of vaccinations was carried out in conjunction with the matron and the hospital resident staff. The vaccination procedure was of interest. Eastwood states:

"On the 13th of March, on the advice of the M.O.H., it was decided to vaccinate all medical nursing and auxiliary staff and patients in the remaining wards of the hospital. It was felt that the situation warranted no exceptions on account of age or illness. Because of the urgency and the number of patients involved, each medical officer carried out vaccination in those wards in which he was normally responsible. This led to difference in both technique and interpretation of results, and greatly reduced the value of conclusions drawn from a consideration of the vaccination records. Cases considered to show a negative result were revaccinated, using a different batch of vaccine. [Under the circumstances the most unlikely cause of failure.] Name, age, technique of vaccination, whether primary or repeat vaccination and the result were recorded and were later transferred on to cards supplied by the local authority. Letters were sent on March 14 to the parents of all minors receiving treatment in the hospital. [Reply-paid telegrams should have been sent on the 12th, to avoid delay.] They were informed of the situation and were requested to state as soon as possible whether or not they wished their child to be vaccinated. They were strongly advised to agree to vaccination being carried out. No parent withheld permission. [With less than 500 vaccinations to be performed, it would obviously have been better policy for these to be done by one or two medical officers, who were specially interested in vaccination. In many countries the question of permission to vaccinate minors under these circumstances would have been glossed over. No information is given as to how much delay occurred before all the requests were received. If a secondary case of smallpox had occurred in one of these wards, vaccination might well have been dangerously late. Eastwood states that supplies of vaccine were ordered greatly in excess of actual need. Vaccine was obtained in batches of 500 or 1,000 doses, far more than would be required.]

"All patients and staff in Ward 12, the infected ward, were regarded as Class 1 contacts, and, as such, subject to close supervision during the relevant period. The patients were visited twice daily, inquiries made regarding headache, backache or malaise. Arms, hands and face were examined for signs of a rash. Temperatures were checked on the charts. Supervision was intensified from the eighth day onwards. Patients in other wards were seen at least daily by the medical officer in charge of the ward. All nurses working in Ward 12, and at a later stage

of the outbreak Ward 15, had their temperatures taken each morning prior to going on duty by the sister in charge and the result recorded, the record being available for daily inspection by the epidemic officer. Some reluctance on the part of certain members of the staff to admit to feeling unwell was met with. One nurse admitted some three months later that about fourteen days after helping the primary case to bed, she had felt unwell, but had concealed this, not wishing to be removed from duty. [This is of common occurrence. Temperatures of staff Class 1 contacts should be checked by the M.O. himself.] In several other instances it was prompt action on the part of friends that compelled a nurse to report some innocent rash that had been worrying her. The Class 1 contacts amongst the nursing staff were not confined to the hospital grounds, but were advised to avoid visiting crowded places and relatives or friends known to be unvaccinated. They were also told to suggest vaccination to all persons they were likely to visit. In the early stages of the outbreak they shared the same accommodation as the nurses engaged on work in other parts of the hospital, with the exception of those engaged on obstetrics. [It would be advisable to restrict the movements of such staff from the tenth to the sixteenth day after contact by arranging segregated sleeping quarters, prohibiting visiting crowded places and not allowing weekend or extended leave and taking the temperature before going off duty. Final details would depend so much on local conditions and striking a reasonable compromise based on assessment of risk.]

"As far as possible, all Class 2 and 3 contacts, i.e. the remainder of the patients and hospital personnel, were seen at least once daily by the medical staff. Special attention was given to the laundry workers and the checkers handling incoming soiled linen. The importance of the latter as a source of infection had been demonstrated in several previous outbreaks. Auxiliary and domestic staff, such as storemen, kitchen and domestic hands, plumbers, painters, electricians, boilermen, gardeners, and mortuary staff, were not forgotten. Certain workmen made a habit of being inaccessible whenever the medical officer was expected. This difficulty was overcome by varying the time of inspection, and explaining the reason behind the visit. The matron and the hospital secretary provided a list of staff absent from duty for any cause; such absences were reported daily to the epidemic officer and notified to the M.O.H., who undertook an investigation into the reason for absence.

"At a conference of the Control of Infection Committee held on March 20, it was decided that since another ward, number 15, was detached from the rest of the hospital, it would be suitable for the reception of any male or female case requiring observation as a suspect smallpox. Males were to be nursed in the main ward, females in one or both of the two side wards. Accommodation for the staff of this ward, separate from that of the remainder of the hospital staff, was not established for some time. Later it was found to be more convenient to transfer the cases being nursed on Ward 16 to other accommodation and to convert this ward into living quarters for the staff to Ward 15. Isolation precautions similar to those operating on Ward 12 were in force. Separate dining-room, bathroom, toilet accommodation were provided for those members of the nursing staff engaged on obstetric work. [Where a smallpox hospital is already open and of sufficient size, it is usually preferable to send suspect cases, who already will have been successfully vaccinated, to a smallpox unit for observation, although this one in Halifax worked quite well and did accommodate four cases of smallpox, until their diagnosis and transfer, without spread of infection.]

"Emergency medical and surgical admissions from the surrounding area after March 12 were referred to other acute hospitals, but it was foreseen that emergency medical or surgical

treatment might be required for a Class 1 contact from the outbreak in the Todmorden area. In such a case practitioners were requested to send the patient to this Halifax hospital and to notify the epidemic officer of details of contact, or in requesting admission. Accommodation for this type of medical case was already available in Ward 15, but was unsuitable for surgical admissions, since operation would involve transport of a patient through the hospital grounds. A further ward, Ward 4, was therefore put into readiness, and the older of the two operating theatres reserved for the use of this ward. Suitable staff volunteered to nurse any case admitted. The accommodation was not, however, needed. [Commendable foresight was used, bearing in mind that a number of smallpox cases present symptoms suggestive of a surgical emergency, and there is always the possibility of a double diagnosis, and might easily have been admitted to some other hospital, so introducing new infection.]

"Lack of accommodation at adjacent hospitals made it impracticable to transfer obstetric work. Arrangements were therefore made for the obstetric unit to function as a separate entity from the rest of the hospital. The accommodation for the nursing staff of this unit has already been described. The medical officers remained in their usual quarters and shared the resident staff dining-room.

"A daily return of all patients admitted from the Todmorden area was forwarded by the hospital secretary to the epidemic officer, to enable this group of admissions to be kept under close supervision. [Helping in general smallpox control.] Midwifery cases were admitted to the unit on condition that they agreed to vaccination and revaccination if considered necessary, but in no case was there any difficulty in enforcing this rule. Husbands were not allowed to proceed to the wards unless they were willing to be vaccinated. [This assumes that if smallpox infection had been present at any time in this unit successful vaccination performed at the same time as contact would prevent the disease. We know that is not always true but is the only alternative to prohibiting visiting. It would seem desirable to revaccinate with three insertions although primary vaccination with three insertions in such a small-risk person may produce local and general reactions in "poor father" at a particularly inopportune time. If Halifax had been unlucky and chance infection had occurred in a ward maid or nurse in this unit, complete protection of the outside community would not have been assured.]

"The out-patient department was closed on March 23, no new appointments or consultations being given after March 13. It finally resumed working on April 13, having been closed altogether for a period of three weeks. The danger of maintaining an out-patient department is that both medical and nursing staff who may have had contact with the in-patient side may report for duty although they are in a pyrexial initial stage."

Eastwood recognized the unsolved problem of mixing the medical staff of the obstetric unit with others who were in the potentially infected part of the hospital, but it only goes to emphasize an extremely important skill in smallpox control, the art of compromise. Medical, sociological, economic and political factors in every situation must be assessed and the general principles applied as far as is practicable and with a reasonable degree of safety. On every occasion some calculated risks will have to be made, but it is important that these are made by one medical officer in a hospital, preferably the medical superintendent. If this office does not exist, a medical officer should be appointed by the "control-of-infection committee", who is absolutely responsible and can give orders to any member of the medical staff in the hospital, including senior consultant physicians and surgeons. The control policy as a whole must, however, be in the hands of the medical officer of health, as it is impossible to regard an

outbreak of smallpox in a hospital as something detached from the general population when there is considerable movement of staff and patients in and out of the community. On the other hand, the medical officer of health will have plenty to do in the outside community and he will not have the intimate knowledge of the day-to-day problems in any particularly hospital. I think Eastwood has shown that it is an ideal method for the epidemic officer of the hospital to act as an additional deputy medical officer of health in the special environment in which he normally works.

CHAPTER 16 Disinfection Disposal of Smallpox Dead

DISINFECTION

Disinfection is important in smallpox control, in particular after the removal of patients to hospital. It is also used extensively in the smallpox hospital, particularly if the unit has to use other services for the provision of food and laundry.

Steam disinfection is by far the most satisfactory method. Bedding, clothing, food containers and many other articles unharmed by high temperatures can be most satisfactorily disinfected in this way. The process, however, will fix stains on bed-linen and some advise that it is soaked in cold water before being passed into the disinfector, but it is inevitable that the linen will become very stained from constant use and in most instances will be subsequently destroyed or kept for smallpox purposes only. In Edinburgh (Clark, 1944) bed-linen was soaked in lysol for twenty-four hours and then laundered in the usual way, without steam disinfection. No laundry workers were infected, but one can assume that they would have been adequately vaccinated or revaccinated. The danger of inhalation of virus from infected clothing has already been stressed, and one wonders whether the handling of the material wet or the action of the lysol contributed most to the success of this method. Given suitable trusted employees, I have little doubt that the wet handling of bedding and clothing would very largely remove the chance of spread of infection, but I think most would feel safer if steam disinfection could be used. For emergency use, there are portable types, particularly those used by the Armed Forces.

The most difficult problem is the chemical disinfection of objects which cannot be subjected to heat or boiling. Three per cent lysol, 1 per cent phenol, potassium permanganate 1 in 10,000 have all been used at various times with apparent success. Formaldehyde has been used very extensively, and the use of this has been reviewed recently by the Committee on Disinfection in Cambridge (1958). The Committee found that smallpox virus on threads dried from a solution of virus suspended in normal monkey serum was killed after half an hour's contact with formaldehyde vapour. In the case of scabs, however, both variola major and variola minor, virus could be grown from the scab after twenty-four hours' contact with formaldehyde vapour. The Committee expressed the view that disinfection by formaldehyde cannot be recommended for the disinfection of fabric contaminated with smallpox virus. I would hardly agree with this but I think the Committee have missed the point. Smallpox scab is a very hard, dense piece of dried exudate, containing smallpox virus in an almost impregnable position, and even very strong vapour disinfectants are unlikely to affect it due to their inability to penetrate. Virus on threads was killed after half an hour's contact which fits in with what has been the common practice, of using formaldehyde vapour, particularly in the disinfection of

rooms that have been vacated by smallpox patients where the infective element of importance is the *respiratory virus*. In the Edinburgh outbreak of smallpox in 1942 (Clark) some experiments were made with formaldehyde disinfection. Vaccinia infected crusts obtained from rabbits were dried *in vacuo* over calcium chloride for eighteen hours and then ground in a mortar and spread as a thin powder in a petri dish. The virus was killed by an exposure of only ten minutes some fifty minutes after the start of the generation of formaldehyde vapour. It was felt that, as in normal fumigation processes for a room contact was for at least six hours, there was a wide margin of safety. Certainly in practice the epidemiological evidence suggests that occupied rooms do cease to be infectious after formaldehyde disinfection by the normal technique.

The use of formaldehyde in disinfection has been reviewed by Darlow (1958). The details form a useful basis for the application in smallpox control. "Formaldehyde can be liberated by heating or spraying commercial formalin, 40 per cent solution of formaldehyde in water, containing 10 per cent methanol, to inhibit polymerization, or by heating paraformaldehyde, which is a solid polymer. Since paraformaldehyde produces a relatively dry gas, its use is not recommended for disinfection purposes. Formaldehyde readily polymerizes to form paraformaldehyde, so that the vapour concentration which can be maintained is limited to about 2 milligrams per litre at 20° C., rising to 160 milligrams per litre at 100° C. However much gas is liberated, these concentrations cannot be exceeded. It is important to note that in order to maintain the higher concentrations, the whole space and the walls must be kept at the appropriate temperature. When fumigation is done by spraying cold formalin in an equal volume of alcohol, industrial spirit must be added to prevent polymerization, both in the spray droplets which cool during evaporation, and on surfaces after deposition. The temperature increases disinfection by increasing the amount in the vapour phase, by reducing the loss of formaldehyde due to polymerization, and where fabrics are present by reducing absorption on to them. A temperature of not less than 18° C. (64° F.) is recommended. The rate of killing increases with the rise in humidity, reaching a maximum at relative humidity 80–90 per cent. Formaldehyde, like any other gas, penetrates only slowly into the air spaces of porous materials such as fabrics, mattresses, pillows, or between piles of paper. Slow penetration makes it impossible to disinfect the interior of folded blankets, unless special precautions are taken. The presence of thin layers of dried organic material, such as pus, blood or sputum, so hinders penetration as to increase tenfold the time required."

For most purposes the gas is best generated by boiling a mixture of commercial formalin with that amount of water necessary to ensure adequate humidity. In small rooms this can be done by heating the solution in a vessel of the electric-kettle type. When this cannot be done, solid potassium permanganate can be added to 40 per cent formalin. This oxidizes some of the latter, generating sufficient heat to cause violent boiling and evaporation of the bulk of the solution. Formalin has the advantage of disinfecting small objects, particularly those of leather, which cannot be heated. One of the most difficult from the administrative point of view is the disinfection of boots. These can be disinfected by vapour in a room, although they have often been done by wiping over as much as possible with formalin solution or lysol. It is not known how effective this really is but secondary cases do not appear when this method is used.

When formalin is used in rooms, both potassium permanganate and bleaching powder should be looked for and removed, as these substances may react with the vapour and can cause an outbreak of fire. Only one room at a time should be sprayed, two operators always being present. Breathing apparatus is required for the operators, and the limited endurance

under these conditions, using breathing apparatus and moving furniture and operating pumps, was found in Edinburgh to be about three hours. Spraying was done with half-gallon hand sprays, but in hospital wards machine sprayers can be used. Operators are protected by heavy rubber gloves, boots and rubber aprons. The one-in-eight dilution of formalin, 40 per cent in hot water, is first used, the purpose being to soak all the surfaces with liquid, to raise the moisture content of the air to as near saturation point as possible. One pound of potassium permanganate is put in a four-gallon pail, which is put inside another containing water. One pint of 40 per cent formaldehyde is then tipped into the permanganate and gas and steam are evolved and, as the vapours may be explosive, the mixture is sprayed with water if the reaction becomes too violent. It also prevents boiling over, and keeps the humidity of the air at a high level. One pint of formalin is used for every thousand cubic feet. The room is closed, sealed as far as practicable and left for six hours. All windows are then opened. It is left for twenty-four hours and any free liquid mopped up, but a period of some days may be necessary before the house is fit for comfortable habitation.

Barrett (1949) describes the method recommended by the Ministry of Health for disinfection in ships. Infected accommodation is defined "as any part of the ship used by the patient from a point three days before the outcrop of the focal rash". One would prefer "from the onset of symptoms", as in some cases the rash appears on the fourth day or even later, or may not be noticed by patient or doctor on the first day. However, crew often deny symptoms before the rash appears, and therefore some period counted from the first day of rash may be needed. Four days would certainly be safer. Apart from the patient's quarters, cabins, dormitories and crew spaces occupied by close contacts during this period of infectivity should be suction cleaned, and all paintwork, woodwork and decks washed with soap and water and, where applicable, repainted. Bedding and personal effects should be boiled or disinfected by steam. Chemical disinfection is not advocated, due to the difficulties of sealing rooms.

Our ignorance on the finer limits in this field and the administrative and ethical responsibility placed on those who have to declare rooms or buildings free from infection has led to some extraordinary degrees of decontamination. In the instructions for the disinfection of the Homerton Fever Hospital issued by the M.A.B. in 1877, sulphur was burnt in the wards for forty-eight hours, then the window frames were entirely taken out and the wards and adjoining rooms exposed for fourteen days to wind and weather. The walls and woodwork were then scrubbed at least twice, and repainted. After the painting, the floors were well scrubbed three times, at intervals of three days. Even the lavatory seats were planed. Linen was to be boiled in different waters twice and dried in the open air. Many objects were destroyed and others sent to smallpox hospitals for further use there.

It is surprising, however, how little has been changed over the years. In a recent outbreak in England the hospital used for smallpox patients was largely disinfected by similar methods. In the smallpox ward, prior to disinfection, smallpox scabs could be recovered with ease between the floorboards, in spite of ordinary methods of cleaning, including the use of a vacuum cleaner. It was thought that scabs had probably fallen into the ventilated space below the floor, and that virus might have been carried into the ventilators and other places difficult of access. The floors were swabbed with a solution of lysol which was allowed to soak in overnight. All the doors, windows and ventilators were then sealed, and the ward was fumigated with formaldehyde of the usual concentration for twenty-four hours. Laboratory samples of dust prior to disinfection contained smallpox virus, while samples taken after

disinfection were apparently free, but nobody seemed very anxious to declare the hospital free from infection, possibly because of preoccupation with the idea of the importance of scabs. The outcome of a considerable amount of procrastination was that the hospital was left empty for some six weeks, except for the ward which had held "severe and fatal" cases, and this was left for a further period of four months before it was completely redecorated and painted. During this time, however, the staff and all patients entering the reinstated geriatric unit were also vaccinated, although in the light of our recent experience this could not be guaranteed to prevent smallpox, should the building have remained infectious. It must appear very unconvincing to patients being admitted to a hospital to find that they have to be vaccinated to protect them against a disease suffered by patients who occupied the hospital some four months before. This rather fantastic procedure is in complete contrast to that used when smallpox occurs in wards of general hospitals where, after the cases are removed and the ward is disinfected, it is then reoccupied within a few days of being washed down. This appears to be similar to the practice carried out at Joyce Green (Marsden, 1960), where buildings which had been used for many years for smallpox patients were fumigated and washed down and soon afterwards occupied by ordinary fever cases, without any untoward effect.

As mentioned repeatedly, too much attention is paid to the visible scab. In my opinion, ordinary routine disinfection is adequate and whether the ward has been occupied by few or many cases, serious or fatal, is of no account.

Today more and more attention is paid to the use of vacuum cleaning, with burning of the dust, the washing of floors with soap and water, and exposure of rooms to air and sunlight. Repainting of wood surfaces is frequently advocated, but if they are satisfactorily washed down this does not appear to be necessary, except as psychological reassurance to the future occupants. Below is a summary of the methods principally used.

Rooms:

Method A—Vacuum cleaning, burn the dust, wash floors with soap and water, leave open to air and sunlight forty-eight hours. Steam disinfection of bedding, curtains, and other removable fabrics.

Method B—Remove fabrics for steam disinfection, etc., followed by formalin disinfection.

Hospital wards: Vacuum cleaning, wash down walls, formalin disinfection, air and sunlight forty-eight hours, reoccupy. Repainting has a valuable psychological effect on further occupants.

Ships: Vacuum clean, wash, repaint. (Inside of ventilation system is normally ignored.)

Ambulances: Spray. (*a*) Use of a spray consisting of 2½ lb. carbolic soap, 1½ lb. white cyllin and 2½ gallons of water, or (*b*) by formalin solution, using 2 ounces of formalin to 1 gallon of water. The ambulance is left sealed for one hour then opened up.

Bedding: (*a*) If stained, soak in cold water, steam disinfect. (*b*) Soak in 5 per cent lysol twenty-four hours, launder.

Blankets: Steam disinfect.

Leather objects and books: Formalin vapour for six hours. Three would probably suffice. Penetration will not occur in closed books, but if these have not been used by the patient, the danger would appear to be negligible. If in doubt, expose to air and sunlight for forty-eight hours.

Toys: Boil, or wash with antiseptic solution, or expose to formalin vapour.
Paper money: Can be exposed to formalin vapour, but easier to iron both sides with electric iron.
Coins: Boil, or treat with antiseptic solution.
Letters: (*a*) Iron separate pages, both sides. (*b*) Expose loose pages and envelope to formalin vapour, three hours, then seal.
Radio sets, television sets, cameras, clocks, etc.: Vacuum clean with Dustette. Wipe surfaces with antiseptic solution. Expose to air and sunlight for forty-eight hours.
Cats and dogs: Wash the fur with soap and water.

Many of the methods used are apparently satisfactory in practice and no cases arise from "failure to disinfect". The infectivity of many of these objects is quite unknown, and little scientific work has been done of practical value. Increasing attention is being given to mechanical methods of cleaning, rather than relying on chemical methods.

DISPOSAL OF SMALLPOX DEAD

It has long been recognized that the corpse of a person dying from smallpox has frequently given rise to smallpox infection in medical students undertaking dissection of a fresh corpse, in undertakers in encoffining the body, mortuary attendants, and even in photographers who have photographed the corpse. Infection occurs mainly from virus on the surface of the skin and on the shroud, derived from the respiratory tract, rather than from gross scab material. In particular, removal of the shroud for examination or other purposes is likely to liberate virus into the atmosphere which can then be inhaled.

There is considerable fear of the whole process of burial due to the great frequency with which visitors to funerals contract smallpox. Although the victims feel there is something sinister about the coffin, and will not even touch it, the mode of infection is almost certainly from relatives present at the funeral who are in the initial stage of the disease. It is common for patients to die from smallpox at about the tenth to twelfth day, which means that contacts will be just at the infectious stage, without symptoms other than "influenza". The smallpox corpse has often been buried with a surprising amount of disinfective ritual. The subject of disposal in England and Wales in recent years has been dealt with by Hudson (1958), who points out that the responsibility for disposal of the body, even if the person has died of smallpox, rests with the relatives and, if there are none, it is the duty of the local authority. Although the Public Health Act, 1936, Sections 162 and 163, ensures that the body of a person, who has died from smallpox, is disposed of "immediately", it does not stipulate what precautions, if any, should be taken against the spread of infection during the disposal, and the responsibility still remains with the relatives.

CREMATION OR EARTH BURIAL

Public health authorities prefer smallpox corpses to be cremated, and in many instances relatives can be persuaded to agree to this, particularly as the ashes may then be present at a special commemoration service. A special dispensation can usually be obtained in the case of Roman Catholics. In Glasgow, however, cremation was apparently not permitted by the cremation authorities, because infected material from the body might be carried up into the

surrounding air with the flue gases! (quoted by Hudson, 1958). This appears to be a quite unnecessary precaution. Polson *et al.* (1953) recommend that the law be amended to allow for the ordinary regulations to be dispensed with if the person has died from smallpox, not only in hospital or on board ship, but in homes as well. When one sees the deaths ascribed to variola minor in old people during the large epidemics between 1920 and 1934 in England and Wales, I feel that this suggestion goes too far. Normal procedure should be waived in deaths from smallpox in homes only with the consent of the medical officer of health. This would ensure notification as well.

Earth burial frequently takes place and, although there is a general suspicion that infection may lurk in the soil for many years, there is no scientific evidence to support this. It is obvious that in vaults and in other situations virus on dry cloth and in the form of scabs might remain viable for some time. In the event of an exhumation being required, the possibility of infection could only be assessed on examination of the contents of the coffin and the state of the body. If there is any doubt, suitable precautions could be taken, by far the most important being the vaccination of any persons before taking part.

In general it is the usual practice in Great Britain for the encoffining of the body to be done by the hospital staff and, where the death occurs at home, to be done by the public health staff, usually public health inspectors. There does not, however, appear to be any real reason why an undertaker, who has been satisfactorily vaccinated or revaccinated, should not carry this out, subject to proper cleaning and disinfection afterwards.

The problem in encoffining is to ensure that virus from the body and any coverings are not communicated to the outside world. For this reason it is desirable that the container should be airtight or provide a virus seal. Some authorities encase the body in a zinc lining, according to Hudson, although in Great Britain these zinc-lined coffins are not sealed with solder. One authority only used zinc linings for bodies with extensive skin involvement, or with discharges, doubtless in conformity with the older ideas on infection. In some the coffins are sealed with pitch or with putty, and others use plain coffins with no lining. The body is usually enshrouded after spraying or powdering with disinfectant, and in many instances is packed in the coffin with cotton wool or sawdust saturated with disinfectant or with chloride of lime. The information on this subject is scanty, but formalin in 40 per cent solution is commonly used and, occasionally, saturated potassium permanganate or cresol. Hudson (1958) in his survey found that the practices were by no means uniform and largely empirical. He points out that the consular regulations (B.I.E. 1957) for the forwarding of bodies to countries abroad all stipulate that the bodies should be in a metal-lined coffin and sealed airtight by soldering. In some countries the body has to be embalmed, and in others packed in sawdust or wood shavings, often saturated with disinfectants, 2 or 5 per cent phenol in water, carbolic powder, lime, 5 per cent formalin and other substances. In one country the regulations required 5 per cent carbolic to be introduced into the abdominal and pectoral cavities, at least a litre to be used, although in these two sites the virus is least likely to be found. Some countries prohibit the entry of bodies of persons who have died from smallpox, and in others an interval of up to ten years after death has to lapse before entry. Although some form of embalming appears to be increasingly done and is claimed by Polson to be of great value in limiting danger to public health, it would appear to be of limited use in rendering a corpse and its covering entirely free from smallpox virus.

Although for many reasons the sealing of a body in a metal container may have been

necessary in the transfer of bodies from one country to another by sea, with transport by air it would seem that if the body were put into a heavy-gauge polythene bag, and this was effectively sealed by tying, then an infected body could be satisfactorily isolated from the outside world. It would be necessary to seal into the opening of the bag a glass tube plugged with cotton wool, so that production of gas or change of temperature would not cause the bag to tear, and yet no infective material could pass the cotton wool plug. Once the body was inside the polythene bag, it should be practicable to wash down the outside thoroughly with antiseptic solution or fumigate the outside with formalin, so that the "clean" package could be inserted into an ordinary coffin, without the problem of the infection of the outside of the coffin, which has been such a trouble in the past. Packing the body inside the coffin and subsequently sealing it led to considerable contamination of the outside, with the subsequent difficulty of sterilizing it. In Great Britain a number of authorities spray the coffin or swab it with disinfectant, but how effective this is nobody knows.

It would seem that if the body was encased in a polythene bag of the type described, and the outside sterilized and put into an ordinary coffin, then normal religious services could take place and the somewhat primitive arrangements of holding services at the gates of a smallpox hospital would be avoided. It should, however, be stressed that all those who are likely to come in contact with the corpse should be adequately vaccinated. Medical officers of health should see that undertakers in their area maintain an adequate immunity, in view of the possibility of having to handle bodies of persons who have died of smallpox, but in whom the diagnosis has not been made.

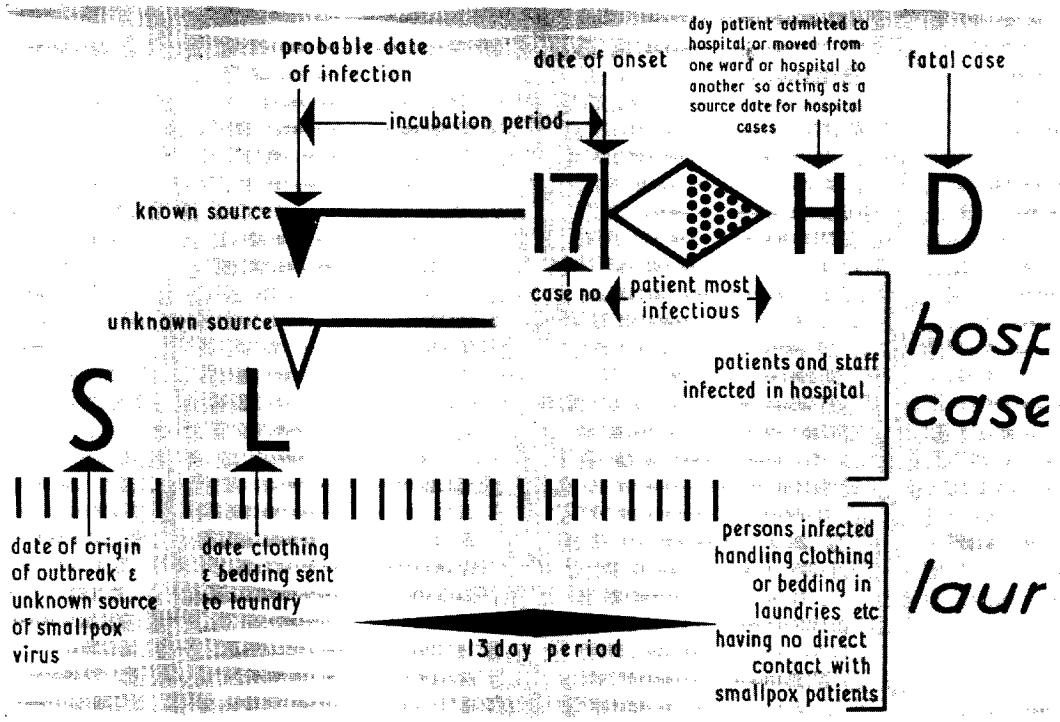


FIG. 274.

CHAPTER 17

Practical Control Measures
Typical Outbreaks

PRACTICAL CONTROL MEASURES

The control of smallpox does not start when the first case is diagnosed. A sensible health officer will from time to time bring up the subject of smallpox to the general practitioners in his area, either in circular letters which he may send on other subjects, or in giving talks at meetings of scientific societies on some aspect of smallpox or its control. The medical officer of health who is well known and respected in his area is more likely to be called in early to see a suspect case of smallpox, either in general practice or in hospital. He should also maintain his own immunity and that of his public health inspectors, public health nurses, ambulance drivers and other members of staff, and even if the hospitals are not under his control he should co-operate and persuade the hospital administrators to ensure the vaccination and revaccination

of their staff. It is sound health education for the medical officer of health to offer to carry out vaccination and if necessary other inoculations of the nursing staff in hospitals, as a public health service. In this way he knows that it will be done properly, and it relieves the medical superintendent of a task which is so often delegated to a junior medical officer and is not done very well.

GENERAL PRINCIPLES, DIAGNOSIS AND NOTIFICATION OF CASES AND DEATHS

Accurate and early diagnosis is a pre-requisite for control and when practitioners lack experience of the disease, it is usual for them to consult the medical officer of health on the clinical aspects of the case. If he has had little or no experience, the practice of having "smallpox consultants" used by the M.A.B. in 1901 and further developed by the Ministry of Health in 1923, has much to commend it. Consultants in infectious disease and others with practical experience of the clinical diagnosis of smallpox are available to assist the medical officer of health. The consultant is paid for his services by the Ministry of Health and not by the local health authority and only if called into consultation by the medical officer of health. This largely prevents a general practitioner calling in a smallpox consultant without first informing the M.O.H. of his suspicions and it relieves the M.O.H. of having to charge his authority with the cost.

It is particularly important, where hospital services are under a different authority, that when a case is suspected in hospital, the M.O.H. is informed immediately and not after some days of procrastination by consultant physicians waiting for laboratory reports and not after there have been attempts to handle the situation entirely within the hospital. It cannot be overstressed that the responsibility, other than the clinical care of a case, whether it occurs within a hospital or in the general community, should rest with the M.O.H.

The control of smallpox is impossible without some system of notification of the disease. Procedures will vary in different countries, but it is essential that notification should be made as quickly as possible, preferably by telephone to the health officer responsible for the area. Besides giving the name, address, age and sex of the patient, it should give the day on which the patient became ill, and the date of the first appearance of the rash. Although the former is the more valuable, in some countries this is likely to be inaccurate. The date of the first appearance of the rash can even be assessed to some extent from examination of the rash, although this may be difficult in some countries because of the absence of trained personnel. A statement as to the severity of the case, or whether the case has died, is also of great value. It is surprising that in some countries a previously unnotified case that dies is not added to the list of notifications as the person is strictly not "suffering from the disease".

As chickenpox is the disease most likely to give rise to errors in diagnosis, immediately an outbreak of smallpox occurs chickenpox should be made notifiable on a formal or informal basis. In most countries with good public health and general practitioner services the latter would suffice. In England and Wales the procedure under the Public Health Act, 1936, is rather cumbersome and slow. In the variola major outbreak of 1902 in London, 2·5 per cent of the cases notified as chicken-pox were found on investigation to be smallpox. In variola minor this is likely to be higher.

Notification is not primarily for national or international statistics, but is an instrument in control. It is therefore important that the health officer acquaints his practitioners of the extreme desirability of notifying the most doubtful case of smallpox, so that it can be seen

either by the health officer or by a smallpox consultant. False negatives are so much better than false positives.

Persons infected with virus soon after coming into contact with it within the confines of the family develop symptoms with some regularity twelve or thirteen days from the onset of the original case. Contacts of these secondary cases will contract smallpox, on an average, thirteen

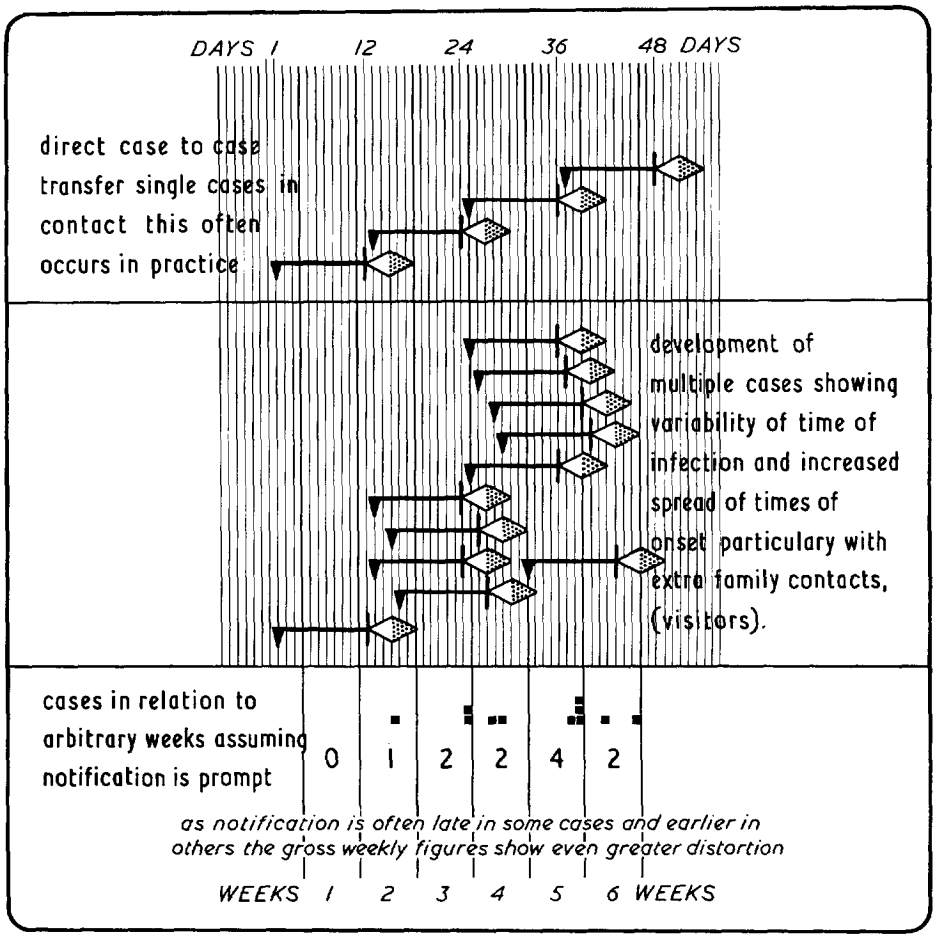


FIG. 275. Principles of smallpox periodicity in relation to notification.

days from the onset of these, unless infection has occurred from dust or clothing. Examined and plotted carefully, not on an arbitrary weekly or monthly basis, smallpox outbreaks show this regular periodicity (see Fig. 275). As the outbreak progresses, uncontrolled infection will spread outside families and irregularity will appear due to the period of infectivity not being limited to one day. An examination of the notifications received, particularly if the day of onset is known, will indicate whether the cases are early generations in an outbreak or the staggered notifications of a number of independent "streams" of cases which have been occurring for many weeks. This gives valuable information for the health officer, even if he

is many hundreds of miles from the source of the outbreak. It is vital to plot the probable date of infection of these cases, and construct an epidemic diagram, preferably on special paper, which has been devised on a light-and-shade basis, with a thirteen-day periodicity. Each point of equal and increasing colour density will be thirteen days and multiples of thirteen days from similar points on the chart—similarly for points of equal and decreasing colour density (Fig. 274).

It should be noted that deaths from smallpox occur at certain rather distinct times, within three to four days of onset of illness in the fulminating cases, which are often misdiagnosed or missed altogether in the early stage of an outbreak, the common ones at eleven to fourteen days after onset of illness in malignant smallpox, and others at more variable periods, but commonly fourteen to twenty-one days, when death is due to complications or sepsis. These tend to occur in children. The sudden notification of many cases and deaths occurring simultaneously always means an outbreak in the third, fourth or even later generation. It is only by understanding the probable evolution of an outbreak that the health officer responsible for control will be able to anticipate where and when new cases are likely to occur, and how best he can use personnel under his control for vaccination and case finding.

The first principle is the control of source of infection as far as is practicable; the second, reliance on recent successful vaccination before contact as an absolute protection against smallpox. A group of immunes therefore can provide a practical barrier against spread, as chronic human carriers do not exist. Although extraordinary ways of spread do occur on rare occasions, one must carry out practical public health work on the basis of well-recognized probabilities.

Although it might be possible to isolate a case of smallpox in a remote farm, in most countries it is the accepted principle that smallpox cases should be removed to suitable isolation accommodation. This is discussed in detail in the chapter on smallpox hospitals.

In most outbreaks, when the first case is diagnosed it is at least of five or six days' duration, and the immediate family contacts may be at least three or four days in their presumptive incubation periods. If vaccination is going to have any effect, it is essential that it is done *without any delay* at all. I would therefore most strongly recommend that any health officer who is called in to see a suspected case of smallpox by a general practitioner or hospital medical officer, should take vaccine with him; even a few hours' delay may make all the difference in preventing or modifying an attack. Unfortunately official announcements frequently state that vaccinations should be done within twenty-four hours, on the assumption that the contact is then *within the first day* of the incubation period. Avoidable delay of twenty-four hours is in my opinion gross negligence. Vaccinations should be done with three insertions and, if revaccination is undertaken, preferably on the opposite arm to that on which the primary vaccination was done. If gammaglobulin is available, it could also be given, but vaccination is a first priority, and gammaglobulin should not be given until the eighth or ninth day of the presumed incubation period. Its real value in the prevention of smallpox is still unknown. It is important to stress that the vaccination of immediate family contacts is more important than the removal of the patient to hospital. In many instances it may be three or four hours before this can be arranged. Examination of the patient may enable one to judge fairly accurately the day or days on which the infection occurred, and the history of movements of the patient or of his contacts at work may give some idea of the possible source of infection. The immediate contacts are told not to leave their homes, and arrangements are made to see that they are supplied with food and other necessities of life. Having vaccinated the contacts, the health

officer can return to his office, arrange for transport to hospital and put into operation his plans for smallpox control. He will obviously call in health inspectors, public health nurses and others, to carry out their functions. The checking of the list of contacts, and those who have visited the house, particularly in the initial phase, when infection is likely, is most important, and these should be visited as soon as is practicable, even at night, to carry out vaccination or revaccination, as the case may be.

This puts into effect the technique known as "expanding ring" vaccination. The person vaccinating starts at the focus, and immediately vaccinates family and other close contacts, the neighbours, friends and relatives, *those who are at greatest risk*. Although done immediately, this does not mean it should be done hurriedly or carelessly. Vaccination should be done with vaccine of known potency stored under satisfactory conditions.

Depending on the reliability of evidence of contact, the public health staff continues to vaccinate in the immediate area for up to three to four days, working at different times of the day so as to do all members of each family. At the end of about four days a return is made to the locality and examination made of all persons, (i) to examine carefully for secondary cases of smallpox, including the very mild types, and (ii) to see the effects of vaccination, if any. Where there is no definite vaccinial reaction it should be repeated. This may cause the double vaccination of a few persons showing a rather delayed response to primary vaccination, but under the circumstances it is of minor importance. The "ring" can then be expanded if the situation requires it. At the end of a further three or four days the locality of the original case or cases should again be visited and all persons examined for possible secondary cases and further revaccination done if doubt exists of the success of the previous two. It must be emphasized that a proportion of contacts who fail to get a successful vaccination on the first occasion may obtain a successful result on the second or third. This intensive but *highly local* vaccination can be carried out by one or two members of the public health staff for each focus. Even if multiple foci are discovered simultaneously, as is not uncommon, the same technique can be used and is preferable to indiscriminate mass-vaccination, where the vaccination of a very large number of people is attempted, in some countries with police and other forms of compulsion. Even if multiple foci are present, as in variola minor, and a relatively large "screen" of immunes is required, the area should be made as small as possible, so that *personnel can be employed with the greatest effect*. Once the persons at maximum risks are *successfully* vaccinated the most important work is case finding. There is too great a tendency to be satisfied with the figures of large numbers of persons "vaccinated", with quite unknown results. In many instances the same persons, exposed to little or no risk, are vaccinated over and over again and important contacts missed.

This briefly is the rationale of "expanding ring vaccination" which is modified to suit local conditions and circumstances. The return of the vaccinator to the focus of the outbreak should coincide with the day or days *when secondary cases are expected*. Under these circumstances sudden pyrexial attacks in contacts, particularly if accompanied by headache and/or backache, should be regarded as smallpox and isolated until observation proves otherwise. It is common for smallpox cases to be diagnosed late, that is about the fifth or sixth day of the disease, so that contacts who are vaccinated may be seen seven days afterwards with successful primary-type vaccinations but with pyrexia and general symptoms. Too often this is regarded as due to vaccinia, but frequently the symptoms are due to a developing smallpox attack which may or may not be modified by the vaccinations. It cannot be emphasized too much that vaccination

performed after contact with smallpox infection often fails to give protection even if it shows on inspection true vaccinial vesiculation. In a partly vaccinated population, when vaccinations are done late—more than seven days after contact—assuming the vaccine is fully potent, cases of smallpox are *more* likely to occur in those showing a positive reaction. This is only to be expected as those who develop successful vaccinial lesions are likely to be susceptible to smallpox at the time of contact, whereas those who do not show successful vaccinial lesions are more likely to be immune or partly immune. The result, however, is unfortunate in that the public may blame the "successful" vaccination lesions as "causing" smallpox in the victim.

Opposition on religious grounds may impede this method of control. In the Southend outbreak (Logan, 1946), cruciform vaccinations overcame these objections.

The definition of "contact" has always given rise to practical difficulty. Particularly in towns it is helpful to grade contacts in the following manner:

Class 1—"Inner ring" contacts. Members of the same household, persons working in close proximity during the early stages of the illness, neighbours and visitors having actual contact with the patient, the patient's room, or patient's clothing or bedding.

Class 2—"Outer ring" contacts. Visitors and neighbours who entered the house but have no known contact with the sick person or his immediate environment. Persons at the same workplace but not in close proximity with the patient.

Class 3—Remote or doubtful contacts—including persons who live or work in the same locality but definitely have no contact with the infected home or inmates.

The most important group to vaccinate effectively and immediately is Class 1. Class 2 is also important, and in countries where housing and environmental conditions are bad can be included with Class 1. Class 3 is a group that administratively is a considerable nuisance—the hundreds of potential contacts in the market-place that the patient visited during the initial stage of the attack; the hundreds of possible contacts at the crowded railway station; or the 10,000 persons who were at a football match which the patient attended. For administrative reasons it is obvious that the health officer will have to draw the line between Classes 1 and 2, important contacts, and Class 3, of little importance. It is often argued that all, even the most remote contacts, should be vaccinated. To be entirely safe this may be true, but completely overlooks the practical difficulties and that fact that by doing so the Class 1 and 2 contacts are *frequently neglected* by not ensuring that their vaccinations are successful. The smaller the number of health personnel available, the stronger is the argument for the former plan of action.

One further characteristic of smallpox outbreaks which probably causes more hasty and irresponsible action than anything else is the occurrence of isolated cases, having at the time no apparent connection with known foci. In spite of the most intensive investigations the health officer has to admit he can find no links between the new case and previous ones. If multiple isolated cases occur he or his political superior feels that the outbreak is out of hand and something drastic must be done. This usually means more and more vaccination, street-corner vaccinations, anybody and everywhere, with confusion and disorganization of public life and industry, but the health department is loudly applauded for its heroic struggle against the disease. In preventive medicine, as in surgery, it is unfortunate that conservative skill receives less acclamation from a public ignorant of the true facts than does the major operation.

The exact mode of spread of infection of these apparently unconnected cases cannot be determined, but it is becoming increasingly recognized that mild smallpox infections without a rash, even in variola major, occur more commonly than was thought even in the unvaccinated,

and with much greater frequency in the vaccinated. Strange as it may seem, very virulent infections with rapid death within two or three days, again without a smallpox rash, are misdiagnosed quite frequently, even in countries with well-developed medical services. Remember that two or even three generations of cases may pass completely undetected, unless subsequent events bring them to light. It is in this way that apparently unconnected cases occur. They always have been a feature of smallpox outbreaks and they should not worry the health officer unduly; he should deal with each focus by ring vaccination when it arises. It is quite clear that most of the indiscriminate mass-vaccination campaigns take so long to get into their stride that isolated cases are rarely prevented at least until the late stages of an outbreak.

Checking of movements from the house should also include the question of material sent to laundries and clothing taken to dry-cleaners from the period when the patient was infectious, that is from the commencement of the initial attack. It is not worth following up laundry or other materials which have been sent during the early incubation period, unless it is thought possible that the source of infection was clothing, and that this had also been sent to a laundry. Although there are so many possibilities, it is important for the health officer not to bog himself or his staff down by following up too many improbable avenues without first dealing with the probable and important ones. At the first opportunity the health officer should contact the registrar of births and deaths, and obtain information, including details of the death certificates, of any person who died within the previous month. In this way it is often possible to spot cases of fulminating smallpox which have been diagnosed as leukaemia, meningitis, purpura or pneumonia.

In most countries it is the duty of the health officer to acquaint central government health departments on the occurrence of smallpox, because of the international repercussions. Under the International Sanitary Convention, it is only necessary for the disease to be notified when an outbreak occurs, but it has become customary for countries to acquaint central office even when a single case occurs, so as to avoid any misunderstanding and the imposition of unnecessary restrictions on travellers.

It is also important that the health officer should acquaint his general practitioners and hospital medical officers as soon as possible. If they are few in number, this is preferably done by telephone, either by himself or his deputy, so that a few words of explanation and possibly advice can also be given. In a large city, it may be necessary to circulate the doctors by letter, but it is vitally important that this is sent with the utmost speed, as it is particularly galling and likely to hinder friendly co-operation if the general practitioners are harassed by questions from their patients when their own knowledge of the outbreak is limited to what they themselves have read in the daily newspaper.

TYPICAL CONTROL PLANS

The general principle in control is to produce a barrier of immune persons in the locality of maximum risk, but perhaps it is worthwhile to show how this principle may be applied to different areas.

In the first type of smallpox outbreak, in the relatively primitive isolated village community, we are nearly always confronted with late diagnosis. Many cases, perhaps 100, are reported simultaneously, and obviously can only mean that an outbreak has been present for some weeks or even months. Briefly the action should be along the following lines:

Check up in the area to determine as far as possible the number in the outbreak, rapidity of

spread within the area and chances of spread outside in relation to movement of population. Obtain supplies of potent vaccine and arrange transport to provide minimum risk of deterioration. Vaccination should commence immediately in the families and immediate contacts of the cases already known, and at the same time operators should be looking for new cases, questioning people, and in that way many other cases will come to light. It must be assumed that cases will be hidden, particularly if repressive measures have previously been in force, and the whole village will have to be screened, but this should progress from the known to the unknown areas of infection. Vaccinations should be done by multiple insertions. At the end of three to four days these should be inspected, if in doubt vaccination repeated, again with multiple insertions. At the same time case finding should be proceeded with whether any form of isolation is practicable or not, as only in this way will a certain barrier of immunes be built up. If staff is available it is wise to proceed to the nearest villages, especially along road tracks or rivers, for signs of any other cases, and to vaccinate whole families where any member has recently been in the affected village; this is to provide intelligent anticipation of where the disease might spread, but it should *not be done* at the expense of efficient measures within the infected village. Co-operation of the village chiefs and headmen must be obtained and vaccination should not be compulsory; police should not be associated in this work. It must be appreciated that adult males, particularly if vaccinated in infancy, are frequently responsible for spread, but are very elusive. At the second inspection round, some progress might be made in solving where the infection originated, as after a few days the investigators should have obtained the confidence of the village people, who should be less reticent in giving details of their movements. If the infection has come from some other area, then obviously action by another team should begin there. Some restrictions on movement of population in or out of the village may be helpful in case finding, but if evasive action is easy it is far better not to impose any restrictions but to obtain willing co-operation. Depending on the facilities, the number of staff and geographical situation, it is usually better to proceed and vaccinate the remainder of a small village while waiting for a new generation of cases to appear. This is what might be called intelligent mass vaccination, but even here it should be noted that persons done first are those who are at maximum risk, namely the immediate contacts. In spite of the apparent vaccination of the whole village, missed modified cases may occur and freedom from infection should not be assumed for at least six weeks after the last case.

As far as is practicable, spread from infected cases should be minimized by some elementary form of isolation, a separate hut or house for the sick, but the most important thing is to ensure that all persons coming into contact with the cases have been successfully vaccinated. Terminal disinfection is not a problem in some places, as religious and tribal practice makes the burning of huts very acceptable, but exposure of clothing and other material to sunlight is usually the only practical way of disinfection.

In a densely populated large city the situation is rather different. There may be quite efficient medical services, but their utilization by the poorer members of the community may not occur, because they are too costly, if insurance or state services are not provided. This will be an important factor in determining whether cases are diagnosed relatively early or whether they are missed and treated by herb doctors and others. Immediately cases are first reported, examination of the clinical state will easily determine the probable date of onset and date of infection. The plotting technique (see Fig. 275) will show possible days of infection and whether a number of foci have been infected from a common source and whether it is early or late in

the generation of cases. In spite of there being three or four generations of cases, spread at first is likely to be relatively slow, except under extremely bad environmental conditions, and even here the rate of spread in the early stages of generation of an outbreak will be much slower than is usually assumed. Commence ring vaccination around the reported cases, doing the family contacts (Class 1 and 2 contacts), and search diligently for new cases, particularly those that are extremely mild and in the adult male.

Cases should be isolated in a satisfactory isolation hospital and given all reasonable facilities so that they attend quite voluntarily, with the knowledge that it is being done for their own good and that of the community. If the accommodation is unsatisfactory, as is frequently the case in the many countries where smallpox is endemic, then it will be far better to leave the patients in their own homes surrounded by a barrier of immunes than to place them in unsatisfactory hospitals where they will abscond to unknown destinations at the first available opportunity, greatly adding to the risk of disseminating infection. The staff who are carrying out this work must know the principles underlying their work and be ready and willing to explain the reason why action is being taken. It is important to instruct the public how smallpox spreads, particularly as a droplet infection in the early stages of the disease, and it is also important to watch out that clothing, infected in this early stage by respiratory droplets, which appears quite clean, is not surreptitiously removed by the relatives to avoid being soiled or stolen. As before, at the end of three to four days all those vaccinated should be examined, vaccinated if necessary and a continuous watch kept for the secondary cases. Case finding should be continued and families kept under surveillance until at least twenty-eight days after the onset of the first case, as it is possible for cases to occur as a result of exceedingly mild missed attacks. It is usually assumed that if vaccination is done all these persons will be immune, but due to the inherent difficulties of revaccination occasional cases may occur in spite of repeated attempts. The tendency to vaccinate a large number of extra family contacts of the primary case must be resisted, particularly in the earliest stages, otherwise the operator will be completely bogged down by the complexity of the ramifications of these contacts. Generally speaking, the chance of any of these giving rise to cases is small. When two or three foci occur close to one another, it is sometimes advantageous to produce a compact immune group by offering vaccination to Class 3 contacts who are living in close proximity, but one must never sacrifice the quality of the vaccination, particularly in immediate contacts, for mere quantity amongst more distant persons. In the city facilities for disinfection should be available and freely used. It is particularly important to train personnel to be reasonable and careful with belongings and effects, as much harm results from resentment and obstruction by the population when police methods are used.

CONTROL PLANS IN A LARGE CITY WITH GOOD MEDICAL AND PUBLIC HEALTH SERVICES

With state financed general practitioner services, where the public are entirely free to call in their doctors whenever they feel the need, early diagnosis rests in the hands of the general practitioner. As already indicated, one of the functions of the public health officer is to be on good terms and to help to teach both general practitioner and hospital medical officer of the importance of joint action over any case of which, in Wanklyn's words, it can be said "Could it be smallpox?" When this occurs, expanding ring vaccination on quite a limited scale, intelligent anticipation of the few secondary cases, allows a smallpox outbreak to be brought

to a close in one or two generations of cases, with the minimum of inconvenience to the public, both personal and economic, and is illustrated in some of the outbreaks described later.

One requires not only good medical and public health services but a co-operative public who are prepared to accept the advice of their medical officer of health. This depends not only on the personality of the medical officer, who will only be known if he has occupied the position for a number of years, but more particularly if he is the head of a well integrated public health service, carrying out all types of personal service from infant to geriatric care, through well trained and thoroughly accepted public health nurses.

This brings us to the problem of the health officer and his relationship with the press, which has also been discussed in the chapter on smallpox hospitals. Quite the worst thing in trying to control a smallpox outbreak is to have statements made by the local mayor, the chairman of the hospital board, medical officers in various positions, spokesmen of the general practitioners, none of whom have a complete picture of what is going on and, what is more important, none of whom are *responsible* for the control of the disease. The medical officer of health is well advised to issue a statement to the press immediately a case is diagnosed, and to point out that no further statement will be made until the following day at some stated time. In most countries cases of smallpox are news, and there is a very grave danger of the work of the health department and to some extent even of the hospitals being severely disorganized by calls from local or national newspapers blocking the telephone system. It is therefore essential to appoint one person as the press officer for the particular outbreak, and to acquaint national news agencies and others of his telephone number straight away. In a small town it is very convenient to make the editor of the local newspaper press officer, as he is well acquainted with the technique, and it gives him a position of importance which will no doubt assist in his co-operating with the medical officer of health. In a larger town, or if there are competing newspapers, it is invidious to choose one or the other, and it may be necessary for the medical officer of health to ask the town clerk or some other responsible official to act as the press officer.

At the same time, it is also advisable for the health officer to contact both radio and television stations and speak to the news editors of these personally. News editors often obtain information from regular reporters, but also use casual sources which quite often are incorrect. To guard against this, early contact is desirable. It is also quite useful to tell the news editors a little about smallpox, how it spreads, and various matters of this kind, as armed with this knowledge they will do their best in the news releases to avoid creating panic. This is particularly important in allaying the demands for mass vaccination.

The foregoing remarks apply to variola major but, particularly in the large outbreaks in the United States and England, the mildness of the disease, public reaction to compulsory vaccination and other factors have led many to believe either that variola minor can only be controlled by mass vaccination or, because of apparent failure, that it hardly needs controlling at all.

The outbreak in Rochdale, 1951–2, described by Innes (page 447), shows that in the absence of mass vaccination and, although diagnosed late, variola minor can be controlled in a highly co-operative population by the methods outlined. I feel that much less vaccination than done in Rochdale would still have been successful, and might have avoided the fatality from vaccination, relatively more important in variola minor than variola major.

It is also important to point out that differentiation into major and minor will not necessarily occur with the first few cases, and if handled as *smallpox* will in countries with good medical

and public health services result in early control with minimum of inconvenience. In countries where poor medical services exist, mass vaccination on the lines of the W.H.O. eradication programmes may be required, but it is an admission of failure only possible in police states, as the public's response to variola minor is likely to be much less than the often poor response to variola major. In London in 1920, in Shoreditch and Poplar, more than 20 per cent of contacts refused to be vaccinated. The emotional effect of compulsion was still being associated with the word "vaccination" and the severe effects of the four-insertion technique would not occur today.

Early diagnosis presents a particular problem in variola minor, and can only be met by giving attention to this disease in the medical curriculum and in post-graduate study for general practitioners and in the practitioner-relations work of the medical officer of health, but the principles of control need be no different from those used in variola major in the same community.

These notes give the barest outline and the health officer is advised to study reports of actual outbreaks of smallpox which are given in this book and in the medical literature of the world. As in all other branches of medicine, he can only learn by his own practical experience or by reading of the experience of others.

It is important, in epidemiological accounts, to record accurately the human failures and not to gloss these over. Practical public health work depends much on this type of knowledge and it is comforting to the health officer that unexpected and sometimes worrying incidents in an outbreak have occurred before.

TYPICAL OUTBREAKS

VARIOLA MAJOR, SIRTE, 1946

Based on "Smallpox in Tripolitania" (Dixon, 1948)

The Sirte outbreak was a circumscribed epidemic amongst Bedouin Arabs living in a desert area of approximately 100 square miles. As is common in this type of outbreak, the epidemic only came to light when seventeen cases were discovered simultaneously on 26 May, most of them at least fourteen days old.

The inhabitants were nomads engaged in grazing sheep and goats, and in view of their relative isolation (Fig. 276) it was decided to allow the cases to remain in their tents and to leave treatment largely to nature. Vaccination of contacts was commenced immediately, but no attempt was made to isolate the population as the area was too extensive. The inhabitants of the town of Sirte were offered vaccination at the same time. For political reasons more stringent measures were inadvisable and the relatively small movement of the older men was not considered too great a risk.

In the first weeks of the campaign the vaccine lymph was not kept cool enough as no refrigerators were available. It was also too old, consisting of the accumulated monthly supplies sent down from Tripoli for the vaccination of passengers from Cyrenaica. The use of this lymph on the contacts of the first cases, with a take rate of only 10 per cent, certainly accounted for the secondary outbreaks between 14 and 22 June.

Tracing contacts was difficult owing to the desert terrain and the fact that the total population of 12,000 was scattered in groups of from three to ten tents, a half to five miles apart.

After much effort lymph, transport and personnel were obtained and intensive vaccination and revaccination were done at intervals of approximately five days, some persons being vaccinated as many as six times before showing a successful result. Only when fresh lymph was used and a high take rate obtained was it possible to convince the Italian doctor that his

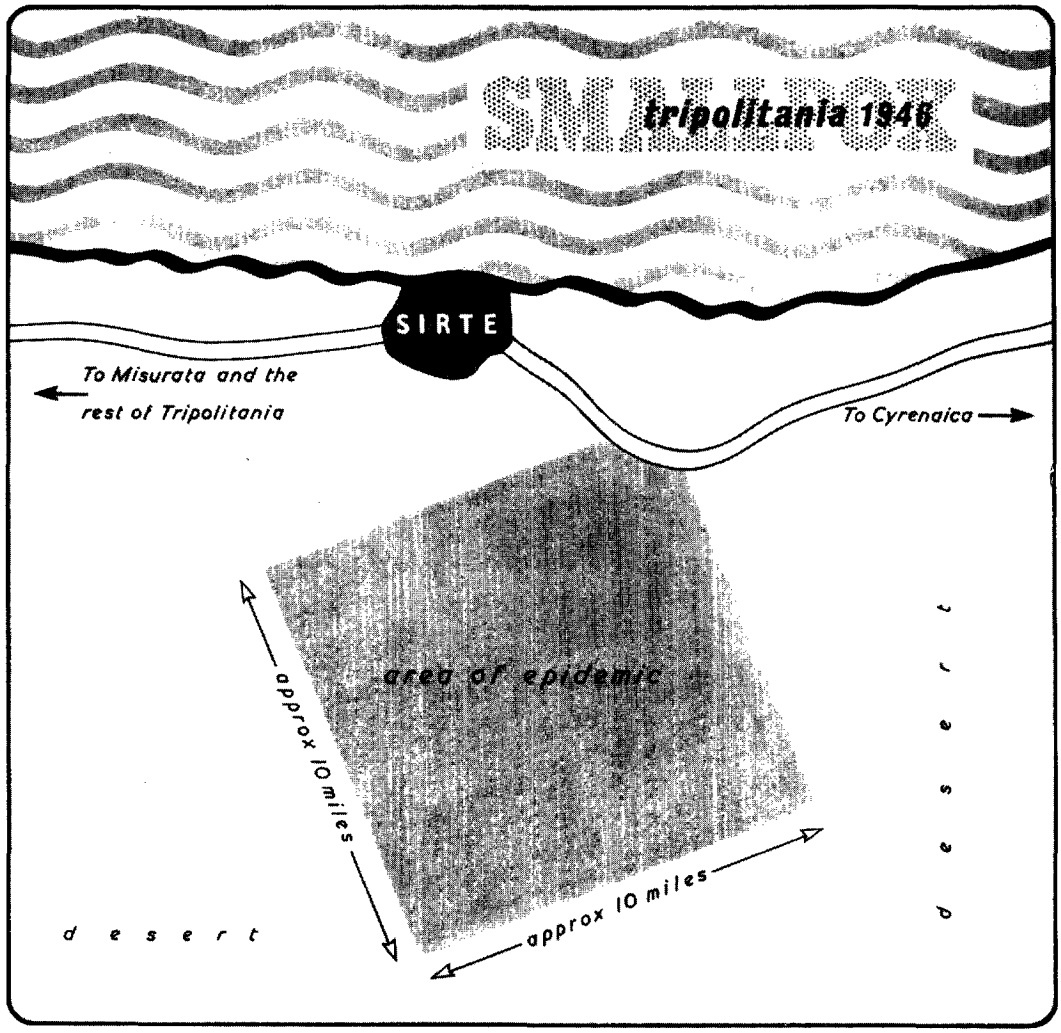


FIG. 276.

old Italian lymph was of no value. Subsequent events show that the attitude of some British medical officers was little better.

In each case the family was vaccinated first, then the inhabitants of the surrounding tents together with close contacts such as relatives, next the village or group of tents and so on, the area covered increasing for five days, after which revaccination started again at the centre concurrently with a search for cases.

This was called "expanding ring" vaccination, and was the most economical way of covering each focus, using as a team an Arab driver and an Arab infirmiere (male nurse). In this particular area no trouble was experienced with male nurses vaccinating the Moslem women, although, when three cases occurred in the town of Sirte itself, it was found that the vaccination state of the women was not, for this reason, as high as the Italian doctor had suggested.

All cases in the desert were treated by their relatives in their own tents. No current or terminal disinfection was possible, although the people were advised to expose their tents and belongings to the sun. Being graziers, they had in their tents quantities of wool destined for market in Misurata (Tripolitania) or in Cyrenaica. An order was therefore made that all wool for market would be disinfected by steam in Sirte before dispatch. An R.A.M.C. sanitary inspector trained a local Arab inspector to do this work, but it is unlikely that all the wool exported from the area was disinfected. A complete ban on export was impossible for political reasons. However, no cases of smallpox occurred in the contiguous territory from this focus of infection and the risk of spread from this type of material is probably slight.

The main coast road between Tripolitania and Cyrenaica continued to be used extensively by military and civilian motor traffic. All staging within ten miles of Sirte was prohibited and no one was allowed to proceed by road from Sirte without a certificate of successful vaccination or attempted vaccination done more than fourteen days previously and within two years. Control of tracking by foot or camel across the desert was impracticable. It would, however, have taken over fourteen days to reach a settlement or town of any size.

Between 12 May and 24 July, approximately eleven weeks, sixty-eight cases occurred with twelve deaths. Using the "expanding ring" technique this epidemic, covering an area of 100 square miles, was completely controlled and apart from the three cases in the town of Sirte no infection spread to other areas, although cases were not isolated and premises were not disinfected.

No cases occurred in persons successfully vaccinated prior to contact. Several people who had suffered from smallpox forty or fifty years previously gave a good vesicular response to vaccination. Statistics are not available. The total number of vaccinations is estimated at 20,000, but, as most vaccinations were done by Arabs and as it is known that many persons were scarified more than once, it is safe to assume that, while an immune population was built up close around the primary and secondary cases, further afield the immune state was progressively less; exactly the state of affairs which should, and did, control an epidemic of this type.

Vaccination of such independent people as nomads required much tact; although the women and children could often be vaccinated, as they would obey the instructions of their husbands or fathers, the men themselves were often more reticent. Rather than cause trouble and further non-co-operation, one had to be satisfied with less than the optimal vaccination. Although reluctant at first, the men could often be vaccinated a little later, when they saw that the effects on their women and children were not very severe. Poor lymph was often the cause of trouble, owing to faulty storage. Many of the so-called vaccinations were no more than septic inoculations, although regarded by the practitioners and more so by the population as positive.

Although it was thought that measures were sufficient to control infection in the desert area, infection gained entrance into the town of Sirte, although it had been officially vaccinated "completely", because the total number of vaccinations recorded by the vaccinators equalled the total population. As usual with this method, a false sense of security resulted.

Following the simple isolation of these patients, even in the centre of the town, no further

cases occurred. This was perhaps understandable, as by then most of the population had been subjected to repeated vaccination. However, the immediate contacts were at least done on the expanding ring and this probably played a final but not necessarily conclusive part. Although disinfection of the wool was probably not very effective, perhaps some interference with trade acts as a stimulus to co-operation in other measures, such as vaccination or isolation. The technique of the quarantine barrier was quite successful. This can only be effective if the route can be easily controlled, as it was at Sirte, with only one road, the rest being desert. It was practicable to have a vaccination point to vaccinate all passengers except those with evidence of recent vaccination or a bona-fide certificate. The latter should be issued by one authority only, and the vaccinator on duty should have the power to override any certificate if he doubts its authenticity. The forging of certificates is quite common under such circumstances. Although this procedure works on the principle of the preventive value of successful vaccination done simultaneously with exposure to smallpox, recent experience in England and Wales has suggested that there are exceptions to the old rule, but I am sure that with multiple insertions, fairly large incisions and conscientious operators unlikely to be bribed, this method can make a major contribution to preventing the spread of smallpox in a community such as this.

VARIOLA MAJOR, TRIPOLI CITY, 1946

Based on "Smallpox in Tripolitania" (Dixon, 1948)

The genesis of the Tripoli City outbreak is given in some detail in Fig. 277 to illustrate some of the clinical and administrative problems.

Cases 1 and 2 were a mother and child. Infection was brought from Tunisia by the husband of case 1 who was ostensibly a fisherman, but actually a smuggler. Having, after much perseverance, gained this information from the wife it was not possible to examine the husband to see if he had had an abortive attack, but this seemed the most probable method of infection as the wife and child developed the disease simultaneously.

The woman had a well-marked pre-eruptive fever with meningitic symptoms and was lumbar punctured by the Italian doctor who first saw her. She and the infant were admitted to the infectious-diseases block of the Colonial Hospital. The mother had a macular rash which, when seen on the next day, 19 May, showed all the typical signs of an early unmodified papular smallpox eruption. The state of the infant was similar.

The two patients came from the crowded centre of Tripoli and it was decided, as accommodation was available, to isolate home contacts as well as cases at the hospital set up at Busetta, because surveillance of Arab civilians was likely to be difficult and to favour spread by missed cases. The course of events confirmed the value of this policy. The first contacts were admitted to Busetta late on 20 May, the third day of the eruption of patient 1. It was found that they had not been vaccinated. This was contrary to the instructions given when the first case was discovered, and vaccination was therefore attempted on 21 May, a significant delay.

Of the six contacts who were vaccinated, only two gave a successful take, an infant aged six months and a girl aged eighteen years, although there was no evidence that any of the remainder had ever been vaccinated previously. One contact who gave a negative response was acting as wet-nurse to case 2; she did not develop smallpox although in long contact with the disease. The two contacts with successful vaccinations developed fever, headache and

malaise on 25 and 26 May respectively. Three days later in each case a macular rash appeared and became papular and vesicular in the typical smallpox manner.

No further cases occurred in this group of contacts, and this phase, phase 1, may be said to have been checked by the measures taken.

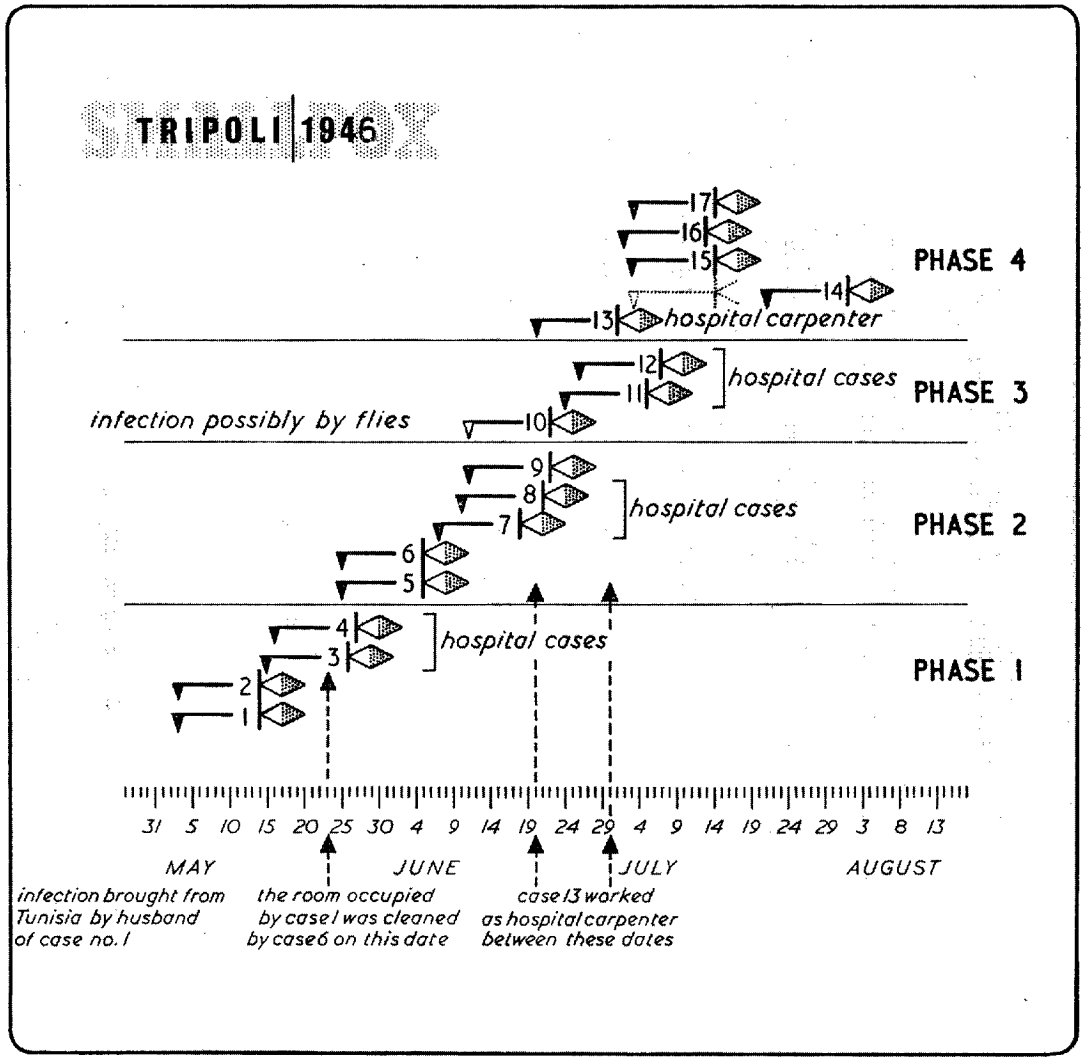


FIG. 277. The initial stage of the Tripoli outbreak, 1946. "Hospital cases" are those occurring in contacts admitted during the incubation period.

When cases 1 and 3 were removed from the infectious-diseases block of the Tripoli hospital to the smallpox hospital on 20 May the rooms were "disinfected" by the perfunctory use of a little formalin and shut up until the 23rd when they were opened and cleaned out and the bedding removed by a nurse. About twelve days later this nurse, who was non-resident,

complained of fever and headache and was sent home. She was seen on 10 June, six days later, and found to have a very slight smallpox eruption with small, drying-up vesicles.

On the same day a porter from the infectious-diseases block was found to have a similar eruption. According to him, he had never had anything to do with the room of case 1 or its contents. He was, however, friendly with the nurse, and everything points to both having been infected on or about 23 May. Both (cases 5 and 6) had been successfully vaccinated in infancy, but neither had given a vesicular response when revaccinated on the occurrence of case 1.

Case 6 (the nurse) was a married woman with four children who were admitted to the contacts' section of Busetta. Vaccination was performed immediately on admission. These children had been successfully vaccinated in infancy and at five years of age and carried definite, but rather superficial scars. All the present vaccinations were negative. Two of these contacts, cases 7 and 8, developed extremely mild attacks.

One patient, case 7, suddenly felt ill with headache and malaise, and the temperature, previously normal, rose rapidly to 103° F. By the second day the temperature had fallen and the patient felt quite well again. On the third day three small superficial, but otherwise characteristic, smallpox lesions appeared, one on the forearm and two on the trunk; there were none on the face, arms, hands or feet. The lesions matured rapidly, so that by the sixth day the scabs had gone and two days later it was very difficult to find the sites, the scars being little more than slight depigmentations of the skin such as might occur after any small impetiginous lesions.

The other, case 8, was very similar, occurring two days later with approximately eighteen lesions.

Case 9 was a child aged ten years whose only known contact was sitting next to case 8 at an examination about 9 June. Infection must have taken place by direct transfer on or about the day when case 8 herself acquired the infection from her mother and not, as occurred in practically all the others cases, from a person in the initial phase. The mode of infection was probably similar to that of case 5 from case 6. Case 9 was admitted with a rubella-like eruption with a centrifugal distribution, well developed on the face, palms of the hands and soles of the feet, but, in the early stages, relatively scanty on the legs. There was a well-marked rash in the flexures, areas that the proper smallpox eruption usually spares. No vesicular eruption occurred and the case was considered one of variola sine eruptione.

Case 9 and her contacts, all of whom had been vaccinated successfully in infancy, were revaccinated; all except case 9 gave a vesicular take. No spread occurred from this focus.

The next case admitted, case 10, was an Arab girl aged ten years with severe smallpox of six to eight days' duration, who died five days after admission. She lived in an Arab village, Amruss (Fig. 278), approximately half a mile from the smallpox hospital and, as far as could be ascertained, she had not been near the hospital. Moreover, contact with the staff or patients was unlikely as the hospital had extensive grounds and was surrounded by wire fencing. No member of the staff came from this village.

Fly-proofing of the hospital had not been completed, however, at the time this case occurred, in spite of repeated requests to the appropriate authorities. The hospital was situated in an extensively cultivated area in which fly-breeding was very active, and although the walls had been treated with D.D.T. it was difficult to keep the rooms free from flies. The Arab village itself was reasonably clean, but fly "infestation" of the population was pronounced, the small children having many flies round the eyes, the nose and the corners of the mouth. There is a distinct possibility that flies breeding around the hospital carried the infection to

the nearby village where they were likely to go in search of food. In spite of the late stage of admission of case 10 and the late vaccination of the population of the village no further cases were discovered there. Fly-proofing of the hospital was commenced on the 20th and was completed by the 28th, so no further spread of the disease by flies from the hospital could have occurred.

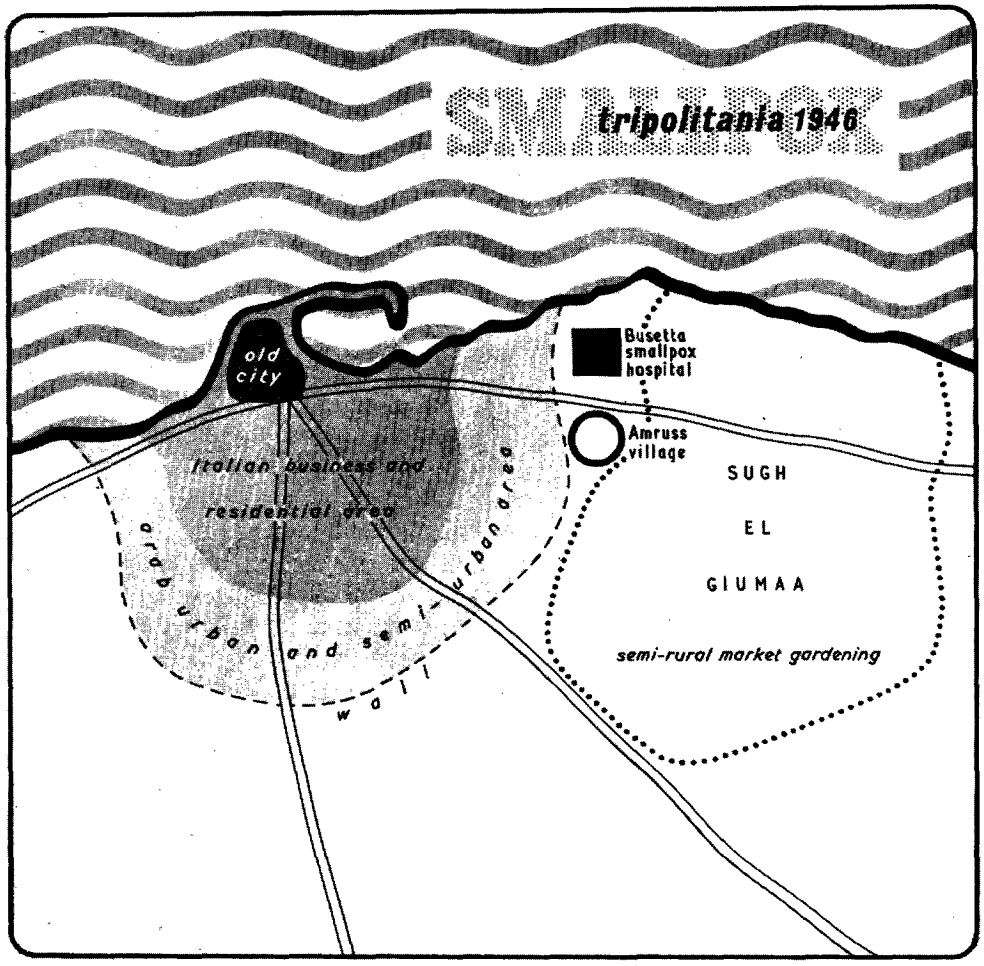


FIG. 278.

When case 10 was admitted the remainder of the family, mother, father and two children, were admitted for observation and were vaccinated immediately. All were unvaccinated previously. They were thus vaccinated on approximately the seventh day after contact with case 10 in the pre-eruptive fever stage: all gave a vesicular response. Both the children had typical mild attacks of smallpox; the adults escaped. Pre-eruptive fever was, as before, of sudden onset and out of all proportion to the severity of the ensuing attack.

One of the children, case 12, was of some interest on account of secondarily infected scabies

of long standing. A number of lesions on the thighs had apparently been inoculated with vaccinia by scratching the primary vaccination, so that this case presented a mixture of lesions, simple sepsis and scabies with secondary vaccinial lesions at about the seventh day of maturation interspersed with a few smallpox lesions (Fig. 93).

About this time it was rumoured that one of the carpenters, who had worked at Busetta from the 20th to the 28th, was away sick with a rash. Enquiries made by the M.O.H. of Tripoli from the Italian doctor treating him only elicitated the story that the man had eczema. However, ten days later he, his wife and three children were admitted to the smallpox hospital. The man had obviously had a mild modified attack with no more than a dozen abortive pocks, although the pre-eruptive stage had apparently been quite typical.

The wife had a few modified lesions; one child, aged two, who died, was unvaccinated and had an early confluent eruption, and another, aged eight, successfully vaccinated in infancy, had a generalized papular eruption of characteristic distribution. The third child, case 14, had had a morbilliform eruption two days previously which the Italian doctor had diagnosed as measles. When seen at Busetta no rash of any kind was present, nor did one develop. The child had been vaccinated in infancy and also one year prior to admission and had definite scars from both. At first it was thought that this child might have had an attack of variola sine eruptione, but subsequent events showed this to be unlikely.

The third child and the father, who were considered free from infection, were discharged four days later. Twelve days from the date of discharge the child was admitted to the Colonial Hospital with fever and, as a precaution, was transferred to Busetta. When seen next day there were signs of broncho-pneumonia at the left base, but no eruption. Penicillin was given and the patient was transferred back to the Colonial Hospital. A vaccination performed on previous admission showed a typical vesicle and was twelve days old. The pyrexia subsided rapidly and by the fourth day a few papules appeared. These were of varying size and erupted over the next three or four days. They were superficial, but in appearance no different from those of any of the other mild cases. Although so scanty, some appeared on the face and neck and the most characteristic were on the backs of the wrists; there were a few on the lines of the points of pressure of the shoulder-blades. There were no lesions at all on the front of the chest or the abdomen.

This case, therefore, presented a diagnostic problem. The first disease with the morbilliform eruption was unlikely to have been smallpox in view of the subsequent vaccination take. Ricketts (1908) noted on rare occasions successful vaccinations up to the third day of the eruption. If this first disease was not smallpox and the second disease was, the child must have escaped infection when she first came into contact with it, but succumbed when she came into contact again a fortnight later. If this view is taken, the morbilliform rash must have been purely coincidental. The second disease started twelve days after successful vaccination, which was unexpected, but smallpox could not be excluded. High fever and chest signs followed by a pock eruption of centrifugal distribution two days later is difficult to explain otherwise. Vesicular response to vaccination within one year of earlier successful vaccination was unusual and suggests a patient who developed very transient immunity. If the case was one of chickenpox it must have been contracted at approximately the time when the other members of the family were first ill. At this time the schools were closed and no other cases had been notified in Tripoli City for many weeks. It could also have been a mild generalized vaccinia but, unfortunately, laboratory aids to diagnosis were not available.

It is interesting that in this epidemic there were four separate family outbreaks with a relatively high infection rate but, in spite of crowded housing conditions, infection did not become widespread. This was probably due to early admission to hospital of cases together with their contacts. It should be noted that, in figure 277, the "hospital cases" are contacts admitted during the incubation period. But for the religious and social practices of the inhabitants, the disease might never have spread beyond these families.

Case 14 was thought to be the last and the smallpox hospital was closed on 12 August when all the patients had been discharged. However, on 26 August it was found that an Arab child had died of smallpox in the Arab section of the city and investigation showed four foci of infection within a hundred yards of each other. There were two cases of a month's duration. The Arab fast of Ramadan had been celebrated during this time and accounted for the concealment of the earliest cases, both males who were probably infected in Amruss, the Arab village. Some mild, ambulant cases must have been missed in the checking done by the Italian M.O.H. and his R.A.M.C. supervisor. Subsequent events once again pointed to over-optimism regarding the vaccination state of the population. The technique of vaccination was not above suspicion.

From 26 June to 31 September all cases were admitted to hospital together with immediate family contacts. Expanding ring vaccination was introduced and every effort was made to keep the Italian M.O.H. to this plan. Lymph and personnel were so scarce that, apart from any theoretical considerations, the only practical policy was to deal with the area of maximum risk first and in considerable strength, rather than to waste resources attempting the impossible over a wide area. Mass vaccination in the accepted sense is a big undertaking for a population of 125,000. If vaccination centres had been set up they would have been flooded by the Italians and Jews, although the risk to them was slight, whereas the Arab population, particularly the women, would not have come, and it was upon them that the major incidence fell.

After about fourteen days many cases were found in Sugh el Giumaa, a large semi-urban market-gardening district on the outskirts of Tripoli, which has a large interchange of population with the Arab section of Tripoli City. The number of patients found was so great that it was soon impossible to admit contacts.

Of the two areas affected, Tripoli City and Sugh el Giumaa, from the former family contacts were admitted to hospital, from the latter they were not. In the former, fairly efficient vaccination was carried out by expanding ring technique; in the latter, due to shortage of female staff and the very large area involved, ring vaccination was less complete, particularly the "follow-up" and secondary vaccination where the primary vaccination had failed. The sequence of events was different in these two areas. Although a number of foci occurred in Tripoli City, they were controlled by ring vaccination, and only in the small area of the Old City, where very gross overcrowding occurred, was complete vaccination carried out. Among the population of 125,000 (approximately 20,000 Italians) in Tripoli City, 114 cases occurred, an attack rate of 0·91 per 1,000; in Sugh el Giumaa, with a population of 38,000, 354 known cases occurred, an attack rate of 9·3 per 1,000.

During September it was pointed out to the Administrators of the Territory that unless Tripoli City and suburbs were put into some form of quarantine it was likely that infection would be conveyed along the lines of communication to other parts of the country. This suggestion was not accepted and shortly afterwards infection was detected at a number of places and subsequently became widespread. By 31 December 1946, 1,450 cases and 118

deaths had occurred in Tripolitania. Most of the cases in outlying parts were nursed in their homes as at Sirte.

Adequate supplies of lymph were becoming available, and vaccination was being practised in most parts of the territory. All was voluntary and therefore tended to attract the Europeans rather than the Arabs until active cases occurred, when the Arab was keen to be vaccinated. In many areas the women had to be vaccinated in their homes, and this often presented difficulties because of the almost universal use of male nurses.

DISCUSSION

The source of this outbreak was almost certainly a smuggler, and illustrates the tact and perseverance often required to finally track down the source. The failure to vaccinate contacts immediately they were discovered was I think largely due to the traditional idea that vaccination would "catch up" quickly in the incubation period of smallpox. Some of the contacts who gave a negative response were in extremely close contact, for example the one who acted as wet-nurse in Case 2, but she did not develop smallpox. The perfunctory use of a little formalin in the infected room of the Tripoli hospital was shown to be ineffective by the use of an un-revaccinated nurse to clean out the room. The possibility of passive transfer of infection to the porter was probably from infected clothing or bedding, although such movements were denied by the personnel, who, I feel sure, had some fears that they would be blamed. The value of admitting contacts to hospital is illustrated by cases 7 and 8, which were extremely mild, and would have been undiagnosed if seen outside. The possibility of transfer of infection by flies in a hot climate, where they search out secretions, both on the skin and on the eyes, nares and mouth, gives a possible route of infection, although it can never be proved. If the infection had been transmitted by persons, one would have expected the first case to have been an adult or adolescent, but this was apparently not so.

The story of the carpenter, who infected his wife and children, is a common one of allowing someone to work in a smallpox hospital who, although previously vaccinated, had not been revaccinated prior to working there. There was also the failure of the medical officer of health to personally check the diagnosis, as this might well have saved some of this family. The child with the diagnostic problem has already been discussed, but it illustrates the value of the old practice of attempting vaccination on every person admitted to the smallpox hospital, even if they appear to be suffering from the disease. The history of such a recent revaccination and scar suggests that this was one of the unusual individuals who lose vaccinial immunity very quickly.

Even apart from the slight differences of social class between the Arab population in Tripoli City and Sugh el Giumaa, the obvious advantages of admission of contacts was demonstrated by the very much lower attack rate, and the use of expanding ring vaccination was of considerable value in a very densely populated area. Lack of available staff and suitable supervision meant that, although smallpox could be controlled fairly easily in Tripoli City in spite of the denseness of population, in the more scattered Sugh el Giumaa it was not possible, and infection subsequently spread to other parts of the territory. I think that if the available personnel from other areas had been concentrated on the Sugh el Giumaa area earlier, then infection could have been controlled there without its spread, but this idea was new in the territory and the assumption that if enough vaccinations were done at random the disease would disappear was deeply entrenched.

VARIOLA MAJOR, BARNSLEY, 1947

Based on the annual report of the M.O.H. (Lewis, 1947)

In this outbreak, figure 279, the first cases were diagnosed because of a case of smallpox in a tramp in Bermondsey, London, who had passed through a common lodging-house in Barnsley. Case 1 was thereupon discovered in the common lodging-house and at the same time,

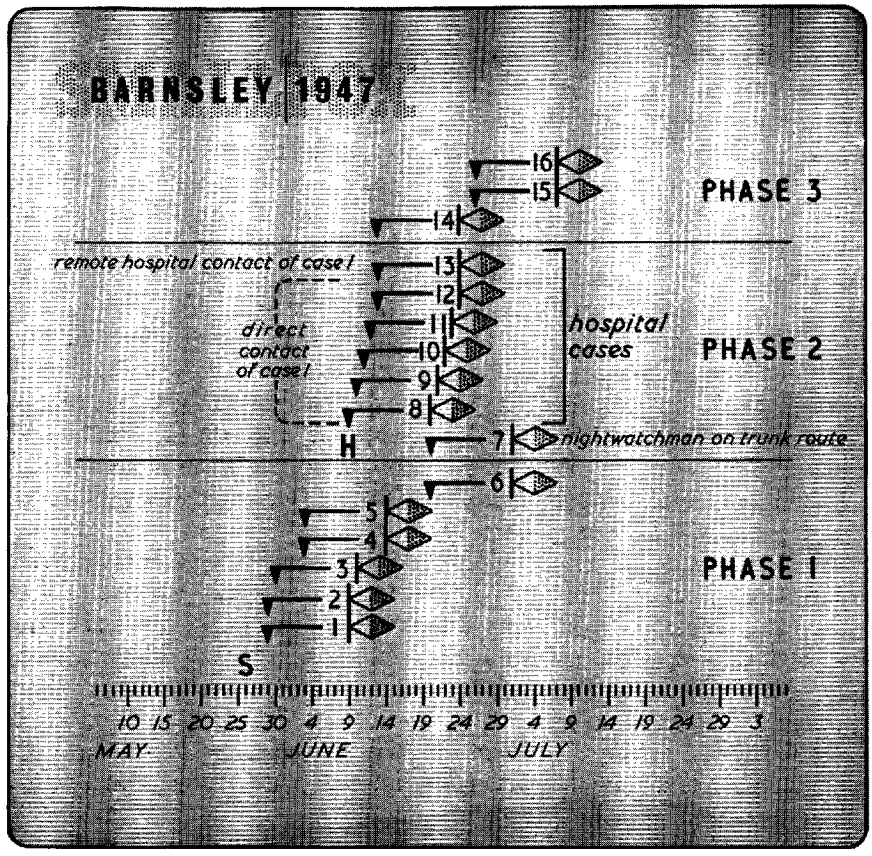


FIG. 279.

case 2, who had been admitted undiagnosed from the common lodging-house to the municipal hospital, was also found to be suffering from smallpox. Next day, another case was diagnosed in the common lodging-house and cases 4 and 5 after an interval of about five days, suggesting that either these cases were infected from clothing or bedding rather than contact with the source case, which was in the common lodging-house probably about 29 April, or, a likely alternative, infection may have occurred in this common lodging-house possibly a fortnight or even a month before, and that the diagnosed cases were really in the third or fourth generation of cases. Smallpox had been introduced into Grimsby in the middle of February

and there was considerable movement of tramps from there into the Barnsley area at all times of the year. No further cases occurred in the common lodging-house until case 6, but it can be seen from the periodicity diagram that he must have been infected from a missed case about the 19th or 20th of June, and it seems possible that this person, a tramp, was also the source of infection to case 7, an isolated night watchman at the roadside on the tramp route some miles away from Barnsley.

Cases 8, 9, 10, 11 and 12 were all infected in the hospital to which case 1 was admitted undiagnosed. In case 14 there was no apparent connection with any other case, but the date of onset is so close to that of the other hospital cases that infection was probably from some individual infected at the same time as cases 1 to 5, and never identified.

Case 14 was a woman who lived a half a mile from the hospital in which the smallpox patients were being nursed, the subsequent two cases being in her family. Her contact with any known case could not be proved, but the date of onset is of interest in coinciding with that of other hospital infections, and only shows that in each outbreak a number of missed cases or routes of spread, particularly by infected dust on clothing, do not come to light.

VARIOLA MAJOR, LONDON, 1927

Based on the Report of the C.M.O. of the Ministry of Health for 1927

Case 1 was a traveller for a London firm who lived in a London suburb, but he had not travelled further than Woking within the previous three weeks, when on 25 March (Fig. 280) he became ill and a rash appeared on the 29th. His illness was mild and diagnosed as chickenpox, and he remained at home. His wife (case 2) and his daughter (case 3) became ill on the 9th and 13th April, rashes appearing on the 11th or 12th and the 15th or 16th respectively. They were diagnosed as chickenpox, and both removed on the 17th to a nursing home situated in Hampstead. On 23 April it was recognized that the two patients were suffering from smallpox. The medical officers of health were informed and the two patients were removed to the smallpox hospital. The wife appears to have been infected about the 28th or 29th, just as the rash appeared in her husband, whereas the daughter was not infected until about the 1st or 2nd April, possibly from virus on the clothing or bedding.

It was then discovered that another daughter (case 4), who had remained at home with her father when her mother and sister had gone to the nursing home, had been taken ill on the 18th, and a rash had appeared on the 20th. She and her father were removed to hospital on the 24th. She was infected about 6 April, and I suspect that her infection was from clothing or bed-linen which perhaps she had packed ready for the laundry. I make this suggestion as the next two cases occurred in laundry workers who had received the laundry sent from the house of case 1, and who would have been infected about 6 April. They were removed to hospital on the 24th. Two more laundry workers (cases 7 and 8) had their initial symptoms on the 23rd and the 24th respectively. No details are given in the official report as to whether further laundry had been sent from Mr. X's house on the 11th or 12th, a week later, but in other outbreaks among laundry workers it has been noticed that infection may persist for four or five days. The next case, No. 9, was a domestic servant employed in an apartment house situated in the same road as the nursing home to which cases 2 and 3 had been admitted, and although no connection could be traced and some might suggest aerial spread, the contact of a domestic from an apartment house with the domestics in the nursing home along the road appears most

probable and the patient, who died, was unlikely to disclose activities which may well have been contrary to the wishes of her employer.

Case 10 occurred in Poplar, some miles away, in a man aged twenty-nine, whose occupation is not stated, but no source of infection could be traced. It would seem, however, that he was infected about the 23rd, which would be before any of the four laundry workers had been diagnosed. Although all inquiries were negative, it would seem probable that this man was infected by some person "in phase" with case 7 or 8. A somewhat similar story concerns case 12,

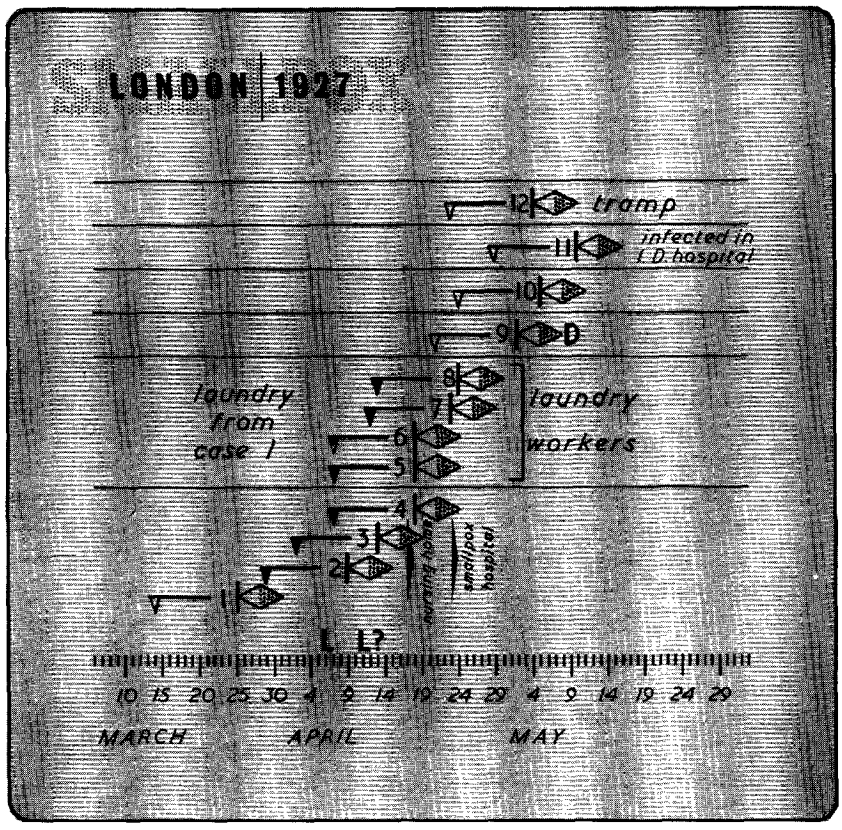


FIG. 280.

that of a tramp who was diagnosed as suffering from smallpox of about a week's duration. The official report says that he had tramped to London from the North of England, but it doesn't state when. Assuming his attack commenced about 4 May, it would appear that he was infected somewhere about 23 April. This would seem to be more than a coincidence; he could have picked up infection from contact with laundry workers, or possibly even from some contact with the nursing home. Patients of this class are very unlikely to give an accurate account of their movements.

The final case in this outbreak, case 11, was a child aged four years, who developed smallpox whilst under treatment for whooping-cough in a fever hospital. The source of infection was

not discovered. He appears to have been infected about the 28th, and I wonder whether the explanation of the mystery might be that a medical officer on the staff of the fever hospital visited the smallpox hospital, which, by the 26th of the month, contained eight patients suffering from variola major, two in the early stages, at a time when no other variola major was present in London.

VARIOLA MAJOR, BILSTON, 1947

Based on the outbreak described by Smith (1948)

The source of infection was an army sergeant aged twenty-three (case 1) (Fig. 281) who was given compassionate leave and flew home from India. He had been vaccinated in infancy and again in 1944 and 1946. On 1 March he felt slightly ill, but remained ambulant until he developed a rash on the 6th, when he said he felt "as if he had the flu". The local medical officer of health, however, apparently saw the case and was not certain of the diagnosis and attempted to have the smallpox hospital opened. However, a further opinion was sought through the regional offices of the Ministry of Health and a confident diagnosis of chickenpox was made on 8 March.

At first sight it does seem incredible that a diagnosis of chickenpox was made in a man who was likely to have had chickenpox as a child, and who had just recently flown in from India. This well illustrates the point made by so many writers that the diagnosis of chickenpox in an adult recently come from overseas should be treated with the greatest suspicion. Air travel has undoubtedly made the problem more difficult. A few years ago I saw a man in England suffering from chickenpox who had flown to the Sudan, where smallpox was present, and back, within the incubation period. The source of infection had been one of his own children.

With a diagnosis of chickenpox, the army sergeant remained at home. His mother became ill on 19 March (case 2) and a rash appeared on the 21st. A diagnosis of chickenpox was again made. An unvaccinated friend, twenty-one years of age (case 3), visited the soldier on 6 March, and became ill on the 23rd. Although the account does not mention it, this man was more likely to have been infected about the 11th rather than, as is suggested, at his visit on the 6th; possibly clothing might have been involved. At this stage further consultations took place over the problem of diagnosis, and material was sent to the laboratory. The preliminary report on 1 April suggested that the condition was smallpox. Further experts were called in, and a conference took place on 3 April, at which time clinical opinion still regarded the cases as chickenpox. According to Bradley (1947), the experts were still incredulous.

The events so far illustrate well the value of laboratory aids to diagnosis when the clinical experts fail to recognize the facts in front of them. On the other hand, if Wanklyn's question, "*Can* the case be smallpox?" had been put, the answer would undoubtedly have been in the affirmative, and the necessary administrative action taken.

On 4 April, the mother (case 4) and brother (case 5) of case 3 were taken ill, but no action was apparently taken until confirmatory reports on laboratory investigations left no doubt that cases 2 and 3 were smallpox, and the smallpox hospital was opened on the 9th, over a month after the medical officer of health had felt the necessity for doing so. This again emphasizes the point frequently made, that the final responsibility for diagnosis and control of smallpox must rest in the hands of the medical officer of health, although he may be aided by other clinical and laboratory opinion. Even at this stage the outbreak was regarded as variola minor, in spite of a semi-confluent rash in case 3 and a confluent rash in case 4, both events illustrating

the important principle of regarding all the early cases in an outbreak as variola major. Cases 6, 7 and 8 were relatives, thought to have been infected from cases 1 or 2. The timing suggests that they might well have been infected from respiratory dust from case 2.

The next case of interest was an old lady of seventy-eight (case 9), who had been ill in bed

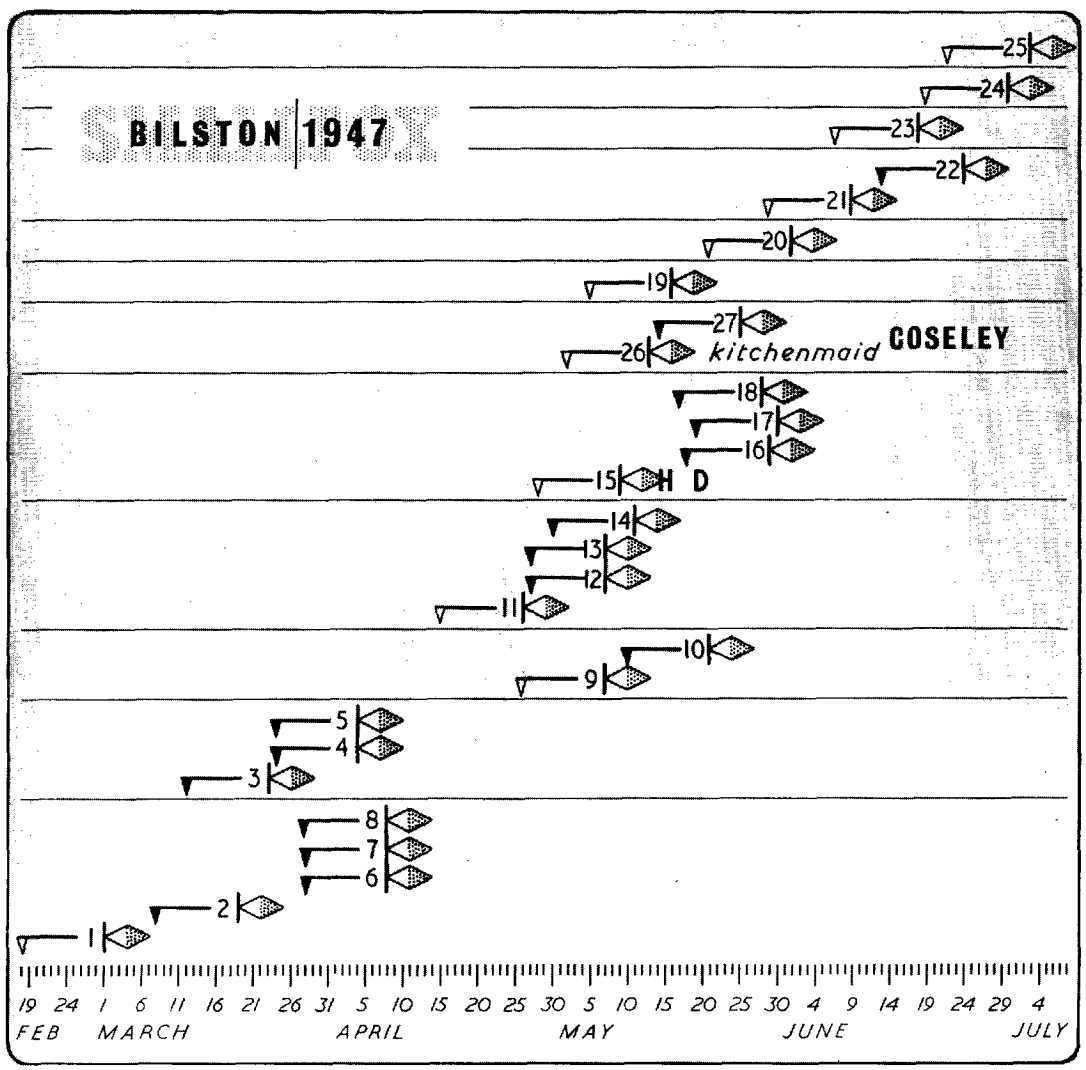


FIG. 281.

for the previous two months, and who lived some two to three miles away from the first cases. Her attack appeared to commence about 7 May, which means that she was probably infected about 24 or 25 April. Somebody must have visited her or conveyed infection to her about that time, and it is interesting that her general practitioner attended some of the cases in the first group. Contact with cases 6, 7 or 8 would fit (Fig. 281). Although this is pure surmise,

I wonder whether he had an attack of variola sine eruptione, labelled influenza, or conveyed virus on his clothes. Some tradesman might also have been involved. The reports of Smith and Murray and Bradley (1948) both refer vaguely to some degree of contact through third persons who claim to have had no symptoms. This emphasizes the importance of keeping under surveillance all contacts of smallpox cases, particularly those who have had contact with the patient or the sickroom in the first five to six days, and this should include general practitioners, medical officers of health and their staff, district nurses and others, and not assuming that professional personnel never contract disease. One could also postulate that the infection in this case occurred not through the doctor visiting cases, but from a series of missed cases, possibly even four in number, going right back to case 1 who it must be remembered was ambulant, recently returned from India, and was quite likely to have had casual contact with many people. As time goes on, the possibility of two or three missed generations of smallpox, even in a relatively non-immune population, is being recognized, and examination of other charts—Brighton and The Pennines, for example—shows how this occurs. This patient (case 9) gave rise to another in the same house, case 10.

From then on a number of unrelated family infections occurred. The first one (case 11) was a man of seventy, and he gave rise to infection in his wife (case 12) and in two other persons, aged thirty and forty-one (cases 13 and 14). The onset is given as the 26th, and if correct would suggest that at the earliest stage of a fulminating attack he infected two other individuals. The onset might have been earlier. One wonders who his general practitioner was. He could have been infected from a missed case in the same phase as case 2.

The next case, 15, was a woman of twenty-seven, and the source of infection was unknown. She was first ill on 9 May, and diagnosed as scarlet fever. She died later, from a malignant attack. Her mother, aged forty-nine (case 16), and two sisters, aged twelve and fourteen (cases 17 and 18), were infected about the 17th, 18th and 16th respectively, apparently just the time case 15 was removed to hospital. No information is given as to whether this daughter resided with her mother and sisters, but the chart suggests that they may have been infected from clothing or bedding at the time the patient was moved.

The next case was a small girl of eleven (case 19), who became ill on the 16th, apparently infected about the 4th. The unknown source is in phase with possible contacts of the late diagnosed cases 6–8. Case 20 was another isolated one, giving rise to no further cases. The onset was on 1 June, infection therefore occurring about 19 May, in phase with the previous case, although there was apparently no connection. The next case, case 21, was again of unknown source. This was a man of sixty-one. The onset was on the 9th, the date of infection about 27 May. He infected his wife, case 22. In case 23, the onset was on the 18 June, presumably infected about the 4th. A brother, aged eleven, had had a rash, but laboratory tests were negative. He apparently had been vaccinated in May. An unvaccinated sister aged two also had a few spots, but the laboratory investigations in this case were negative, although the Ministry of Health expert thought both of these cases were smallpox. The next case was a boy of ten (case 24), again an unknown source of infection. The onset was on the 30th, giving the 18th as the possible day of infection. Another unknown case was a female aged nineteen (case 25), who lived in another area, who became ill on 3 July, being infected about the 21st.

The last episode of interest was the occurrence of smallpox in a kitchenmaid (case 26), who worked at Moxley isolation hospital, not the hospital in which the smallpox cases were being nursed. She became ill on 13 May, and was presumably infected about the 1st. She infected her

mother. The source of the kitchenmaid's infection is of interest, as there was some individual contact between the two hospitals by senior medical staff, and also by ambulance personnel. It seems highly probable, as has occurred in other outbreaks, that these apparently unconnected cases in hospital personnel are due to staff movements and staff contacts which do not come to light in spite of very careful questioning. It once again emphasizes the necessity for the medical officer in charge of the smallpox unit to keep himself and any members of his staff under surveillance for the possible occurrence of pyrexial attacks indicating infection, and for the possibility of transfer of infection on clothing.

Smith, who briefly described this outbreak, pointed out that experts failed to diagnose smallpox occurring in 1947 at Scunthorpe, in the Middlesex outbreak of 1944, the Edinburgh outbreak of 1942, and Birkenhead in 1946. Laboratory tests were of considerable value in ending a clinical deadlock, rather than in bringing an outbreak to light. There was delay in taking action in opening the hospital, waiting for results, but this was no fault of the laboratory. It must be emphasized that opening a smallpox hospital unnecessarily is a small "insurance" cost compared with the cost of a late-diagnosed outbreak. Laboratory confirmation was not necessary in many of the cases, where the diagnosis was only too obvious, and in two cases at least Ministry of Health opinion was that they were clinically smallpox, although laboratory tests (not specified) were negative. One case, a girl aged twenty-two, had been vaccinated in infancy and again (result not stated) nearly a month before the onset of a clinical syndrome consisting of sickness, abdominal pain, backache and conjunctivitis, three papules on the forehead, one on the chin and one on the right leg, which became vesicular. This was highly suggestive of an abortive smallpox but laboratory evidence (not specified) was negative for both variola and vaccinia.

It was noted that vaccination did not wholly protect when done within the first week of the incubation period. In one "haemorrhagic" case successful vaccination had been carried out twelve days before, but the patient died. In a comment on this outbreak by Murray and Bradley (1948) a point is stressed that in three cases, of which one died, all had been vaccinated in infancy, and revaccinated on the twelfth, thirteenth and fifteenth day before onset of the disease. As these did not appear to take, the vaccinations were repeated on the seventh, sixth and eighth day before onset respectively. Murray and Bradley state: "It is reasonable to suppose that had the initial vaccination done on 17 May, when one person in the house was diagnosed as having smallpox, taken normally, that smallpox would not have occurred in the first and third cases and almost certainly would have modified it in the first. Subsequent investigation into the failure of vaccination showed that batches of this lymph were potent and that these failures, together with 43 others out of 375 done on the same day, were due to using lymph which had been kept under adverse storage conditions." Smith (1948), however, reports that these first revaccinations did in fact take, and the second revaccinations, which appeared to take after two to three days, support this. In the case of two of these patients, aged fourteen and twelve, even their infant vaccinations might have had some effect, and this shows the ready assumption even as late as 1948 that vaccination, and particularly revaccination, done within the first few days *ought* to have prevented an attack, whereas we can see that vaccination in these three instances although done as early as is normally possible in smallpox contacts, did not produce the desired effect. Much as one regrets it, we unfortunately just have to face these facts. The failure of the 43 out of the 375 suggests that the writers, by implication, felt that there must have been some inherent fault in the lymph for this "unexpected" result, but the

failure of 43 out of 375 mixed contacts, some 11 per cent, is virtually the same as the failure of 10 per cent in the outbreak in the industrial Pennines in 1953, where no one suspected the lymph. The need to get back to the type of vaccination used with success in 1900 is obvious.

The delay in making the original diagnosis in an ambulant patient probably meant that a number of his friends or colleagues may have been infected and not traced and, apart from the cases indicated in the diagram, until the middle of May there was almost certainly a parallel stream, or streams, of missed cases which finally showed up in "indicator cases" during the latter part of May and the month of June. It would seem that cases 19 and 20 are possibly the end results of one stream as they are in phase with one another, and cases 15, 23 and 24 are on a second stream. Apart from case 1, case 3 would appear to be the most likely one to have given rise to further streams. Coming in 1947, amongst a population with a large number of not completely immune ex-Servicemen, ideal conditions were provided for this type of spread.

VARIOLA MAJOR, BRIGHTON, 1950–51

Based on a description by Cramb (1951)

This outbreak has a number of features of interest. Infection was brought from India by a R.A.F. officer (case 1) who had travelled by air and landed in Scotland on 27 November 1950. He became ill on the following day with a mild febrile attack but, doubtless, having just returned from abroad, he did not wish to waste any time, and from then until 22 December he travelled about the country extensively, by rail from Scotland to Brighton and then back again to Scotland and return. In spite of these journeys, with many contacts, no clinical attacks resulted, quite different from the case cited by Wanklyn (1913*b*) where a railway journey left a trail of nearly 100 secondary cases. However, perhaps the significant feature not mentioned by Cramb was that he travelled from Scotland to King's Cross, London, by night, presumably asleep in a first-class compartment, took a taxi across London and travelled to Brighton between 9.30 and 10.30 a.m., when traffic in that direction would be light, so that the number of contacts might be very few. On 12 December, nine days after the rash appeared, he travelled back to Scotland by day, and had many contacts on this journey, but by then he was, in my opinion, not infectious.

He first arrived in Brighton on 29 November, and went to bed as he did not feel well, at the house of friends, a taxi-driver and his daughter. He thought he had a recurrence of malaria, called in a doctor and was treated for that disease. Not until 3 December did he develop a sparse rash on the face and wrists. He was not seen by a doctor, but by 11 December he felt well, was then given a clearance certificate by his doctor and travelled back to Scotland, returning to Brighton on 21 December.

The daughter (case 2) where he stayed was taken ill on 11 December, twelve days after her first possible contact, suggesting that she was infected by the patient in the initial stage of the disease (Fig. 282). She was admitted to hospital, and as she had a stye on her eye was diagnosed as a staphylococcal septicaemia. The father (case 3), who had been vaccinated in infancy, was also admitted to hospital. The medical officer of health was first made aware of this on 27 December, when a clinical diagnosis of smallpox was made. Specimens were, however, taken from each patient, and sent by train to the virus laboratory. The next day, 28 December, the virus laboratory "confirmed", presumably by complement-fixation test, the diagnosis of smallpox. Although smallpox was clinically diagnosed on 27 December, vaccination of nurses

in the hospital was not done on that date, but on 28, 29 and 30 December, *after* laboratory confirmation, an entirely unwarranted delay.

Case 2 gave rise to eight cases in the hospital, and case 3 gave rise to seven cases. Nine nurses

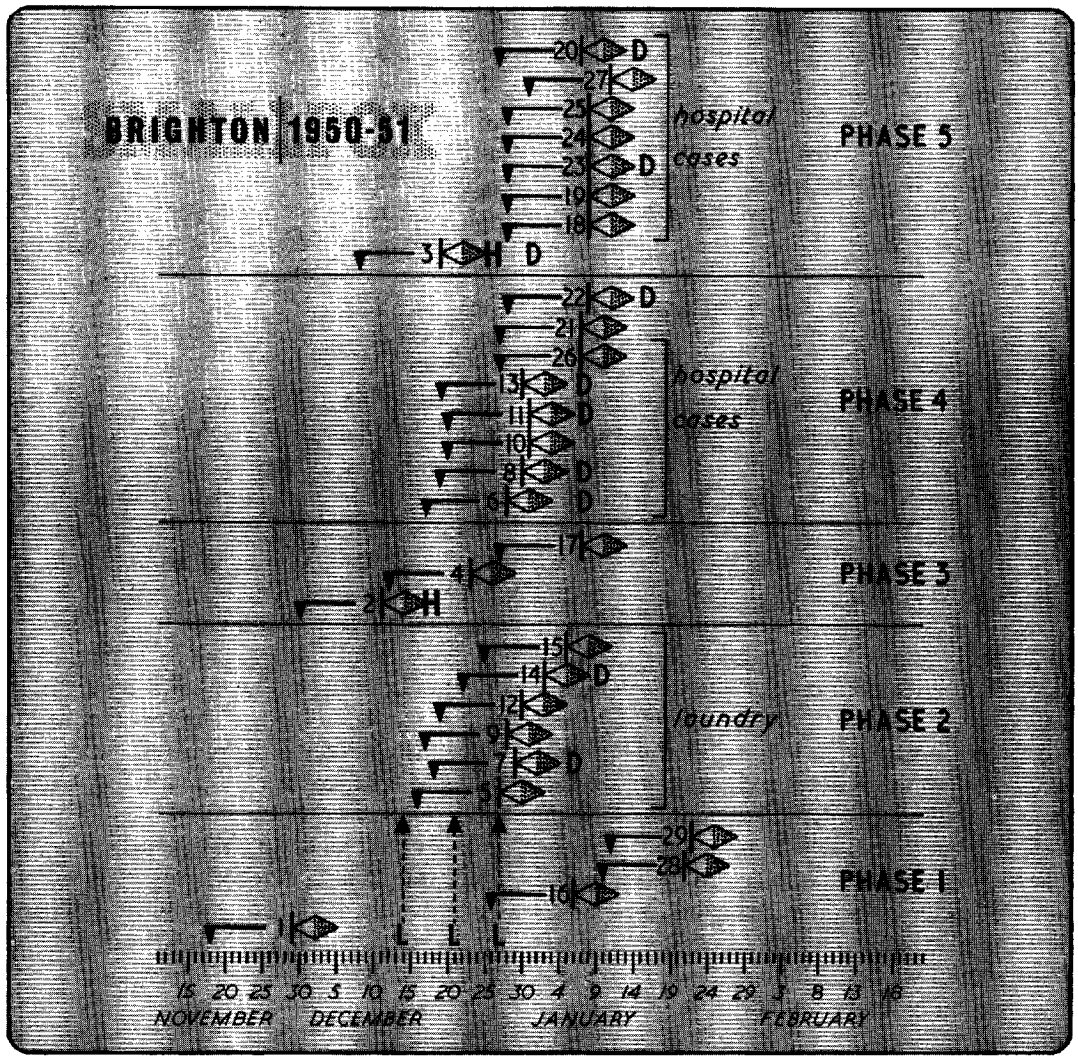


FIG. 282.

contracted smallpox, of whom three died, two domestics, both of whom died, one gardener who died, and one patient who survived. This part of the outbreak emphasizes the importance of having a well-vaccinated staff at a hospital for infectious disease, although the particular one in question would not knowingly admit smallpox cases. Although it is sometimes stated that this neglect has followed the abolition of compulsory vaccination in England,

it is quite unconnected with it. Legally, compulsory vaccination has not applied to adults, although in the past many medical superintendents made vaccination a condition of employment, but in 1950 this rule had largely become unenforceable, due to the shortage of nursing staff.

The other aspect of the outbreak which is of interest is the infection in the laundry. Soiled linen from the house of case 1 was handled by patients 5, 7, 9, 12, 14 and 15. All handled soiled linen on the 14th, but cases 12 and 14 also handled soiled linen on the 21st, after the daughter had been admitted to hospital on the 18th. There is no information as to when case 15 handled infected laundry. There is always a possibility that once infection has been introduced in dust on clothing it may be present in the sorting-room for a number of days. Brighton was particularly unlucky with its laundries. When case 17 was diagnosed her washing had already been sent to another laundry. The premises were opened late that night, and a search made amongst bundles of articles, and fortunately this washing was found unopened, so that it could be removed for disinfection, and the premises disinfected.

Phase 3 of the diagram shows the classical case-to-case transfer of infection. Phase 1 shows the possibility of two missed cases; a woman (case 16) contracted smallpox and infected two other members of the family. Her husband, who was well vaccinated, had, together with a son, visited a hairdresser frequented by case 1. Although there is no history that either the husband or son had a pyrexial attack of any kind, it would seem possible that virus, possibly on the clothing, was brought from the hairdresser's shop, and that the most likely event was that the hairdresser or his assistant contracted a mild attack, which they would not admit for business reasons, or that a customer, who was possibly infected at the time when case 1 visited the shop, returned for his fortnightly haircut at the same time as the husband and son of case 16, and transfer of virus took place on that occasion. The barber's shop as a centre for dissemination is of interest in that this also was a possible source of infection in the outbreak in Bebington in 1958. Only two other cases, nos. 21 and 22, occurred amongst the general public. Case 22 was a grocer's assistant and although no definite source could be ascertained, it appeared probable that case 6 made purchases at the shop. Case 21, a school-boy was a direct contact of case 6.

One could agree with Cramb (1951) that the chief points that may be learnt from the outbreak are: (i) the importance of hospitals reporting to their local health departments, without delay, the admission of doubtful and suspicious cases with undetermined rashes; (ii) the protection of nurses and hospital staff by successful vaccination on recruitment and revaccination at stated intervals (particularly isolation hospitals); (iii) the vaccination and revaccination of laundry workers before being employed should receive consideration; (iv) vaccinated or revaccinated persons should be inspected after the operation and only those with successful takes registered as vaccinated; (v) the importance of the earliest tracing of contacts, vaccinating them and keeping them under surveillance for sixteen days.

For the routine vaccination of laundry workers to be a real contribution to smallpox control, they must be kept immune. Partial immunes might be more dangerous as missed cases than the fully susceptible. Due to the casual nature of much of this type of employment, such staff would have to be surveyed for vaccination or revaccination at very frequent intervals. In my opinion it would be better to offer vaccination immediately in any outbreak where there is a possibility that clothing has been sent to laundries. The personnel should be included in the "special occupational risk" group.

The absence of spread from the primary case, except to close contacts and possibly the

barber's shop, is in keeping with what has been seen frequently in recent years, and I feel suggests caution should be used before instituting widespread tracking of all chance contacts on a bus or train journey which creates great disorganization of normal life and much public alarm.

Only five cases occurred in the general public, but a great deal of work was involved in preventing the spread. In a population of 156,000, the total number of ascertained contacts was reputed to be 14,000, and the public health department paid some 65,000 visits. Unfortunately, due to much pressure from the public, and possibly with little reluctance on the part of the medical officer of health, in view of the obvious potentialities of the outbreak at the beginning, some 90,000 vaccinations were carried out, although this probably had very little effect in controlling the outbreak. The number of contacts is very much greater than has occurred in many other similar outbreaks, and personally I feel that some classification of contacts would have helped. Otherwise, the health department is likely to carry out some of this work in a somewhat perfunctory manner, simply because of weight of numbers. On the other hand, the telephone exchange had a staff of three hundred, and unfortunately in the laundry the same workers who sorted soiled linen on Mondays, Tuesdays and Wednesdays packed for despatch clean linen on Thursdays and Fridays, and could possibly have disseminated infection in a very big way. A vast amount of disinfection work was also done because of this. In addition, the weather was very bad with snow and fog. Such is public health.

VARIOLA MAJOR, GLASGOW, 1950

From the account by Laidlaw and Horne (1950)

The Glasgow outbreak is of interest as it is virtually a single phase, and therefore no diagram has been given. The infection was introduced by a Lascar seaman, who had been vaccinated in infancy, and had a very mild attack. He arrived in London by sea, went to Glasgow by train, arriving there on 6 March. Two days later he became ill with fever and headache, and on the 10th was diagnosed as pneumonia and admitted to an isolation hospital. On the 14th, that is six days after the pyrexial attack, he developed a papulo-vesicular rash and was transferred to an isolation ward. He was examined by very experienced physicians, thought to be suffering from chickenpox, and was eventually discharged on 23 March. On 26 March, sixteen days after the admission of the seaman to the fever hospital, on the appearance of rashes three cases of smallpox were diagnosed, and during the following six days a further seventeen persons were sent to the smallpox hospital as cases or suspected cases. The spread over the six days is partly accounted for by the fact that the original patient was present in two different wards, and therefore infected two different groups of people. Of the twenty-one persons ultimately admitted, nine were members of the staff, eight were patients, and the other three were a visitor, a visiting physician, and a post-graduate medical student.

Three unvaccinated nurses died, but their vaccinial histories are interesting. One was reputed to have been vaccinated in infancy three times, all unsuccessful, and there was no evidence of scar. The second was said to have been vaccinated in infancy, and again no scar was visible. The third had been vaccinated unsuccessfully three times in infancy, twice in 1949 and once in 1950. This tragic episode emphasizes the dangerous fallacy, so often believed, that the person who cannot be vaccinated successfully is immune to smallpox. In my opinion no nurse who has not been successfully vaccinated at some time should be allowed to remain in

an isolation hospital at all. It should be made perfectly clear to her that she is not immune to smallpox, and should even practise general nursing in an area of low risk.

One of the ward sisters of the isolation hospital, who sickened on 24 March, travelled by bus on the same day to visit relatives, and returned on the 26th. Later in the same day she was admitted to the smallpox unit. The medical officers of health from counties and towns, through which the outward and inward buses passed, were notified and a public appeal was made for possible contacts on city and long-distance buses to come forward. No cases of smallpox appeared to have occurred from these peregrinations, as in the Brighton outbreak and the Pennine outbreak. When a case was removed from home to the smallpox unit the home contacts and the neighbours were vaccinated and, in the case of tenements, also tenants and families living in adjoining properties. On the evening of the day of removal of the patient, the home contacts were transferred to special accommodation in another infectious-disease hospital, and were retained overnight while the house was being disinfected. Clothing, bedclothes and furniture were disinfected or steam sterilized at the local authority disinfecting station, where some 10,000 articles were treated during the outbreak. Papers and other disposable effects were burnt. The following morning the contacts were permitted to return home, after the clothing in which they had come to hospital had been disinfected and the household and personal articles returned from the disinfecting station. This method, the disinfection of contacts and allowing them to return home, was popular in the late nineteenth century, when there was complete faith that vaccination or revaccination of contacts done on the day the case was removed was entirely reliable in preventing attacks in the contacts, and once the house and occupants were also disinfected the episode was closed. In the light of recent experience in England and Wales it would seem that this public health practice is based on a false premise, and surveillance of class 1 contacts at home or in part of the smallpox hospital is a safer procedure.

VARIOLA MAJOR IN THE INDUSTRIAL PENNINES, 1953

From an account by Lyons and Dixon (1953)

The outbreak was first recognized in Todmorden, Yorkshire, although the origin of the first case in the country is not and never will be known. The Todmorden cases comprised a number of connected infections, whereas those occurring in the neighbouring districts were isolated, single cases or small groups, with no verified connection with the primary focus.

Todmorden is a town of 19,000 inhabitants, situated at the confluence of three Pennine valleys. Although within the West Riding administrative area, it bears a Lancashire postal address, and shares its main industry, the spinning and weaving of cotton, with the neighbouring Lancashire towns of Bacup, Rochdale and Burnley. Raw cotton, shipped to Merseyside from every major growing area of the world, is largely transported by road. Many of the lorry crews reside in the Merseyside area. There is much traffic by road across the Pennines from Liverpool through Todmorden, connecting with Halifax, Huddersfield, Bradford and Leeds.

The map (Fig. 283) shows the principal towns in the area, those concerned in this outbreak, the chief road transport routes across the country, and the probable route of spread. Figure 284 shows the epidemiological pattern of this outbreak, and the relationship of the cases described in the text, the order in which they were diagnosed, and the division of the outbreak into the period before and after the first case became known.

The last recorded death from smallpox in Todmorden prior to this outbreak was in 1893, and there had been no notified case since the 1920's. The Rochdale outbreak of variola minor in 1952 had not given rise to any known cases in Todmorden, and only a relatively small number of Todmorden residents were vaccinated at that time. The vaccinial state of the population at the beginning of 1952 was low. During the period 1947 to 1952 inclusive the percentage of infants vaccinated was approximately 20, and it has been estimated that about 50 per cent of the adult population had had a successful primary vaccination at some time,

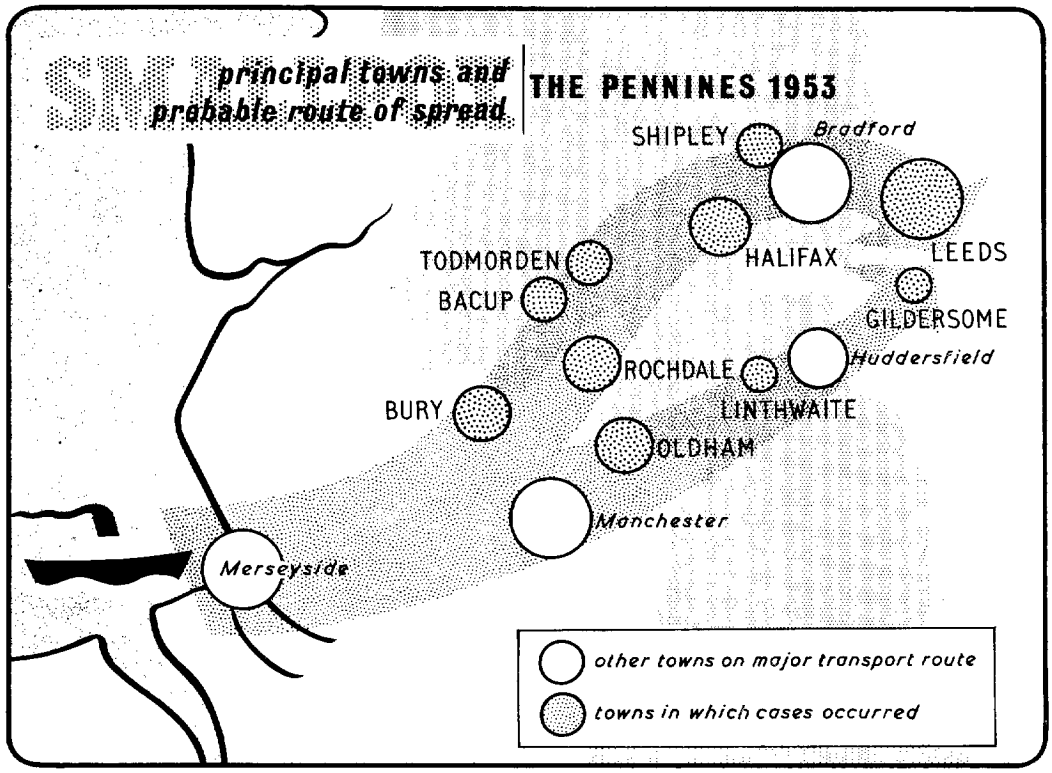


FIG. 283.

mostly during infancy or early childhood. It is interesting to note that in 1947, the last complete year of so-called "compulsory" vaccination, 101 infants were vaccinated, representing 40 per cent of the infant population. In 1948 the figure had fallen to 35 (14 per cent). Vaccination in contiguous areas was also at a low level. The infant vaccination level given by Conybeare in 1950 for the West Riding was 6 per cent, Halifax 4·8 per cent, Huddersfield 6·9 per cent, Bradford 3·2 per cent, Leeds 14·4 per cent, Oldham 18·8 per cent, and Burnley 5 per cent. Although these estimates were shown by Blaikley (1950) to be slightly too low, even if they are doubled the level is insufficient to produce any significant herd immunity.

The Todmorden Health Department first became aware of the existence of smallpox in the town on Thursday afternoon, 12 March 1953, when I telephoned the Medical Officer of Health to the effect that a Todmorden patient in the Halifax General Hospital, whom I had been

invited to see was a typical benign confluent variola major. There had been no recorded variola major in Britain since the Brighton outbreak, and one did not expect it to suddenly appear in an inland town. This was, nevertheless, clinically certain smallpox (Fig. 134), and action had to be taken with the minimum of delay. To have awaited laboratory confirmation would have been the height of folly.

The first move of the Medical Officer of Health was to order a supply of vaccine lymph from the Public Health Laboratory, in order to vaccinate contacts. The director of the laboratory was at the same time advised of the possibility of further supplies being required. The West Riding Deputy County Medical Officer of Health with all medical officers of the neighbouring areas, both in Yorkshire and Lancashire, were advised of the situation by telephone and a circular letter was immediately despatched to all local general practitioners. The latter were requested to notify the Medical Officer of Health of any suspicious cases encountered, including any adult or atypical cases of chickenpox.

Immediately after ringing the Medical Officer of Health of Todmorden, I notified the Medical Officer of Health of Halifax that a patient was suffering from smallpox in a hospital in his area, and notified the senior medical officer to the regional hospital board of the occurrence and of the necessity for action on his part. The problems confronting the medical officer in the general hospital are discussed in Chapter 10, in a review of Eastwood's paper describing his experiences.

In the Todmorden area the long and arduous task of contact tracing was begun immediately with a visit to the home of the patient A.J. (case 1), a man aged forty-five years, employed as an under-carder in one of the large cotton-spinning mills in Todmorden. He had been vaccinated in infancy, but not since. The family consisted of the man's wife, aged forty-two years, and a daughter aged thirteen years, who attended a local secondary school. The wife had been successfully vaccinated in infancy; the daughter was unvaccinated. The information from the wife, and also from the family doctor, revealed that the patient had had a "cold" on 2 March, but that he did not feel very ill, and continued to work up to and including 5 March. On this day he became much worse, complaining of severe malaise, headache and feverishness, and took to his bed. A typical herpetic lesion was observed on the face, but no general eruption appeared until two days later, 7 March, when "red pimples" were noted on the face and lower arms. There was vomiting at this stage, the vomit being described as "mixed with blood". The development of the eruption during the ensuing few days caused the general practitioner to consider the possibility of smallpox—he had in his younger days been a resident physician in a smallpox hospital—but two features persuaded him to dismiss the possibility from his mind. Firstly, the initial lesion appeared to have been a typical herpetic spot, and secondly "the general rash did not appear until five to six days after the earliest symptoms". In the light of subsequent developments it is almost certain that the man's early symptoms were due to a common cold with labial herpes. The first day of illness due to variola was on 5 March, when he became much worse and was compelled to give up work, the rash appearing two days later. The doctor did not convey his transient suspicion to the medical officer of health, but on 11 March called in a consultant dermatologist. The latter made a provisional diagnosis of generalized herpes simplex, and arranged for the man to be admitted to the Halifax General Hospital. Consultation between the dermatologist and the virologist in the University Department of Bacteriology about the possibility of a culture for herpes virus resulted in a telephone conversation and my being invited to see this interesting case on the day of admission,

not because it was thought that there was any likelihood of it being smallpox, but to photograph it as an interesting eruption.

According to a prearranged plan, the Oakwell Smallpox Hospital was opened in the evening of the same day, and the smallpox patient was transferred at the same time. He had been in the general ward for eight hours, in fairly close contact with other patients as well as medical and nursing staff.

The late diagnosis of A.J. (case 1) resulted in there being a large number of contacts. Contacts were graded into Classes 1, 2 and 3, according to the plan outlined in the section on general principles (p. 403). As the patient was infectious on and after 5 March, and since he was at work on that day, exhaustive inquiries had to be made at the mill, so as to list as contacts for vaccination and surveillance all those who worked in close proximity (Class 1) in addition to any persons who had stopped to talk to him. Other contacts included relatives and friends who had visited the patient at his home between the 5th and 12th of March 1953, and also the ambulance staff who removed him to the Halifax General Hospital. Persons who had walked past him on 5 March without stopping and who did not work in the same room were regarded as Class 2 contacts. As it was obviously desirable to reduce alarm and industrial dislocation to a minimum, precautionary measures were also graded. The general action taken may be summarized as follows:

VACCINATION

All contacts were offered vaccination, priority being given to Class 1 contacts, all of whom were vaccinated within twenty-four hours of the clinical diagnosis of A.J. The only contacts to refuse vaccination throughout the entire outbreak were three or four Class 3 contacts. Members of Class 1 households, that is secondary contacts, were also vaccinated at the same time, so as to produce a ring of immunes around all potential secondary cases. In theory it is not necessary to vaccinate "contacts of contacts", but the possibility of unsuccessful vaccination and of the failure of successful vaccination in the incubation period to protect, made it advisable to start as early as possible if one were to ensure that in all families secondary contacts were successfully vaccinated before the primary contacts reached the end of their presumptive incubation period. As an example of what may occur, one of the secondary contacts was revaccinated at the same time as her husband who was a primary contact. The husband's vaccination three days after contact was successful, and he developed a modified variola nine days later. His wife's vaccination failed, as did a second and third attempt, performed by a different doctor with a different technique. A fourth attempt at vaccination was made on the first day of her husband's illness, and there was considerable anxiety, but an accelerated vesicular reaction became evident three or four days later. Even this successful vaccination, on the first day of exposure to infection, did not preclude the possibility of the lady developing a highly modified infection. Her subsequent free passage through the quarantine period may have been due as much to good fortune as to good management, but it is clear that the position might have been worse if the initial attempt at vaccination had been postponed a few days and not repeated. Repeated failure to vaccinate successfully proved to be rare, but it was noticed that approximately 10 per cent of contacts required a second attempt. Unsuccessful efforts were not related to any particular doctor or any particular technique, nor was there any reason to suspect the quality of the lymph. Fewer "no takes" might possibly have resulted from giving three insertions instead of one, especially if done on different arms.

SURVEILLANCE

All Class 1 and 2 contacts were placed under daily surveillance up to and including the sixteenth day after contact. The Class 3 contacts were told to take to bed if there was any illness, feverishness or rash, and to arrange for the health department and their own doctors to be notified. In the absence of symptoms, arrangements were made for them to be examined on the sixteenth day and given clearance. This examination of all contacts on the sixteenth day was carried out *very thoroughly* by the medical officer of health, so as to ensure that a highly modified case was not missed. The contacts were examined unclothed, and special attention was paid to the face and extremities and in particular to pressure points, so that isolated lesions should not be missed. The history of dates of contact was also carefully checked to ensure that the quarantine period was in fact terminated. The daily surveillance was in the early stages carried out by medical staff, but as the number of contacts grew the task was partly delegated to health visitors and sanitary inspectors, who covered the first nine or ten days of the contact's quarantine period, thus allowing the medical staff to concentrate on the crucial later part. In the later stages of the outbreak the sanitary inspectors were completely occupied with disinfecting and other epidemiological inquiries, and the health visitors were given the entire responsibility of surveillance during the first nine or ten days. Fortunately many of them had had experience in vaccination, and had been taught smallpox control methods in their training in the University of Leeds. They were able to check and revaccinate where necessary, and were well aware of their special responsibility. They were also qualified to deal with the social problems that frequently arose among the quarantined contacts. Class 1 contacts were, in addition to daily surveillance, requested to stay off work and avoid mixing with other persons as much as possible, although this could not be enforced. All contacts off work were offered National Insurance certificates entitling them to sickness benefit for the period of exclusion. The National Insurance office was, however, reluctant to handle certificates or deal with callers in any way connected with homes which might at any time be infected. It was decided to send the certificates *en masse* directly from the Medical Centre to the insurance office. This arrangement worked well.

It should be emphasized that in no case were close contacts *ordered* to stay off work. In England and Wales there is no statutory power to enable this to be done, nor could any compensation be paid for loss of earnings, although this is possible in some parts where local acts enable the local authority to do this. This was apparently not applicable in Todmorden, and had to be explained in every case, so as to avoid as far as possible any misunderstanding or any subsequent claims for damages. No claims were made, nor was there a single deliberate refusal to adopt the advice of the medical officer of health. The attitude of the public throughout the outbreak was remarkable. All precautionary measures, although they lacked the force of law, were accepted with extraordinary readiness. Indeed one was constantly being requested to consider the imposition of more stringent precautions. Many responsible citizens were quite prepared to have places of assembly closed, and a travelling fair, which was about to visit the town, was stopped by the Markets Committee, although advised that such action was unnecessary. Many commercial firms inquired as to the safety of allowing certain contacts to continue at work. Many of these were secondary contacts, and the position had to be carefully and painstakingly explained to each inquirer. Requests to undertake mass vaccination in factories and schools were also received, and had to be reassuringly warded off. Individual queries came in their hundreds, such as: "Am I a contact?", "Can I go to the football match?",

"Should I cancel my holidays?", "Should I allow my child to return from boarding school?", and many more.

Up to this time the medical officer of health had not given any public statement to the press, and the newspapers of Britain now began to direct their long-range artillery on the medical officer of health's headquarters along two telephone lines, often blocking them for important outgoing calls. The local telephone exchange was extremely helpful in keeping out apparently unimportant calls, but the situation was not satisfactory until it was decided to appoint the editor of the local paper as publicity agent, and give prepared statements to him for distribution to newspapers. With one or two exceptions this arrangement worked well and helped to spare both the medical officer of health and the telephone for urgent work.

There was now evidence of strong public demand for vaccination, and it was equally clear that the public looked to the medical officer of health to provide facilities at centrally situated and well-appointed medical centres. Mass vaccination was considered to be neither desirable nor necessary, and included in the first press report was the following: "Dr. Lyons said full precautions were being taken. The Health Department were concentrating on the vaccination and supervision of persons who had been in direct contact with the patients, but the medical officer stressed that there was no urgent need for other people to be vaccinated."

In spite of this assurance, queues began to form at the medical centre and additional medical and nursing staff had to be borrowed from neighbouring areas to cope with the rush. The doctors and nurses engaged in this random vaccination were instructed to avoid wherever possible vaccination of pregnant women or persons suffering from eczema or diabetes, unless they were contacts. Among those advised against vaccination was an eczematous schoolboy. The advice was accepted by the boy's mother, but his sister was later vaccinated by the family doctor, and during the course of play at home the boy's skin was infected by the girl's primary vesicle. He developed a generalized vaccinia, but fortunately recovered, and, as is not uncommon, the eczema almost cleared up during the course of the vaccinia.

During the first weekend of the outbreak, further intriguing developments occurred (they nearly always happened at weekends). The early notifications to neighbouring medical officers of health bore fruit. It was learnt that a Bacup man (case 4), employed at the same mill in Todmorden as case 1, had felt ill when he had gone to work on 9 March, and three days later was sent by his doctor to an infectious-disease hospital as a "severe scarlet fever" with skin petechiae. His condition deteriorated very rapidly and he died about twenty-four hours after admission, on 13 March. In the light of the news from Todmorden the possibility of this man having died from fulminating smallpox was considered. Fortunately, the post-mortem had not been completed, and specimens of heart blood and a piece of skin were sent by the hospital authorities to the virus laboratories. On 18 March, it was reported that the blood had given a strongly positive test for variola antigen, and the virus had been recovered on culture. But before the receipt of this report circumstances were regarded by the medical officer of health of Todmorden as sufficiently suspicious to merit the tracing of all contacts. These consisted of mill contacts of 9 March, the first day of the illness, in addition to a few persons who sat close to the patient on a bus on that date. Some of this number had already been vaccinated as possible contacts of case 1; the remainder were vaccinated on 15 and 16 March, and all were placed under surveillance. It was not considered desirable to publicize the fact that the patient had travelled on a Corporation bus on his first day of illness. Such publicity would certainly have assured that all bus contacts would be vaccinated, but it also would have caused consider-

able alarm. The possible effect on transport workers had to be considered too. Discreet inquiries enabled the medical officer of health to discover those persons who had been sitting in close proximity to the patient; the risk to others on the bus was thought to be minimal, and it was thought justifiable to take no further action.

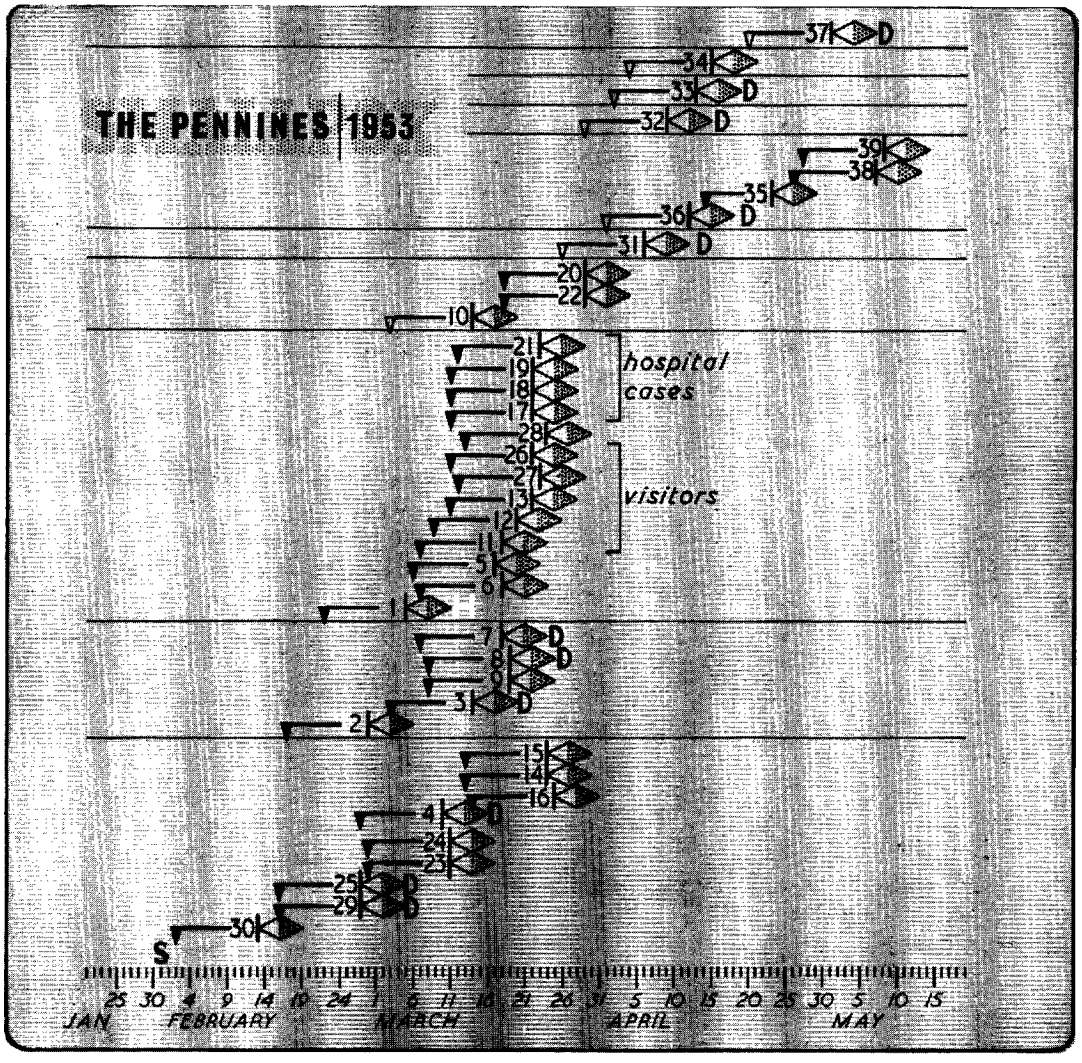


FIG. 284.

This Bacup man gave rise to no secondary cases in Todmorden, but the man's wife (case 16) had a moderately severe attack, and two children (cases 14 and 15) who were with this man on 12 March in hospital also developed mild attacks. The wife's onset of illness was on 25 March, so that, assuming the incubation period to be not longer than thirteen days, it would appear that she did not become infected until the fourth day of her husband's illness.

The second interesting development in the early days of this outbreak arose out of the request to general practitioners to report any adult or atypical cases of chickenpox. One such patient was a man, J.N. (case 2), employed at the same cotton mill as the previous cases. He was sixty years of age, and had been vaccinated in infancy and during the 1914–18 War. He gave a history of severe malaise and feverishness, beginning on Saturday, 28 February, when he was at work. He took to bed on the following day, and called the family doctor. The rash was first noticed by the patient on 4 March; it was said to have extended over the forehead, chest and arms. When seen by the medical officer of health and myself, on Sunday, 15 March, the man said he had recovered and was hoping to return to work on the following day. On examination, however, there was evidence of a past modified eruption. The peripheral distribution of suspicious scars, together with the existence of four minute seeds on the hands, were strong indications of variola, and a clinical diagnosis was made (Fig. 111). This was the sixteenth day of the disease. The man was questioned about the health of his family. He said that his wife had been in bed the previous day, but that she was "often like this". I examined Mrs. N., who was fifty-seven and had been vaccinated in infancy with four insertions. She was very pale and restless, almost shocked, and complained of headache, backache and vomiting; there was no rash. This picture fitted perfectly the initial stages of smallpox, particularly of the fulminating kind; we therefore decided to admit Mrs. N. (case 3) as a clinical smallpox, along with her husband. The latter had largely recovered, but he was theoretically still infectious. Mrs. N. developed an erythematous rash within twenty-four hours of removal to hospital. She was a true type 1 fulminating purpura variolosa, and died (Figs. 6 and 7).

The family contacts of Mr. and Mrs. N. consisted of two unvaccinated sons, aged nineteen and fourteen years, an unvaccinated middle-aged lodger, Mrs. S., and the son of Mrs. S., an R.A.F. youth on leave who had been successfully vaccinated only two months previously. In view of the very late diagnosis of Mr. N., it was not considered that vaccination of his family contacts would be likely to afford any appreciable degree of protection. They had already been exposed to infection for a fortnight. Vaccinations were nevertheless performed within an hour of Mr. and Mrs. N. being diagnosed. Vaccinations late in the quarantine period have an administrative advantage in that, if the vaccinated contact subsequently develops any rash, one need not hesitate to admit him to a smallpox hospital. The mill contacts of Mr. N. (case 2) were already out of quarantine at the time they were traced on 16 March, since the man had not been at work since 28 February, but they were all examined to exclude the possibility of mild modified infection and all were found to be clear. Two relatives, who stayed overnight on 28 February to 1 March and who were therefore close contacts on the first day of illness, also reached the end of their quarantine period uneventfully.

The other family contacts did not fare so well. Out of a household of six persons, the only one to escape infection was the recently vaccinated R.A.F. youth. Of the five infected, one was Mrs. N. (case 3), with type 1 fulminating purpura variolosa; one son (case 8), who closely resembled his mother in looks and physical development, died from type 2 (Figs. 24 and 25), malignant confluent, while the other son (case 9), apparently equally exposed and equally vaccinated late in the incubation period, but of a different physical type, developed an unmodified discrete attack. The lodger (case 7), no relation, developed a malignant semi-confluent attack and also died (Figs. 42 and 43).

The fate of the contacts of case 1 showed a similar pattern but with less severe results. None of the mill workers in contact with case 1 on the first day of illness developed the disease. All

Class 2 contacts remained free of infection, but several of the other Class 1 contacts were infected. These included the other members of his family, his wife (case 6) and daughter (case 5), and three of the persons who had visited him on the 10th or 11th of March, and had been inside his bedroom (cases 11, 12 and 13). One of the latter (case 11) insisted that he was in the bedroom for not more than two or three minutes, but it must be supposed that on 11 March the condition of case 1 was such that the concentration of virus in the bedroom would have been quite high. The most probable source of virus would be in the dust from bedding infected from the respiratory tract of the patient during the early stages of the disease. Case 1's short stay in the Halifax General Hospital—he was in the ward for eight hours—produced a batch of four secondary cases (17, 18, 19 and 21) among patients, three in nearby beds, the other being ambulant. All four were highly modified by successful vaccination performed immediately after contact.

In addition to the contacts already mentioned were two Todmorden general practitioners who had attended both case 1 and case 2 between 2 and 11 March. Both doctors subsequently developed influenza-like symptoms, one on 22 March and the other on 23 March. They at first attributed their illness to the after-effects of revaccination performed on 14 March, and they carried on with their duties until 24 March. Their revaccinations at the time showed a well-marked vesicular reaction. Both doctors had been vaccinated several times before, but the last occasion was thought to have been about twenty years ago. The persistence of symptoms on 24 March induced them to notify the medical officer of health who examined them and asked me to see them. We were able to demonstrate three small macules on the forehead and hands of one of the doctors (case 27), whose pyrexia had commenced exactly twelve days following the one contact with case 1. The other doctor (case 26) had no skin lesions, but the first vaccination attempt had failed and only the second one done on the fifth to sixth day of the presumptive incubation period was positive and, being definitely of primary type, suggested that immunity at the time of exposure might well have been low. It was agreed that the existence of these lesions on sites of election was sufficient to warrant the provisional diagnosis of variola and the precautionary removal of the doctors to a smallpox hospital was advised. It is to the credit of both doctors that they readily consented to this course of action being taken, although fully aware of the unwelcome publicity that was bound to follow. They were sent to the smallpox hospital in Lancashire so as to avoid admittance to the same ward as their own patients.

This unfortunate turn of events was a heavy blow to the Health Department. Every one of the hundreds of patients examined by the two general practitioners since the morning of 22 March was now a potential new case. The general practitioners' normally busy practice had moreover been swollen by many people wishing to be vaccinated and, although it was easy to obtain lists of patients visited in their own homes, the only way of effectively tracing all the surgery contacts was by an appeal to the public. It was of course recognized that the risk to these contacts was small, as both the doctors had probably been infectious for a very short time, but not short enough to be ignored. A statement was carefully prepared by the medical officer of health, being designed to achieve the almost impossible task of tracing the contacts without alarming the public. It read as follows: "Drs. —— and —— are today being admitted to hospital for investigation. They had both been in contact with the first two cases of smallpox before the diagnosis had been established. They are showing only mild symptoms, but in view of the nature of their work and in order to avoid the possibility of spreading infection they have

agreed to be placed in isolation in hospital. There is no cause for alarm, but as a precautionary measure all persons who have been seen by either of these two doctors since Sunday morning last, the 22nd of March (to the 24th inclusive) are advised to attend the Medical Centre, Todmorden, this evening between 6 and 8 p.m., so that arrangements can be made for vaccination, examination, and supervision where necessary. There is no necessity for special action in respect of patients last seen by either doctor before last Sunday. Persons unable to attend should try to notify the Health Department through a neighbour or friend."

The statement was placed on notice-boards outside the Medical Centre and in other prominent sites in the town, and was also broadcast by the local relay radio service. A slightly amended version, leaving out the names of the doctors, was broadcast in the general news by the B.B.C.

A questionnaire was rapidly prepared and duplicated so that it would be possible for clerks to obtain all the relevant information: for example, name, age, address, date and duration of contact, date of any recent vaccination. Vaccination sessions for the general public were suspended, so that for that evening the staff could concentrate on this work. Over two hundred persons attended. After preliminary interview by clerks, each contact, armed with his or her completed questionnaire, was referred to a doctor. Where there was a history of recent vaccination the lesion was examined. If the reaction was clearly positive, i.e. vesiculation, and the vaccination had been done three or more days before contact, the person was advised that no further precautions were necessary. Where the reaction was doubtful or negative, or where there was no evidence of successful vaccination within the last two years, vaccination was performed then and there. The person was also advised of the arrangements for surveillance. Where the inquiries revealed contact of a very transient nature, for example persons who had been in and out of the surgery in a matter of a minute or so, they were regarded as Class 3 contacts, and were not placed under surveillance, but were told to report any illness.

The evening's work went off with remarkable smoothness. Doctors, nurses and staff, all of whom had been requested to be as reassuring and cheerful as possible in their approach, achieved the required result with complete absence of friction or alarm. Not a single contact rejected the advice offered, and as a result of the inquiries approximately one-third of the persons interviewed were placed under surveillance.

The subsequent progress of the two doctors in hospital was interesting. The macules noted at the initial examination disappeared; one which had been scraped failed to grow any virus on chicken embryo, a result of doubtful significance. Serological tests could not be done because of the recent vaccination. The appearance and subsequent abortion of the few macules supported a diagnosis of variola sine eruptione, but the smallpox hospital consultant, who had not seen the lesions, was unable to concur, and was in favour of discharging the two doctors forthwith. This situation was discussed with a medical officer of the Ministry of Health, at a meeting where three of the panel of smallpox consultants were present. It was not agreed by all that the patients had smallpox, although I maintained that they were both variola sine eruptione, and notified them as such to the medical officer of health. He acted on this information. No one, however, would affirm that these two patients could *not* have had an attack. It was therefore agreed that after seven days they were not infectious. All their contacts reached the end of the quarantine period uneventfully.

Investigations into the source of the outbreak led to some fascinating if rather grim discoveries. The fact that the first three cases were men working at one cotton-spinning mill

naturally focused attention on raw cotton which is imported from a number of areas in the world where smallpox is endemic. Two of the men, cases 1 and 2, worked in the carding room and cotton chamber respectively, where the density of raw cotton dust in the atmosphere was very high. But case 4 was a cotton packer, handling spun cotton (yarn) only, a much cleaner job. The date of onset of case 4, 9 March, was ten days after that of case 2 and five days after that of case 1. He could not therefore have been secondary to case 1. It was unlikely that he was secondary to case 2. It seemed more probable that he acquired his infection from a missed case belonging to the same generation as cases 1 and 2. As will be seen later, this supposition was almost certainly correct (see Fig. 284). The hypothesis in favour of raw cotton as a source of infection appeared to be given fresh support by the appearance of a case of smallpox in the Oldham area. The patient (case 10) was a man employed in the "blowing" room of a spinning-mill. His onset of illness was on 13 March, twelve days after the onset of the earliest Todmorden case then known, but no direct link could be established with any person in Todmorden. There was, however, one factor of possible significance, namely that raw cotton from the same consignment was being used at both mills at the material time, and few if any of the other mills in the area were using it. The weight of circumstantial evidence incriminating raw cotton was now far from negligible, and investigations had to be made over a wide area of Lancashire. Individual medical officers of health were naturally handicapped when attempting a regional check-up outside their own boundaries so medical officers of the Ministry of Health carried this out with much energy and enthusiasm. They advised the holding of the suspected consignment of raw cotton and of cotton waste from the Todmorden mill. This was readily agreed to by the cotton firms. No restrictions were placed on the movement of yarn (spun cotton), which was considered to be innocuous. The medical officer of health nevertheless received a long succession of anxious inquiries from firms in various parts of the country who had had recent deliveries of yarn from Todmorden. All were given the appropriate reassuring advice.

A new line of inquiry leading to more concrete results arose indirectly out of the fatal Bacup case (case 4). One had been impressed by the virulence of the infection leading to a fulminating viraemia, with no characteristic eruption and therefore no clinical diagnosis. Mrs. N. (case 3) was somewhat similar and, had her illness occurred a week earlier, she too would probably have gone undiagnosed. Were there others? Inquiries at the mill revealed that one of the older employees, Mr. H. (case 25), had not been at work since 26 February, and was said to have died of pneumonia on 3 March. There was a history of chest trouble, and the registrar's returns confirmed that the certified cause of death was broncho-pneumonia. As the man had been cremated, one could assume that he had been examined by at least two doctors, one of the examinations consisting of a post-mortem inspection. There seemed little ground for suspicion, but further investigation was considered worthwhile, especially after a clerk in the health department reported that a rumour was prevalent in the neighbourhood to the effect that the man had died of smallpox.

Mr. H.'s married son was sought. He gave a history of his father feeling ill after returning from work on 26 February. He became much worse during the following two days and complained of headache, backache and vomiting. He normally lived alone, but the son and also a married daughter decided to stay with him throughout the weekend, 28 February to 2 March, when a blotchy red rash was observed on the arms and body. The doctor saw him on this day and also observed a rash—later described to the medical officer of health as patchy and scarlatiniform—and took it to be a toxic rash arising out of his acute pyrexial chest condition.

Mr. H. died on 3 March. The rash was still evident after death, being noticed by the doctor giving the cremation certificate and also by the undertaker.

The interview with Mr. H.'s son took place nearly three weeks after his father's death. Both he and his sister had had "influenza" on 11 March, fourteen days after the onset of their father's illness. I made a careful clinical examination, but this did not produce any lesions other than one small scab over the son's tendo achilles. This was scraped and sent to the laboratory, but no virus was grown. Blood specimens were also sent for serological tests, and the laboratory reported that the results on both the son and daughter were strongly suggestive of either recent variola or recent vaccination. The daughter (case 23) had not been vaccinated since infancy, thirty-three years before, and the son (case 24) was last vaccinated in 1946, seven years before. A diagnosis of variola sine eruptione was clearly justified, the father's illness being fulminating smallpox. This also solved the problem of the Bacup man's source of infection. Mr. H.'s work brought him into frequent contact with the Bacup man (case 4) and they were also friendly outside the mill. The time interval between their respective dates of illness was approximately eleven to twelve days. Neither the doctor who treated the case, the second doctor who saw the body, the undertaker nor any of the neighbours who visited Mr. H. contracted the disease, although their vaccination states did not suggest immunity. The contacts of Mr. H. junior and his sister during the first four days of their illness were vaccinated, although very late, and placed under surveillance, but no further cases arose.

Further inquiries at the mill led to the discovery of two more "missed" cases, including yet another death. On 2 March, three days before the onset of case 1, at 11 p.m., a Mrs. J. (case 29), wife of a cotton-waste bagger at the mill, was admitted into a hospital in Halifax with a three-day history of toxaemia, pyrexia, anorexia, vomiting and abdominal discomfort. Intestinal obstruction was suspected, and a laparotomy performed, but the patient died four hours after admission. At the post-mortem examination an erythematous eruption was observed on the chest. The only other positive finding was some congestion of the jejunum, and death was certified as being caused by "toxaemia due to acute enteritis". Mr. J. was interviewed approximately three weeks after his wife's death. On being questioned about his own health, he stated that he had had a rash on his forehead and arms about a fortnight before his wife took ill, but he did not consult a doctor. He had been vaccinated in infancy, revaccinated in 1906 and again during the 1914–18 War. He consented to examination, and a dozen or more scars, about one-eighth of an inch in diameter, were observed, chiefly on the arms and legs. Their number and distribution were highly suggestive of smallpox. A specimen of blood was sent for complement-fixation test, and the report supported a diagnosis of recent variola.

Mr. J. (case 30) had intermittent contact at work with cases 1, 2 and 25, and the dates of onset of illness are consistent with his being the source of infection of the other three. As direct human-to-human infection is always more likely than through the agency of fomites, it can be safely assumed that the other cases did acquire their infection from Mr. J., and not from raw cotton. It is extremely unlikely that Mr. J. himself was infected by cotton, for although he was the first known case in the mill, his job as a bagger of cotton waste was such that he handled cotton at the *last* stage of its process and passage through the mill.

The source of Mr. J.'s infection unfortunately remained unsolved. Investigations were hampered by the lapse of time between early February, when Mr. J. acquired his infection, and late March, when the inquiries were first instituted. Mr. J. co-operated to the best of his somewhat limited ability but, not unexpectedly, it was impossible to obtain a consistent and

reliable account of his movements and contacts at the material time. From the jigsaw of information received from relatives, friends and workmates and Mr. J., it seemed that the most likely contact with the outside world was through lorry drivers unloading cotton and collecting cotton waste at the mill. It will be remembered that Mr. J.'s job consisted largely of the bagging of cotton waste for dispatch to a depot in Lancashire. It was known that several of the drivers spent an hour or two at the mill, waiting for loads, but their inability to remember specific instances after six or seven weeks was understandable. Some of the drivers resided in or near Merseyside, and inquiries were made through the respective medical officers of health as to whether there was any history or clinical evidence of missed modified infection, and whether any gave a history of contact at or near the ports with people recently arrived from Asiatic countries. It had been supposed that the peregrinations of lorry drivers would extend to dock-side cafés, public houses and other depots of social intercourse, but they were remarkably reticent about the recreation habits and no information of a positive nature was obtained. Indeed, the account of movements of contacts in general throughout the outbreak indicated a level of social and moral rectitude which would delight our religious brethren and disappoint the Sunday newspapers. The probing of private lives is distasteful and often impracticable, but had it not been for this gap in our knowledge, valuable clues would have been obtained of the genesis not only of the Todmorden outbreak but of the apparently isolated cases that occurred subsequently in other parts of the West Riding.

The back-dating of the onset of the first known Todmorden case to approximately 5 February by the discovery of cases 30 and 29 now provided a possible link between Todmorden and the Oldham case, case 10, whose onset was 13 March. The interval of twenty-six days between the two left just enough room for an intermediate case, about 1 to 3 March. The two men were unknown to one another, and although doctors of the Ministry of Health discovered two persons who were likely to have had contact with both, close investigation, however, including sampling of blood for C.F. tests, exonerated the two suspects, and the missing link was never found.

To complete the picture in Todmorden, it is necessary to mention one further person, case 28. On 27 March, I saw this woman, who had an early maculo-papular rash on the face and arms and a few on the legs, following a history of headache, malaise, vomiting, commencing three days previously, on 24 March, an epidemiologically significant date. Vaccination with a successful outcome had been performed five days before the commencement of symptoms, but there was no known contact with smallpox. Clinically this case had to be regarded as a possible smallpox, and admitted to hospital; contacts were immediately vaccinated and other precautions were taken. In hospital, the rash did not develop but aborted, leaving very minute scabs the size of a pin-head. Some were removed and sent to the laboratory for examination for virus. Because of the recent successful vaccination, serological tests were not done. The first laboratory report after three days gave only one virus colony growth—significance doubtful. After a further three days the second report was negative. At the end of six days, therefore, all that could be said was that it could or could not have been smallpox—no other diagnosis was made. Administratively, however, it had been treated as smallpox, the right procedure I am sure, and no secondary cases occurred.

The Todmorden outbreak proceeded to its conclusion "according to plan". There were no solitary, unconnected cases, and no further contacts under surveillance developed the disease. A cautiously worded "all clear" was issued to the press on Monday, 13 April.

The Oldham case, case 10, although having many contacts of a rather distant nature, only gave rise to two secondary cases, a girl aged seventeen (case 22), who had visited the house, and the mother, aged fifty-five (case 20).

The situation in Halifax Hospital was likely to give trouble. Case 1 had been admitted to a ward containing thirty general medical and dermatological cases. He was in the ward for three hours before the diagnosis of smallpox was made and some ambulant patients spoke to him. Following the diagnosis of smallpox the Medical Officer of Health for Halifax was immediately informed and vaccination of patients in the ward, and the remainder of the staff and patients of the hospital was done under his direction. Four patients in the ward contracted mild smallpox. Points of great interest were, firstly, the limited time of contact with the patient, about eight hours, and secondly, that of the thirty patients in the ward, three of the nearest were infected (see Chapter 15). Vaccination performed on the day of contact within eight hours, and undoubtedly positive in three of them, failed to prevent an attack, although considerable vaccino-modification was seen (Eastwood, 1955).

One of the patients (case 18) suffered from constitutional eczema, a second (case 19) from sclerosing lymphogranuloma affecting the legs, the third (case 17) was convalescent from acute hepatitis, and the fourth (case 21) was convalescent from pneumonia. These cases were under close observation and it was thought that the pyrexial onset was on the 19th, which gives a rather short incubation period. The rashes, however, were seen by me on the 26th, and early vesicular lesions were present. In view of the vaccino-modification, these need not have been present for more than twenty-four hours. The incubation period seems more likely to have been ten or eleven days, and the earlier pyrexia could have been vaccinial. A further complication was present in one of the patients in that he had suffered from some secondary vaccinial lesions around the primary lesions. It was at first thought that his whole condition was generalised vaccinia. It was possible, however, to see the age of the vaccinial lesions. Those of variola were quite different (see Fig. 105).

On 27 March, a woman in another Halifax hospital was thought to have a suspicious rash. I examined her, and found that after a mild pyrexial attack three days before a few macular lesions had appeared on the arms and face. The patient was not very co-operative, the history was rather doubtful and the lesions not very typical. The patient, however, had been in the hospital a few days and had come from Todmorden during the time when unknown cases of smallpox were present. The patient was an inmate of a large institution for the chronic sick, a particularly dangerous situation, and was therefore regarded as a suspect smallpox, vaccinated and admitted to the smallpox hospital. It certainly satisfied Wanklyn's dictum—"Could it be smallpox?"—and contacts in the hospital were vaccinated. I think my diagnosis was clinically wrong, but administratively right. No alternative clinical diagnosis was made.

Another doubtful case was admitted by the acting Medical Officer of Health of Halifax. This was a man who, after a pyrexial attack, showed a profuse maculo-papular eruption on the lower arms, hands and neck. He had recently been vaccinated, and might have been a contact, as he was a gas fitter, and engaged in the hospital where case 1 was admitted. Unfortunately he washed his face, neck and hands in a strong disinfectant and this apparently, in conjunction with a vaccination, set up a local reaction. However, the trauma to these sites could have caused a local profusion of smallpox lesions, so this again was the sort of case that had to be admitted for observation. The man had attended a football match in the Lancashire area during the pyrexial attack and this unfortunately led to advice being given there that all who had been

at the football match, some 11,000, ought to be vaccinated! This is the type of case where twenty-four hours' clinical observation could quite easily disprove the diagnosis of smallpox (see Fig. 183).

The next surprise in this outbreak was the diagnosis of smallpox in a boy aged eight years (case 31) at Leeds. He had been sent to the Seacroft infectious-disease hospital by ambulance with a diagnosis of measles (Figs. 15 and 16) and, fortunately, was examined before admission, very competently diagnosed and diverted to the smallpox hospital. This child had lived in an overcrowded part of Leeds, close to the cattle market. There were family and other contacts, all unvaccinated, but fortunately the schools were closed. The vaccination of contacts was done straight away, but at this late stage, six or seven days after contact, the outlook was not very hopeful. However, no secondary cases occurred.

Four days later, a boy of sixteen (case 32) living in Linthwaite, near Huddersfield, was diagnosed as smallpox and removed to hospital. He was a lorry-driver's mate, and travelled in the Huddersfield, Halifax and Leeds areas. He had no known contacts with Todmorden. There were four others in his family who were isolated in the smallpox hospital as a precautionary measure from the tenth day of the presumptive incubation period. Three other close contacts were isolated because of slight pyrexia. No secondary cases occurred from this focus.

Two days later, a fulminating case was diagnosed in Gildersome, on the outskirts of Morley, not far from Leeds. This man (case 33) worked in a clay pit, and was concerned with the loading of lorries. He had a small cabin to which it was believed he not infrequently invited lorry drivers. In spite of extensive inquiries by the Medical Officer of Health of Morley, no contact could be traced with any of the known cases.

The next case reported was in a woman of sixty-nine (case 34) in Bury, Lancashire, who was sent into hospital as a case of uraemia. No source of infection was discovered.

On 2 May, I was asked to see a post-mortem porter (case 35) who worked in the City of Leeds public mortuary. He had had a febrile attack followed by a rash which was thought to be chickenpox. He had been vaccinated in infancy, and although his rash showed considerable modification and cropping, the distribution was sufficiently characteristic to enable me to make a definite diagnosis of smallpox. This was subsequently confirmed by the laboratory. On investigation, it was found that he had pricked his finger when attending to a body in the mortuary some nine days prior to the onset. This resulted in a "septic" finger, affecting the pulp, but although untreated it never suppurated but only produced a rather deep nodular lesion (Fig. 101). It seems almost certain that this was an inoculation with variola virus, and accounted for the nine-day incubation period. Investigation of the port-mortem records at the mortuary showed that the source of the infection, Mrs. B. (case 36), a woman of forty years of age, was suddenly taken ill two days before death, with a violent headache, backache and vomiting, accompanied by a moderate pyrexia. She died without any signs to suggest the cause of death. The post-mortem, at the coroner's request, revealed nothing abnormal beyond small haemorrhages in the larynx (Fig. 5) and others in the pericardium. The blood film showed cells consistent with a diagnosis of acute leukaemia, and a death certificate to that effect was given. Although specimens had been taken from the body, unfortunately none were in a condition to isolate virus, and it was therefore impossible to confirm the diagnosis by any laboratory investigations. I have no doubt that this was a fulminating smallpox.

The repercussions from this event were considerable. The mortuary, although a public one for the city, was situated in the grounds of a large general hospital, and there was sufficient

contact of staff to necessitate control measures being taken there. One pathologist, who had never been vaccinated, was in contact with the mortuary porter during his initial febrile attack. The pathologist was vaccinated late, on the tenth day, and was given a dose of vaccinia gamma-globulin on the twelfth. The vaccination was successful, and the pathologist escaped an attack of smallpox; the two events and the dose of gammaglobulin are not necessarily connected. The second pathologist, who did the autopsy on Mrs. B., was taken ill some seven days after and had no eruption but did have a number of febrile attacks over a period of ten days. He was fully investigated in the teaching hospital, the Leeds General Infirmary, but no diagnosis was arrived at. When his previous contact with smallpox came to light, a specimen of blood was examined for the presence of antibodies, and a titre of 1 in 20 obtained. This was first reported as diagnostic for smallpox, but was later changed to "indicating contact with smallpox virus", a fact already known. The picture was complicated in that although no vaccination had been done for about four years, the individual had been vaccinated many times in the Army and had served in Burma and the Far East. Although patients who recovered from quite severe smallpox were perfectly well within a few weeks and back at work quite soon after their attack, this individual had recurrent fever and malaise for some six weeks, and was not fully recovered even after three months. The cause of his illness ultimately came to light. At the time his illness did not satisfy Wanklyn's dictum, and I have no doubt that the clinical syndrome from which he suffered at this time was not due to the variola virus, and the control measures, based on the laboratory report, were unnecessary.

The last isolated case in this outbreak (case 37), occurred in a miner of nineteen from Shipley, on the outskirts of Bradford. He visited football matches and cinemas, and possibly other forms of recreation, to a considerable extent, but no known contact could be found between him and the other cases, or any known contacts. Diagnosis was made early on the fourth day and contacts promptly vaccinated. No secondary cases occurred. The final episode was the occurrence of smallpox in Leeds in the son (case 39) and daughter (case 38) of the mortuary attendant. They were vaccinated when the diagnosis was made in their father on the eighth day of their incubation period. The bitter irony of life showed itself in the boy having a very mild attack, type 7, with virtually no residual scarring, while the girl, eighteen years of age and a hairdresser, had a full discrete attack, with severe scarring (Figs. 110, 157). These cases had been under surveillance, and no secondary cases arose from them.

All the cases were diagnosed by clinical and epidemiological means, and the laboratory tests made no direct contribution to the work of smallpox control, although giving interesting confirmation *after* the administrative decisions were made, except in an area with which I was not directly associated, where waiting for a laboratory report delayed the vaccination of two hospital contacts by three days. They had mild attacks. This is not the fault of the laboratory, but merely emphasizes the possible harm that may occur through the clinician or health officer passing diagnostic responsibility to the laboratory.

Payment of full compensation for loss of wages of contacts under surveillance should be part of the Public Health Acts, and not limited to powers under local acts. In the Tottenham outbreak (Hogben *et al.*, 1958) only £100 was spent in this way, which is trifling compared with the thousands spent on unnecessary vaccinations.

The public health control was by limited ring vaccination, case-finding and surveillance of contacts. Unfortunately public pressure, not resisted enough by health officers or general practitioners, resulted in many thousands of unnecessary vaccinations with one death from

generalized vaccinia, one from encephalitis, and one non-fatal case of encephalitis—none in contacts of Class 1, 2 and 3.

Although Paul (1952) and others have pointed out that if anyone requires vaccination he should be given it, it does not seem to be correct medical ethics if there is no risk, any more than carrying out surgery on request of the patient and in the absence of medical indications. The medical adviser is still responsible if severe or fatal complications of vaccinia occur when the risk of smallpox is nil.

Smallpox control is hindered, not helped, in Britain, by paying the general practitioner, who otherwise provides his service on a capitation system, five shillings for a vaccination certificate. Many thousands of persons far remote from smallpox risk were vaccinated, some practitioners getting an extra £200 income during this outbreak. It demonstrates, if anyone requires it, that preventive medicine can never be practised satisfactorily if the general practitioner is paid on a fee-for-service basis.

VARIOLA MINOR, GLOUCESTER, 1923

Based on the account by Painton (1923)

A full account of this outbreak is not available as there were difficulties with the medical officer of health, and an acting medical officer of health was appointed during the course of the outbreak. The story is interesting because of the attitude of various members of the medical profession. Gloucester, it may be remembered, was a town in which there was a very strong antivaccination feeling, and which had a large outbreak of variola major in 1895–6. Then, in the words of McVail, "Gloucester became the most vaccinated town in the British Empire", but it would appear that subsequently infant vaccination was just as unpopular.

Gloucester had notification of chickenpox, and during December 1922 there were twelve notifications of this disease. During the month of January 1923, there were fifty cases notified, and in one case the notifying doctor had suggested that the medical officer of health might see it, as the child seemed neglected, but there was no suggestion that the disease was other than chickenpox. During January, however, a case of smallpox occurred, but was not put in the register at all. The mother thought it was smallpox, and took it to the infirmary, where the doctor thought it was smallpox. Having kept her at home for six weeks, she then took the child to a general practitioner, who said that it had been a bad case of chickenpox. Other cases appeared in the neighbourhood, and two, in children aged nine and ten, were entered as chickenpox, having been notified by the school nurse, although in all probability they were smallpox. During the month of February there were seventy-three cases of chickenpox notified. In the case of one at least, the retrospective diagnosis from the history and the presence of scars made it fairly certain that it and many others were smallpox. During the month of March, 176 cases of chickenpox were notified, and three cases of smallpox. Two notifications during the month of March, however, were put as ?chickenpox by the doctors, with notes as to rash on the face only, headache, backache, etc., but the medical officer of health entered them as chickenpox. In one, on 19 March, the medical officer of health had been asked to see the case. In another on the 27th, although notified as smallpox, the entry in the register was chickenpox, although the case was removed to the hospital. By 27 or 28 March, there were five men and one woman in hospital at Longford, all suffering from smallpox. Although some cases were subsequently notified as smallpox, they were treated at home as chickenpox by the

doctor concerned. Cases were also seen in the month of March by the medical officer of health, who diagnosed them as chickenpox. During the month of April there were 206 cases of chickenpox notified, making a total of 517 since the beginning of the year, and three cases of smallpox were notified and registered as such, all being notified by one practitioner. Five notifications, however, during the month of April, were either made first as smallpox or ?chickenpox and were subsequently put into the register as chickenpox. During May, 329 cases of chickenpox were notified, making a total to date of 846. There were no notifications of smallpox registered as such, although a large number of cases subsequently examined by Dr. Hutchinson of the Ministry of Health and Dr. Cameron of the River Hospitals were rediagnosed as cases of smallpox. Seventeen cases notified by practitioners as smallpox and three notified as ?chickenpox had all been put in the register as chickenpox. During the month of June there were 270 notifications of chickenpox, many of which were notified as ?chickenpox, making a total to date of 1,116, and in addition 163 cases of smallpox and ?smallpox were notified. Of the 270 cases of chickenpox, many were subsequently diagnosed as smallpox. On 1 June, six months after smallpox had been present in Gloucester, Dr. Hutchinson of the Ministry of Health visited the town, saw a number of cases which had been notified as chickenpox, found them to be smallpox, and informed the Mayor, the chairman of the Health Committee and the medical officer of health. As this diagnosis was not accepted, experts from London were brought down. All agreed that most of the cases of notified chickenpox were cases of smallpox, but this was not accepted by the medical officer of health. It was only at this juncture that the Health Committee of the City Council became acquainted with the situation. Due to the impasse the Health Committee obtained the services of Dr. W. H. Davidson of Birmingham and subsequently of Dr. Painton, and the medical officer of health was ultimately relieved of his control, but not before a considerable amount of obstruction on his part and on the part of a number of general practitioners and refusal to accept the diagnosis of these cases as smallpox. Up till 31 August 1923, 621 cases of smallpox had occurred in 404 houses. In 272 houses there was one case in each, in 81, 2; 28, 3; 16, 4; 3, 5; and 4, 6. Of the 621 cases, 115 were not admitted to hospital. Dr. Painton's report states: "It is not saying too much to express my opinion that if the facts had been known and faced openly and squarely in the beginning, most of the distress and all of the scare caused by the press writing up the epidemic in the interests of other communities outside Gloucester would have been avoided, and also, mark you, that the cost to the community of this city would have been comparatively small." What was rather pitiful was the fact that when cases of smallpox occurring in contacts came to light it was not unusual for the patient to immediately go to one or two of the local doctors, who it was known would give a certificate saying that the patient was suffering from chickenpox. No details are given as to the method of control, but it would appear to have relied principally on isolation due to the intense antivaccination feeling prevalent in Gloucester at the time, although doubtless vaccination of contacts was done as much as possible. It is surprising that even when a mother was admitted to hospital with smallpox and an unvaccinated child accompanied her, she still refused to have the child vaccinated. There were three deaths altogether out of 498 admissions, and only one of these, in an infant of six weeks, was probably directly due to smallpox. About 5 per cent were permanently marked.

This outbreak is of interest in showing the lack of social conscience in a group of county town general practitioners who were prepared to give false certificates of chickenpox to persons who wished to escape isolation and any control measures for smallpox. The local medical officer of

health also appears to have acted in collusion with some, in altering smallpox notifications to chickenpox, but for what purpose is not at all clear. Although Dewsbury in 1904 was to some extent also antivaccination, its general practitioners were most co-operative with the medical officer of health, and allowed all patients diagnosed as chickenpox to be seen and checked by him. The contrast between this outbreak in 1923, part of the large outbreak in England and Wales between 1922 and 1934, and that of variola minor in Rochdale in 1952, is most striking. It emphasizes the need in the practice of public health for the development and use of skills in the assessment of the character or personality of a town, and its probable reactions to outbreaks of a disease such as smallpox, and to plan control measures accordingly.

VARIOLA MINOR, ROCHDALE, 1951–2

Based on the account by Innes (1953)

The outbreak first came to light by the discovery of a case in Milnrow, outside Rochdale, on Friday, 15 February. A search in Rochdale showed that there were thirty cases present. Presumably they had been regarded as chickenpox. The search backwards from known cases showed that the disease had been present in Rochdale at any rate as far back as early December, and probably in mid-November.

Between the 15th and the 25th of February, thirty-nine cases were discovered in Rochdale. On the 1st, 2nd and 3rd of March fresh households were discovered to be infected, not all of which could be directly linked with any known cases, so that there were sixty-four cases by 3 March and seventy-four by 5 March. Of the last ten cases no fewer than seven were children, all of whom showed the disease in a very mild form. These would have passed for chickenpox but for the careful search, and in view of the roughly equal number of cases in the unvaccinated under fifteen and over twenty-five, one wonders whether in some of the earlier outbreaks, for example the Australian one of 1913 where the majority of cases were over ten years of age, the reputed simultaneous outbreak of chickenpox in children might not have been wholly true.

In view of the large number of cases detected in such a short space of time, there was considerable public alarm, and Innes makes the plea that the disease should be called alastrim and not smallpox. In a report to his health committee, he says: "It is not changing, indeed cannot change, into true Asiatic smallpox, which brings disfigurement and death in its train." Unfortunately variola minor also brings disfigurement, and in his paper (1953) he agrees that variola minor is a more serious condition than chickenpox.

From 5 March to 11 April, thirty-eight new cases occurred. It was thought that a small number of cases existing in the middle of February produced a wave of forty-four, but this large number a fortnight later had only produced a further twenty cases. The earlier wave included no fewer than seventeen cases of which the source was unknown, whereas the later wave included only five. Innes regards the number of cases as less important than the number of households, as multiple cases in one household are not as important as the same number distributed in separate households. Multiple cases are, however, fewer than usually assumed. Because of the possibility of a large number of isolated and apparently unconnected cases at this late stage in the outbreak, the public were advised to remain indoors during any attack of supposed influenza and to report the presence of a rash to the family doctor. They were warned that there was no magical protection in a doctor's waiting-room, and therefore a person with

smallpox should remain at home and call the doctor. Both the general public and the medical profession co-operated extremely well with this arrangement.

Although possibly not meaning it, Innes does not put the vaccination of contacts as the first item of importance in his report. There is perhaps more stress on disinfection of the house and furnishings than is really necessary.

Much social work was required for patients in hospital. They were unable to send letters outside, although they could receive them, and in view of the trivial nature of many of the attacks, this was a very important part of their care. Messages were sent out by telephone to deal with all manner of household problems.

Innes sums up the outbreak by saying it must have started in November 1951, if not earlier; it rose to a peak at the end of February and the beginning of March and came to an end in mid-April. The 116 cases occurred in the borough, of whom 43 were under fifteen years; 26, fifteen to twenty-five years; and 47 over the age of twenty-five. Of the 116 cases, twelve had been vaccinated in infancy and three later in life, showing that practically the whole of the clinically recognized infections were in the unvaccinated. It seems probable that far more cases really occurred, probably many abortive ones in the vaccinated, which were much more likely to have been missed, particularly in February, before the disease was recognized at all. Only one case occurred outside the Milnrow–Rochdale area, and this gave rise to no further cases. Here we have the interesting occurrence of an outbreak of variola minor lasting about six months and controlled within two and a half months. More emphasis was put on mass vaccination than on intensive vaccination on the ring plan. On ten occasions vaccination of contacts was apparently carried out by a round-up visit to the homes, but this procedure was apparently only done *when the public demand for random vaccination was considerably reduced.* In my opinion this is the wrong way of tackling control, but probably Innes felt infection was so widely dispersed when first discovered that wide-pattern vaccination was the simpler remedy. However, no map or details have been published to show the location of the cases, and whether they were as widely distributed as would appear at first sight. Apparently a team of vaccinators was on call in the event of a case of variola minor becoming known, but it was apparently used not for the vaccination of limited contacts, but for anybody who cared to be done.

Approximately 5,900 persons were vaccinated or revaccinated by the local health authority staff, and some 5,200 were vaccinated or revaccinated by private medical practitioners, giving a total of just over 11,000 out of a population of 87,000. There was one death from post-vaccinial encephalitis and no deaths from variola minor. Liberal vaccination was done in schools. Apparently six schools were vaccinated completely.

The inspection of vaccinations was probably done more effectively than usual. Apparently only 10 per cent of those attending the public sessions did not return, in spite of follow-up letters. Although there may have been social class differences, only 0·3 per cent of those done by private medical practitioners did not return for inspection, which supports my contention that random vaccination of the public is best left in the hands of the general practitioner, and that the health department should concentrate on vaccinating and inspecting by personal visit those classified contacts who require it for smallpox control purposes.

Why did the outbreak in Rochdale cease so promptly, when the infection introduced into England some thirty years before smouldered for over ten years and produced at least 80,000 cases? The production of herd immunity with the vaccination of about 12 per cent of the population may have produced some barrier to spread of variola minor, but all the evidence

suggests that even at that stage the herd immunity in Rochdale was less than in similar towns in the 1920's. I think Innes deserves credit for carrying out vaccination and surveillance of variola minor contacts much more efficiently than often before, but I think the real reason behind the success of the control was the changed attitude of the public towards vaccination, largely I feel because it was no longer compulsory. With a generally high level of education and understanding of medical matters and of the spread of disease, and with good local government, they were prepared to trust and follow the advice of their medical officer of health. A further point, and one which I think is of importance, is that with full employment and prosperity there was almost a complete absence of that traditional spreader of smallpox, the tramp, and of the common lodging-house, a major focus of infection in the late 1920's.

The improvements in the housing of people in the last thirty years has had an effect, particularly because of the lower infectious potential of variola minor, and the need for much closer, almost slum-family, contact to keep the infection going. It is probably for this reason that the lorry drivers, who I believe can transfer variola major, are less likely to do so in variola minor.

It is always easy to be wise after an event such as this, but I feel if variola minor occurred in a similar community, with highly co-operative people and well-organized and efficient medical and public health services, it could be controlled by very limited ring vaccination and surveillance of contacts in the same way as variola major. However, if the health authority regarded variola minor as "not smallpox" or as of no more consequence than chickenpox, and adopted half hearted control measures, it is likely that the outbreak would continue for a long time and the attitude of the people would almost certainly change.

APPENDIX I

A STABLE DRIED SMALLPOX VACCINE

Summary of the method of preparation based on methods described by L. H. Collier (1955)

(Tenth World Health Assembly, May 7–24, 1957, *Official Records of the World Health Organization*, p. 538)

(*Note:* This vaccine is prepared from a partially purified suspension of vaccinia virus elementary bodies derived from sheep pulp in 5·5 per cent peptone freeze-dried and sealed *in vacuo*. Repeated batches of the vaccine have been shown to retain satisfactory potency after exposure to 45° C. for at least eight weeks, and 37° C. for at least three months. For full details reference should be made to Collier's article. One batch has been exposed to 45° C. for two years, after which time it still produced 100 per cent successful primary vaccinations.[1,2] In series production the conservative claim of retention of potency for one month at 37° C. is made, but in practice this period may be expected to be considerably longer.)

Twenty-five grams of crude sheep pulp are ground in a mortar with 80 ml. McIlvaine's phosphate-citric acid buffer, 0·004 M PO_4, pH 7·2, and 1·0 g. powdered neutral glass. The crude suspension is centrifuged at low speed (1000 ***g***), the supernatant kept and the deposit re-extracted in buffer. This is repeated twice, and the three supernatants are pooled. The virus is sedimented by centrifugion, in an angle centrifuge. The speed and duration of centrifugion necessary to sediment the virus depend on the radius of rotation of the centrifuge head and the angle of inclination of the tubes (at 40 degrees from vertical, 2500 ***g*** for sixty minutes should be enough). The resulting deposit is re-suspended in 15 ml. of the same buffer, containing 0·5 phenol. This suspension is clarified by low-speed horizontal centrifugation for two minutes. The supernatant is saved, the deposit re-suspended in a further 15 ml. of buffer, and clarified again. The pooled supernatants constitute the final elementary body suspension (E.B.S.), which is then incubated for forty-eight hours at 22° C. to reduce the bacterial contamination. The E.B.S. is then plated to determine the bacterial count, and titrated in eggs for virus content. It is not used unless the bacterial count is less than 1000 organisms per ml., and the virus titre more than 5 by 10^9 i.u./ml. After passing these tests, one volume of E.B.S. is diluted ten times with 5·5 per cent peptone made up as follows:

A 5·5 per cent solution of bacteriological peptone is made in distilled water. The pH is adjusted to 8·0 with 40 per cent NaOH, after which the solution is heated to 90° C. and filtered while hot. The pH is then changed to 7·4 with 50 per cent HCl. The peptone solution is sterilized by autoclaving for fifteen minutes at 15 lb. pressure. The suspension is then ampouled in 0·24-ml amounts and dried in an Edwards centrifugal freeze-drier.

The ampoules are closed with caps made of a layer of cotton wool between two layers of gauze. Such caps maintain sterility without interfering with the passage of water vapour.

[1] Cockburn, W. C., Cross, R. M., Downie, A. W., Dumbell, K. R., Kaplan, C., McClean, D., and Payne, A. M-M. (1957). *Bulletin of the World Health Organization*, **16**, 63.

[2] Cross, R. M., Kaplan, C., and McClean, D. (1957). *Lancet*, **1**, 446.

Primary drying. The ampoules are placed in the primary chamber. The centrifuge is started and evacuation begun.

"Snap-freezing" occurs about fifteen minutes later, when the vacuum has reached 1–2 mm. Hg. The rotor is stopped shortly afterwards, and drying is allowed to proceed for about five hours at a vacuum of 0·05 mm. Hg. During this time heat is supplied to the drying heads, the total input of watts being approximately equal to the number of millilitres of material being dried. Drying can be satisfactorily carried out overnight, if necessary, without the application of heat.

Constriction, secondary drying and sealing. After primary desiccation, the ampoules are removed from the chamber, and constricted at the necks in a blowlamp flame to facilitate subsequent sealing. No ampoule is allowed to remain in contact with the atmosphere for more than two or three minutes during this process; those not actually being constricted are kept in glass desiccators over P_2O_5. They are then attached to the manifolds, and left for a further eighteen to twenty hours at high vacuum over P_2O_5. They are sealed under a vacuum of 0·01–0·03 mm. Hg.

Vacuum testing. The sealed ampoules are held at 4° C. overnight, and are then examined next day with a high-frequency tester for retention of vacuum, those failing to give a blue-green fluorescence being discarded.

Reconstitution. The dried material is reconstituted by adding 40 per cent glycerol in buffer to the original volume.

(The description given here is modified from the original in Collier's paper in order to include modifications in procedure since his paper was written. The pressures given in Collier's paper were measured by McLeod gauge. Those given here are measured by Pirani gauge.)

APPENDIX II

(From *Epidemiological and Vital Statistics Report*, June 1948, Vol. I, No. 13)

TABLE 1. *Smallpox cases and deaths reported from 1920 to 1933*

Countries		1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933
Africa															
French Equatorial Africa	C.	.	.	.	.	.	.	.	.	21	2	> 230	> 49	> 70	132
	D.	.	.	.	.	.	.	.	.	.	*29*	.	*3*	*14*	
French West Africa	C.	.	.	.	.	.	1,595	767	> 3,009	1,361	1,586	> 4,084	1,477	> 1,837	2,635
	D.	.	.	.	.	.	*> 102*	.	*> 257*	*145*	*325*	*> 535*	*185*	*217*	*245*
Algeria	C.	1,172	755	184	141	483	1,747	2,473	4,336	383	191	30	21	17	14
Angola	C.	.	.	.	.	.	.	.	174	67	95	1,107	1,612	848	371
	D.	.	.	.	.	.	.	.	*7*	.	*1*	*273*	*76*	*71*	*9*
Basutoland	C.	.	521	421	617	227	52	32	28	.	8	1	1	1	1
	D.	.	*52*	*46*	*14*	*15*	.	*5*	*5*	.	—	—	—	—	—
Bechuanaland	C.	.	.	.	.	.	.	.	.	5	425	14	16	12	4
	D.	.	.	.	.	.	.	.	.	—	*32*	—	*2*	.	.
Cameroons	C.	.	.	.	.	.	32	85	138	120	32	185	265	492	475
(*French Mandate*)	D.	.	.	.	.	.	*1*	.	.	.	.	*34*	*53*	*123*	*171*
Belgian Congo	C.	.	.	.	.	.	.	.	.	1,337	1,343	1,497	1,241	2,270	3,417
	D.	.	.	.	.	.	.	.	.	*27*	*27*	*10*	*7*	*7*	*13*
Gold Coast	C.	.	.	.	13	153	1,468	883	57	8	184	185	278	12	1
	D.	.	.	.	—	*4*	*150*	*33*	*9*	—	*7*	*97*	*21*	*1*	—
French Somali Coast	C.	.	.	.	.	.	.	.	.	—	199	—	—	—	—
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	—
Cyrenaica	C.	.	.	.	.	6	25	4	—	—	—	—	4	2	—
Egypt	C.	3,021	93	309	519	799	762	2,676	240	20	26	14	10	609	5,691
	D.	*805*	*24*	*90*	*145*	*221*	*158*	*542*	*34*	*4*	*4*	—	—	*142*	*976*
Eritrea	C.	.	.	.	.	.	.	.	.	.	.	.	.	16	7
Ethiopia	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Gambia	C.	.	.	.	.	.	.	2	1	13	83	2	3	—	2
Portuguese Guinea	C.	.	.	.	.	.	.	.	.	.	264	402	110	88	7
	D.	.	.	.	.	.	.	.	.	.	*14*	*40*	*12*	*10*	—
Kenya	C.	.	.	.	108	1	239	4	22	5	1	21	—	—	3
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Liberia	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Madagascar	C.	.	.	.	.	.	*> 25*	*> 6*	15	11	10	5	21	—	—

Spanish Morocco	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
French Morocco	C.	.	.	.	.	330	471	851	.	254	280	219	727	1,575	112	
Mozambique	C.	.	.	.	.	.	.	.	1,292	42	345	75	454	34	484	
	D.	.	.	.	.	.	.	.	.	.	.	.	*64*	—	*4*	
Nigeria	C.	.	1,031	.	1,222	119	1,932	847	4,483	3,895	3,216	5,119	2,315	9,464	12,601	
	D.	.	*182*	.	*189*	*20*	*196*	*96*	*1,275*	*904*	*847*	*1,038*	*568*	*2,998*	*2,883*	
Nyasaland	C.	.	.	.	14	.	—	—	11	20	1,092	4,762	7,414	4,106	3,412	
	D.	.	.	.	.	.	.	—	—	*1*	*44*	*211*	*239*	*180*	*96*	
Uganda	C.	.	506	104	97	7	13	6	17	1	32	2	—	—	—	
	D.	.	.	.	*10*	*1*	*4*	*1*	*2*	.	.	.	.	.	.	
Northern Rhodesia	C.	.	.	.	59	258	98	305	1,241	4,042	3,856	3,400	152	61	179	
	D.	.	.	.	*9*	*17*	*2*	*8*	*282*	*267*	*302*	*306*	*11*	*2*	*4*	
Southern Rhodesia	C.	.	515	501	16	2	12	1	7	255	427	696	44	40	80	
	D.	.	*145*	*21*	*8*	.	—	.	—	*15*	*17*	*20*	—	—	*6*	
Sierra Leone	C.	6	.	44	18	2	6	.	16	1	6	2	6	998	2,378	
	D.	.	.	.	.	.	.	.	.	.	.	—	—	*20*	*288*	
British Somaliland	C.	.	.	.	.	.	.	.	.	1	121	122	13	14	38	
	D.	.	.	.	.	.	.	.	.	.	*52*	*60*	*1*	—	*6*	
Italian Somaliland	C.	.	.	.	.	.	.	.	.	.	.	.	.	—	76	
Anglo-Egyptian Sudan	C.	.	.	.	.	.	.	> 63	218	2,402	6,467	2,179	218	> 47	228	
	D.	.	.	.	.	.	.	*4*	*7*	*475*	*885*	*343*	*38*	> *2*	*22*	
Swaziland	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Tanganyika	C.	.	1,267	390	217	30	1,388	22	84	26	178	4,335	1,733	768	626	
(*British Mandate*)	D.	.	*151*	*46*	*33*	*12*	*466*	—	*8*	—	*22*	*734*	*148*	*48*	*38*	
Tangier	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Togo (*French Mandate*)	C.	.	.	.	.	.	3	2	5	42	78	66	11	7	7	
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Tripolitania	C.	.	.	.	.	63	52	25	7	3	—	—	3	—	—	
Tunis	C.	.	.	.	279	606	1,270	188	101	101	138	59	18	2	5	
Union of South Africa	C.	1 036	1,108	713	285	346	71	115	60	51	53	63	28	19	24	
	D.	.	*19*	*23*	*8*	*2*	—	*20*	—	—	*2*	*1*	—	—	*1*	
Zanzibar	C.	7	160	177	236	10	3	53	150	2	4	212	13	—	3	
	D.	*1*	*56*	*54*	*60*		—	*15*	*19*	—	—	*49*	*1*	—	*1*	
America																
Alaska	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	—	
Argentine	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
	D.	.	.	.	*1*	—	.	.	.	.	.	.	.	.	.	
Barbados	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Bolivia	C.	.	.	.	.	.	.	.	.	.	.	.	> 716	> 10	293	
	D.	.	.	.	.	.	.	.	.	.	.	.	*324*	.	*197*	
Brazil:																
Pernambuco State	C.	.	.	.	.	.	.	.	.	.	.	.	.	93	112	
Rio de Janeiro	C.	.	.	.	.	13	683	4,146	107	2	—	—	1	2	—	
	D.*	*99*	*49*	*117*	*40*	*4*	*359*	*2,187*	*69*	*1*	—	—	—	*1*	—	
22 towns	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
	D.*	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Canada *b*	C.	.	.	.	.	2,791	1,248	1,535	2,845	3,337	1,952	1,292	865	347	100	
	D.*	.	.	.	*15*	*64*	*15*	*33*	*11*	*7*	*8*	*2*	*3*	*17*	*6*	
Chile	C.	15	11,701	8,494	3,502	410	.	.	.	.	.	.	.	.	—	
	D.*	*30*	*5,234*	*4,290*	*1,808*	*269*	*26*	*15*	*14*	*14*	*11*	*2*	*5*	—	—	

TABLE I—*continued*

Countries		1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933
America—*continued*															
Colombia *c*	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	419
	D.	.	.	.	.	.	.	.	*444*	*524*	*254*	*308*	*206*	.	*32*
Costa Rica	C.	.	.	.	.	.	.	.		.	.	36	.	.	—
	D.	.	.	.	.	.	.	—	.	5	—	*1*	.	.	.
Cuba	C.	817	7,339	1,086	13	—	2	—	—	—	—	—	—	—	—
Ecuador *c*	C.	.	.	.	158	9	1	1	16	196	31	374	505	203	234
	D.	.	.	.	*5*	*1*	—	—	.	.	.	*16*	*3*	.	.
United States *d*	C.	96,684	102,787	32,800	29,176	56,488	39,450	33,391	36,600	39,396	41,705	48,782	30,151	11,194	6,460
	D.	.	.	.	.	.	.	.	*167*	*141*	*144*	*173*	*104*	*52*	*35*
	D.*	.	.	.	.	.	.	.	.	.	.	.	.	.	*39*
Guadeloupe	C.	.	.	.	.	.	22	2	2	—	—	—	—	—	—
Guatemala	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.*	.	.	.	.	.	.	.	.	.	.	*10*	*29*	*23*	*9*
British Guiana	C.	.	—	—	1	—	—	.	.	.	.	.	.	.	.
French Guiana	C.	.	.	.	.	.	2	1	—	—	—	—	—	—	—
Honduras	C.	.	.	.	.	.	.	—	—	—	—	—	—	> 134	> 38
British Honduras	C.	.	.	.	.	.	.	.	.	.	.	.	1	—	7
Jamaica	C.	.	.	.	1,804	1,266	930	1,108	210	47	2	1	—	—	—
Martinique	C.	.	.	.	.	.	11	3	9	—	—	1	—		—
Mexico	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.*	.	.	*11,966*	*13,074*	*12,964*	*11,008*	*5,477*	*6,639*	*8,794*	*11,304*	*17,405*	*15,003*	*8,456*	*6,049*
Nicaragua	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Panama	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Panama Canal Zone *e*	C.	25	215	14	—	—	—	—	—	2	396	—	2	—	—
	D.	—	*2*	—	—	—	—	—	—	—	*1*	—	—	—	—
Paraguay	C.	.	.	.	.	.	.	.	.	—	—	—	—	—	—
Peru	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	363
	D.*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Puerto Rico	C.	2	1	6	—	—	—	.	.	—	—	6	—	—	—
Dominican Republic	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	*1*	*2*	—	—	*105*	—
St. Lucia	C.	.	.	1	—	—	—	.	.	.	.	.	.	.	.
Salvador	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.*	.	.	.	.	.	.	.	.	—	—	—	*6*	*18*	*37*
Trinidad and Tobago	C.	.	.	.	.	.	.	20	—	—	—	—	—	—	—
Uruguay	C.	.	31	—	569	176	15	4	—	—	4	—	8	11	1
	D.*	*2*	*15*	—	*16*	*7*	—	—	—	—	—	.	—	—	*1*
Venezuela	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.*	.	.	.	.	.	.	.	.	.	.	*28*	*13*	*2*	*6*
Asia															
Aden	C.	.	.	.	43	9	16	17	7	3	410	9	1	6	4i
	D.	.	.	.	*6*	*1*	*5*	*2*	*2*	*2*	*158*	—	—	—	*2*

Sa'udi Arabia	C.	.	.	.	.	.	.	.	.	.	525	291	606	212	145
	D.	.	.	.	.	.	.	.	.	.	*264*	*148*	*359*	*203*	*107*
Burma	C.	.	.	.	.	.	.	.	.	7,378	6,235	3,397	1,467	9,907	6,604
	D.*	*2,853*	*987*	*1,439*	*2,846*	*2,501*	*3,852*	*2,339*	*1,704*	*2,825*	*1,841*	*921*	*490*	*2,484*	*1,506*
Burma Federated	C.	.	.	.	.	.	.	.	.	276	1,970	271	555	1,860	1,097
States	D.	.	.	.	.	.	.	.	.	*33*	*157*	*39*	*49*	*187*	*110*
Ceylon	C.	126	18	337	175	40	28	65	27	18	8	41	9	106	337
	D.	.	.	.	*33*	*2*	*3*	*4*	*5*	*4*	*2*	*6*	*3*	*16*	*87*
China	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Shanghai *g*	C.	.	.	.	.	.	.	.	.	.	.	> 112	> 275	561	264
	D.	.	*> 204*	*> 230*	*60*	*112*	*70*	*> 221*	*> 10*	*> 172*	*> 196*	*> 58*	*154*	*262*	*94*
Chinese Eastern	C.	.	.	.	.	.	.	.	9	34	47	12	9	9	34
Railway Zone	D.	.	.	.	.	.	.	.	*1*	*5*	*4*	*1*	.	*2*	*5*
South Manchurian	C.	.	.	.	.	150	468	249	99	235	71	21	18	163	420
Railway Zone	D.	.	.	.	.	*21*	*37*	*31*	.	.	.	.	.	.	.
Cyprus	C.	17	8	86	1	—	—	—	—	—	2	—	—	—	—
Korea	C.	11,532	8,316	3,676	3,722	439	699	1,010	626	290	523	1,418	1,376	2,787	4,928
	D.	*3,614*	*2,527*	*1,160*	*1,120*	*85*	*170*	*237*	*149*	*82*	*126*	*323*	*343*	*544*	*966*
Straits Settlements *j*	C.	105	155	330	36	12	11	39	117	8	19	145	167	8	4
	D.	*43*	*37*	*80*	*3*	*3*	*9*	*16*	*26*	*2*	*2*	*59*	*48*	*5*	*3*
French Settlements in	C.	.	.	.	.	.	.	1,063	600	1,600	591	677	792	1,261	1,999
India	D.	.	.	.	.	.	*> 830*	*787*	*465*	*1,286*	*486*	*477*	*662*	*1,133*	*1,144*
Formosa	C.	.	.	.	.	7	16	43	1	1	—	82	2	61	1
	D.	.	.	.	.	.	.	.	—	—	—	*8*	—	*8*	*1*
Hejaz	C.	.	.	.	.	.	.	.	.	425	525	291	.	.	.
	D.	.	.	.	.	.	.	.	.	*225*	*261*	*142*	.	.	.
Hong Kong	C.	34	191	212	1,320	913	66	49	149	616	972	270	15	212	566
	D.	*21*	*162*	*189*	*1,141*	*795*	*41*	*26*	*126*	*517*	*854*	*249*	*8*	*175*	*433*
India *l*	C.	.	.	.	.	.	174,660	219,158	221,556	163,675	148,068	231,386	88,380	114,691	250,366
	D.	.	.	.	.	.	.	*54,847*	*51,776*	*39,981*	*34,393*	*57,806*	*18,926*	*26,898*	*65,635*
British India	D.*	*98,476*	*39,459*	*39,397*	*41,238*	*52,879*	*82,134*	*114,727*	*116,493*	*93,298*	*71,043*	*71,893*	*36,782*	*42,441*	*102,135*
Indian States:		.	.	.	.	.	.	.	.	.	.	.	.	.	.
Baroda	D.*	.	.	.	.	.	.	.	.	*865*	*2,556*	*6,915*	*316*	*56*	*189*
Hyderabad	D.*	.	.	.	.	.	.	.	.	*682*	*455*	*2,046*	*489*	*326*	*1,092*
Jammu and Kashmir	D.*	.	.	.	.	.	.	.	.	*1,002*	—	*2*	*106*	—	*28*
Mysore	D.*	.	.	.	.	.	.	.	.	*4,571*	*7,589*	*6,134*	*2,296*	*2,980*	*2,801*
Rajputana	D.*	.	.	.	.	.	.	.	.	.	*1,214*	*882*	*77*	*63*	*2,513*
Portuguese India	C.	.	.	.	.	.	.	.	459	183	168	268	77	15	383
	D.	.	.	.	.	.	.	.	*74*	*7*	*40*	*40*	*18*	—	*22*
Netherlands Indies:															
Java and Madura	C.	2,400	1,445	1,236	4,922	5,941	4,658	843	297	46	271	408	69	349	7
	D.	*467*	*274*	*640*	*686*	*1,304*	*508*	*99*	*8*	*11*	*69*	*85*	*8*	*2*	—
Outer Provinces *m*	C.	.	.	.	.	776	23	12	469	252	343	11	107	213	50
	D.	.	.	.	.	*32*	—	—	*16*	*61*	*134*	.	.	.	.
French Indo-China	C.	.	.	.	.	.	4,753	2,658	745	1,432	4,954	4,919	2,058	3,968	2,969
	D.	.	.	.	.	.	*775*	*525*	*157*	*418*	*1,693*	*1,795*	*554*	*1,538*	*1,023*
Iraq	C.	.	475	1,862	1,692	459	832	1,062	761	1,956	2,374	762	744	2,318	1,260
	D.	.	.	.	*581*	*235*	*356*	*361*	*335*	*862*	*652*	*180*	*250*	*722*	*216*

TABLE I—*continued*

Countries		1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933
Asia—*continued*															
Iran	C.	.	.	.	.	.	.	.	.	.	.	.	552	1,745*n*	765
	D.	.	.	.	.	.	.	.	.	.	.	.	*234*	*809n*	*387*
Japan	C.	3,167	889	679	1,922	1,703	430	1,256	352	723	114	7	21	305	375
	D.*	*723*	*203*	*120*	*399*	*294*	*69*	*158*	*90*	*100*	*11*	*4*	*8*	*44*	*55*
Kwantung	C.	.	.	.	42	59	271	327	58	268	72	62	19	30	220
Kwangchow-Wan	C.	.	.	.	.	.	.	.	2	—	—	—	—	—	—
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Macao	C.	.	.	.	.	.	.	.	.	.	.	10	—	1	32
	D.	.	.	.	.	.	.	.	.	.	.	.	—	*1*	*28*
Federated Malay States	C.	.	76	16	32	6	51	1	237	10	10	23	21	1	—
	D.	.	—	*2*	*9*	*1*	*10*	—	*24*	—	*2*	*2*	*3*	—	—
Non-Federated Malay States	C.	.	1	.	5	31	4	5	38	4	18	34	2	3	—
	D.	.	—	.	—	*3*	—	*2*	*8*	—	*2*	5	*1*	—	—
Oman	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	92
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	*56*
Pakistan	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Palestine	C.	.	2	159	9	23	—	3	1	—	—	—	—	—	31
	D.	.	*2*	*16*	5	*2*	—	—	1	—	—	—	—	—	1
Philippines	C.	.	.	.	.	.	20	30	1	5	367	192	4	—	—
	D.	*6,632*	*728*	*19*	*4*	*6*	*1*	*7*	—	—	*59*	*49*	*1*	—	—
Siam	C.	*85p*	*404p*	472	1,451	588	287	1,113	418	125	405	56	33	20	42
	D.	*26p*	*102p*	*117*	*743*	*173*	*111*	*400*	*117*	*22*	*73*	*17*	*6*	*5*	*15*
Syria and Lebanon	C.	.	.	.	60	40	46	1	98	423	375	158	6	109	435
Timor	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Trans-Jordan	C.	.	.	.	.	.	.	1	1	16	7	—	—	9	9
	D.	.	.	.	.	.	.	.	.	.	—	—	—	*3*	*3*
U.S.S.R.:															
Transcaucasia	C.	.	.	3,261	734	458	268	384	135	190	359	173	215	2,123	494
Uzbekistan	C.	.	.	1,163	710	541	468	1,490	591	585	604	1,548	86	673	260
Turkmenistan	C.	.	.				61	219	234	35	40	100	82	162	158
Tajiskistan	C.	.	.	.	.	.	.	.	.	.	.	.	217	332	221
Other Territories in Asia	C.	.	.	6,292	8,161	5,044	3,845	3,753	2,333	1,388	897	290	2,728	11,051	1,104
Europe															
Albania	C.	.	.	.	.	.	.	.	.	.	.	.	.	—	—
Germany ("Altreich")	C.	2,042	698	215	17	16	24	7	4	2	2	2	—	—	—
	D.*	.	*109*	*26*	*10*	*6*	*9*	—	*3*	—	—	—	—	3	—
United States Zone	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
British Zone	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Austria	C.	253	18	4	17	—	—	—	—	—	—	—	—	—	—
	D.*	*66*	*2*	*1*	*1*	—	—	—	—	—	—	—	—	—	—

Belgium	C.	91	21	23	31	31	12	13	—	1	—	—	—	—	2
	D.*	*45*	*12*	*15*	*30*	*16*	*19*	*14*	*18*	*8*	*16*	*11*	—	—	—
Bulgaria	C.	527	22	24	20	5	—	1	2	—	—	—	—	—	—
Denmark	C.	—	7	—	—	25	—	—	—	—	—	—	—	—	—
Danzig	C.	22	—	—	—	—	—	—	—	—	—	—	—	—	—
Spain *r*	C.	.	.	.	.	.	.	.	.	.	.	.	910	1,066	624
	D.*	*3,285*	*2,097*	*1,325*	*525*	*1,217*	*849*	*112*	*162*	*153*	*2*	*4*	*8*	*6*	*2*
Estonia	C.	435	136	50	13	4	5	6	.	.	.	.	.	.	.
	D.*	.	.	.	*3*	*4*	*5*	*5*	*9*	*3*	*2*	*10*	*6*	—	*5*
Finland	C.	77	27	91	12	1	2	1	—	2	1	1	5	4	1
	D.*	*18*	*2*	*7*	—	*2*	*1*	—	—	*1*	*1*	—	—	*1*	*2*
France *s*	C.	392	341	172	195	210	456	554	410	153	84	217	162	134	180
	D.*	*113*	*96*	.	.	.	*113*	*115*	*119*	*16*	*22*	*19*	*14*	*24*	*27*
Gibraltar	C.	.	.	3	.	6	3	.	.	.	.	—	—	11	—
Greece	C.	.	.	.	2,101	250	16	27	102	24	7	27	12	8	9
	D.	.	.	.	.	.	.	.	.	.	—	—	—	—	—
	D.*	.	*250*	*292*	*924*	*118*	*34*	*9*	*36*	*2*	*17*	*9*	*11*	*14*	*13*
Hungary	C.	.	131	2	9	1	1	1	.	.	.	.	.	.	.
	D.	.	*25*	—	*4*	—	—	*1*	.	.	.	.	.	.	.
	D.*	.	.	.	.	*11*	*10*	*2*	*4*	*1*	—	—	—	—	—
Ireland (Eire)	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Italy	C.	26,453	4,644	534	495	432	195	112	60	52	6	—	—	—	—
	D.*	*11,073*	*1,360*	*37*	*16*	*46*	*13*	*10*	*5*	*21*	*3*	*2*	*4*	*2*	*2*
Latvia	C.	422	255	160	23	25	17	3	1	3	—	—	1	—	—
	D.	.	.	.	.	.	.	.	*1*	*3*	—	—	.	.	.
Lithuania	C.	1,213	1,035	345	25	58	12	3	.	.	.	.	.	.	—
	D.*	.	.	.	> —	> *12*	*22*	*11*	*7*	*10*	5	*4*	*3*	*2*	—
Luxemburg	C.	.	.	—	—	—	—	*2*	—	—	—	—	—	—	—
Malta	C.	.	.	1	—	—	84	20	—	1	—	—	—	—	—
	D.*	—	—	—	—	—	*16*	*3*	—	—	—	—	—	—	—
Norway	C.	—	1	—	—	—	1	—	2	—	—	—	—	1	—
Netherlands	C.	50	1	—	2	3	2	15	—	—	700	2	1	—	—
	D.*	*3*	—	—	—	—	—	*1*	—	—	*21*	—	—	—	—
Poland	C.	3,948	5,078	2,399	502	861	77	69	36	21	12	21	9	3	5
	D.	*687*	*823*	*519*	*83*	*126*	*3*	*5*	*5*	*2*	*1*	—	*2*	*2*	*1*
Portugal:															
Mainland	C.	.	.	.	.	.	.	.	.	923	800	815	2,210	4,246	1,800
	D.*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.*	*1,154*	*209*	*425*	*659*	*748*	*468*	*394*	*385*	.	*115*	*134*	*580*	*1,030*	*529*
Azores and Madeira	D.*	*54*	*58*	—	*1*	*3*	—				—	*1*	—	*1*	—
Roumania	C.	3,467	2,744	865	89	9	28	6	4	9	4	5	13	10	6
	D.	*781*	*560*	*153*	*11*	*1*	*2*	—	—	—	—	—	*2*	—	—
	D.*	.	.	.	.	.	.	.	.	.	*1*	—	*8*	*10*	*6*
United Kingdom:															
England and Wales	C.	263	315	973	2,485	3,765	5,365	10,146	14,767	12,420	10,968	11,839	5,664	2,039	631
	D.	*30*	*5*	*27*	*7*	*13*	*9*	*18*	*47*	*53*	*39*	*28*	*9*	*3*	*2*
Scotland	C.	725	106	7	3	4	2	1	154	146	23	14	—	—	—
	D.	*152*	*24*	—	—	—	—	—	—	—	—	*2*	—	—	—
Northern Ireland	C.	.	.	.	.	.	.	—	—	—	—	—	—	—	—
Sweden	C.	11	2	—	—	1	—	1	—	—	—	—	—	10	—
	D.*	*3*	—	*1*	—	—	—	*1*	—	—	—	*1*	—	*1*	—

TABLE I—*continued*

Countries		1920	1921	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931	1932	1933
Europe—*continued*															
Switzerland	C.	2	596	1,153	2,126	1,234	329	54	—	1	—	1	—	2	—
	D.★	—	*7*	*3*	*2*	*2*	*1*	*1*	—	—	—	—	—	—	—
Czechoslovakia	C.	4,529	1,542	70	36	.	.	.	.	.	.	—	.	—	.
	D.	*554*	*316*	*12*	*5*	*2*	*1*	*1*	—	—	—	—	—	—	—
	D.★	*1,600*	*757*	*76*	*49*	*33*	*4*	*8*	*6*	*7*	*1*	—	*1*	—	—
Turkey	C.	.	.	.	.	1,615	483	487	73	47	561	906	256	189	188
	D.	.	.	.	.	*391*	*69*	*17*	*4*	*8*	*139*	*160*	*33*	*20*	*40*
U.S.S.R.:															
Ukraine	C.	.	.	11,095	3,710	1,188	501	277	168	116	59	88	126	1,252	127
White Russia	C.	.	.		118	159	193	129	102	58	32	129	207	690	117
Other Territories in Europe	C.	.	.	37,656	29,015	20,253	10,804	9,895	10,344	6,880	4,269	3,463	8,298	12,794	1,892
Railways and waterways	C.	.	.	3,183	2,178	731	356	401	247	263	116	139	380	80	19
Yugoslavia	C.	4,156	2,119	728	1,042	330	14	4	3	—	—	1	—	—	—
	D.	—	*483*	*165*	*198*	*64*	*3*	*2*	—	—	—	—	—	—	—
Oceania															
Australia	C.	—	—	—	—	—	—	.	—	—	*5i*	—	—	—	—
	D.	—	*2*	*2*	—	—	—	*1*	—	—	—	*2*	—	*1*	—
French Settlements in Oceania	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Hawaii	C.	.	4	2	1	3	2	.	—	—	—	*1i*	—	—	.
New Zealand	C.	—	—	—	—	—	—	1	—	—	—	.	.	.	.

NOTES

† Figures recorded by the Health Authorities.
★ Figures recorded by the Central Statistical Office.
a Widespread epidemic, total number of cases unknown.
b Exclusive of Yukon and the North West Territories and, from 1925 to 1929, the Prince Edward Island.
c Variola minor and major.
d From 1923 to 1934, variable number of States.
e Inclusive of the cities of Panama and Colon.
f Year ending 30 June.
g From 1920 to 1925, International Settlement only; 1926–1928, International and French Settlements.
h South Korea only.
i Imported cases.
j 1946 and 1947, Singapore (City) only.
k Included under China
l Aggregate of reporting British Provinces and Indian States; inclusive of Burma up to 1936.
m From 1925 to 1929, principal ports only.
n Year ending 21 March.
o Towns only.
p Siamese civilian year beginning 1 April.
q 53 weeks.
r From 1932 to 1938, inclusive of Spanish Morocco.
s Up to 1936, inclusive of cases of chickenpox.
t 87 departments.
u 86 departments.

Note

Symbols used in the tables:

C. Cases.
D. Deaths.
. No data available.
— Nil or less than half the final digit shown.
> Incomplete figures.

TABLE 2. *Smallpox cases and deaths reported from 1934 to 1947*

Countries		1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
Africa															
French Equatorial Africa	C.	40	17	32	13	842	520	.	.	.	.	2,453	1,691	248	41
	D.	*3*	*2*	*11*	*4*	*192*	*50*	.	.	.	.	*519*	*389*	*5*	—
French West Africa	C.	2,296	4,691	3,909	3,079	2,348	2,353	1,620	954	2,003	7,584	4,674	7,442	7,163	6,597
	D.	*400*	*714*	*323*	*205*	*178*	*117*	*29*	*97*	*198*	*486*	*357*	*462*	*553*	*596*
Algeria	C.	19	19	101	15	13	7	7	974	1,206	1,956	1,188	363	544	512
Angola	C.	693	406	640	198	451	465	348	1,659	442	628	80	129	198	288
	D.	*35*	*33*	*30*	*12*	*13*	*21*	*3*	*25*	*9*	*3*	—	*2*	*7*	*5*
Basutoland	C.	—	—	—	—	—	—	1	2	161	149	576	277	63	*2q*
	D.	—	—	—	—	—	—	—	—	*5*	*2*	*4*	*1*	*1*	— *q*
Bechuanaland	C.	4	—	2	6	3	4	—	1	2	3	2	7	14	38
	D.	.	.	.	.	.	—	—	—	—	—	—	*8*	—	—
Cameroons (*French Mandate*)	C.	463	138	1,061	20	271	.	.	.	.	.	>989	>846	107	140
	D.	*90*	*27*	*194*	*11*	*75*	.	.	.	.	.	*>175*	*>537*	*15*	*25*
Belgian Congo	C.	3,253	2,574	2,873	3,792	3,269	6,495	6,394	4,614	2,658	4,257	2,148	6,350	4,122	2,756*q*
	D.	*108*	*15*	*41*	*44*	*54*	*299*	*168*	*144*	*84*	*158*	*54*	*59*	*14*	*13q*
Gold Coast	C.	48	—	*59*	43	123	389	85	1,752	1,933	23	150	702	1,569	852*q*
	D.	*14*	—	*9*	*2*	*9*	*70*	*10*	*206*	*110*	—	*38*	*128*	*311*	*169q*
French Somali Coast	C.	—	42	—	—	—	.	6	.	.	.	.	.	.	.
	D.	—	*15*	—	—	—	.	*4*	.	.	.	.	.	.	.
Cyrenaica	C.	—	—	—	—	—	9	.	.	.	.	.	>46	>52	.
Egypt	C.	1,344	165	3	1	1	—	2	—	—	4,138	11,194	1,355	415	172
	D.	*252*	*19*	*1*	—	—	—	—	—	—	*384*	*1,016*	*115*	*50*	*10*
Eritrea	C.	4	27	146	459	.	50	5	.	.	.	.	2	2	.
Ethiopia	C.	.	.	.	.	.	151	159	.	.	.	.	.	.	62
Gambia	C.	—	—	140	*a*	—	.	.	.	.	.	.	79	29	*5q*
Portuguese Guinea	C.	56	13	32	6	8	227	532	123	4	2	12	7	—	3
	D.	*2*	—	—	.	.	*19*	*29*	*6*	—	—	—	—	—	—
Kenya	C.	1,781	15	1	116	—	—	—	—	—	3,551	3,150	763	818	462*q*
	D.	.	.	.	.	—	—	—	—	—	*2*	*15*	*122*	*181*	*75q*
Liberia	C.	.	.	—	—	.	.	.	.	.	.	.	.	87	14
	D.	.	.	.	.	.	.	.	.	.	.	.	.	*13*	*4*
Madagascar	C.	1	—	.	.	—	—	.	.	.	.	.	.	.	.
Spanish Morocco	C.	.	.	.	.	.	.	11	9	—	3	3	10	8	1
French Morocco	C.	55	42	40	23	26	16	103	1,951	2,078	1,170	793	2,678	1,870	61
Mozambique	C.	681	415	513	286	239	147	35	78	61	1	4	1	—	30*q*
	D.	*23*	—	*3*	*2*	*4*	.	*2*	.	*24*	—	*1*	—	—	*3q*
Nigeria	C.	10,389	5,498	4,883	3,675	7,511	5,035	2,362	1,097	2,623	6,321	5,147	5,576	8,298	5,354*q*
	D.	*2,538*	*1,403*	*611*	*527*	*1,593*	*701*	*458*	*210*	*504*	*1,228*	*912*	*844*	*1,099*	*946q*
Nyasaland	C.	814	170	190	94	9	44	>74	6	—	13	1	202	944	2,562
	D.	*25*	*11*	*4*	.	.	*3*	*>3*	—	—	—	—	*2*	*30*	*193*
Uganda	C.	—	2	32	—	—	—	10	32	—	128	4,737	1,363	587	396*q*
	D.	—	*1*	*5*	—	—	—	—	—	—	—	*3*	.	.	*11q*

TABLE 2—*continued*

Countries		1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
Africa—*continued*															
Northern Rhodesia	C.	23	32	96	27	59	20	9	3	10	124	355	6,384	490	87*q*
	D.	—	*2*	—	—	*4*	—	—	—	—	*12*	*2*	*28*	*1*	*8q*
Southern Rhodesia	C.	41	1	17	246	1,864	223	> 171	69	—	—	—	33	177	635
	D.	*1*	—	—	*2*	*7*	*1*	> *2*	*1*	—	—	—	—	—	*116*
Sierra Leone	C.	2,333	1,981	565	134	55	52	29	7	.	3	484	649	750	462*q*
	D.	*313*	*322*	*48*	*1*	—	.	.	—	.	—	*96*	*38*	*113*	*82q*
British Somaliland	C.	91	243	152	1	2	7	2	.	.	.	.	.	.	—
	D.	*2*	*23*	*7*	—	—	—	*1*	.	.	.	.	.	.	—
Italian Somaliland	C.	—	2	10	49	1	71	1	.	.	.	.	.	3	—
Anglo-Egyptian Sudan	C.	173	72	577	425	527	553	515	46	12	.	2	1	55	953*q*
	D.	*1*	—	*132*	*57*	*158*	*103*	*104*	—	—	.	*1*	—	*2*	*173q*
Swaziland	C.	.	—	—	11	—	.	.	.	.	.	.	.	3	11
Tanganyika	C.	411	503	1,649	1,462	1,095	599	156	92	90	201	5,735	12,283	12,671	> 2,423
(*British Mandate*)	D.	*37*	*4*	*50*	*17*	*27*	*27*	*5*	*6*	*4*	*2*	*38*	*1,815*	*1,935*	> *544*
Tangier	C.	.	.	.	.	.	.	.	.	.	.	.	.	> 179	> 25
Togo (*French Mandate*)	C.	19	3	33	—	29	301	13	1	—	—	174	535	470	75
	D.	.	.	.	.	.	*27*	*5*	.	—	—	*22*	*30*	*31*	*1*
Tripolitania	C.	—	—	—	—	—	.	.	.	.	.	.	.	> 1,138	2,284
Tunis	C.	3	7	3	13	—	2	—	—	1	4	19	190	797	1,203
Union of South Africa	C.	23	21	24	306	521	328	717	1,511	1,936	> 655	2,238	2,802	778	> 433
	D.	—	—	*6*	*5*	*4*	*3*	*5*	*13*	*32*	*32*	> *136*	*125*	*24*	> *8*
Zanzibar	C.	—	—	—	—	—	—	—	—	.	—	—	—	1	.
	D.	—	—	—	—	—	—	—	—	.	—	—	—	*1*	.
America															
Alaska	C.	—	1	11	—	2	1	1	—	.	—	1	—	—	—
Argentine	C.	.	.	545	80	53	4	—	—	120	6	41	—	71	46
	D.	.	.	*32*	*5*	*20*	*1*	—	—	*31*	*4*	*9*	—	*21*	*1*
Barbados	C.	—	3	—	—	—	.	—	—	—	—	—	—	—	—
Bolivia	C.	618	490	220	289	235	286	348	211	205	300	1,159	1,793	1,034	.
	D.	*553*	.	.	.	*96*	*84*	*19*	*30*	*47*	*41*	*362*	*275*	*126*	.
Brazil:															
Pernambuco State	C.	.	.	.	.	.	2	—	—	—	—	.	.	.	.
Rio de Janeiro	C.	—	13	21	121	64	84	123	126	49	73	.	.	.	.
	D.★	—	*1*	—	*2*	*2*	—	*6*	*4*	*2*	*2*	*5*	*2*	.	.
22 towns	C.	.	.	.	.	.	.	.	.	66	16	1,325	> 729	1,237	> 607
	D.★	> *11*	> *40*	> *78*	> *54*	> *21*	> *2*	> *10*	> *11*	> *26*	> *12*	*33*	> *28*	*26*	> *13*
Canada *b*	C.	17	34	62	59	120	169	11	26	6	6	—	5	2	—
	D.★	*3*	*4*	*2*	*2*	*3*	*1*	—	—	—	—	—	—	—	—
Chile	C.	—	7	—	.	.	.	.	.	.	—	38	—	—	—
	D.★	—	*1*	—	*5*	—	—	—	—	—	—	*9*	—	—	—
Colombia *c*	C.	742	298	.	520★	453	2,772	1,992	1,334	1,443	2,659	1,445	.	> 460	3,989
	D.	*29*	*18*	*640*	*13*	*36*	*313*	*168*	*34*	*15*	*35*	*3*	.	> *9*	*44*

Costa Rica	C.	1	.	.	.	.	.	.	.	.	.	.	1	.	9
	D.	.	—	—	*1*	—	.	.	.	.	.	.	—	—	.
Cuba	C.	—	—	—	—	—	—	.	1	—	—	—	.	—	.
Ecuador *c*	C.	237	89	58	401	18	18	1	.	10	12	29	37	116	3,003
	D.	.	.	*11*	*83*	*7*	*7*	.	.	*1*	*3*	*4*	*2*	*3*	27
United States *d*	C.	5,285	7,957	7,834	11,673	14,939	9,877	2,795	1,396	865	765	397	346	356	1734*q*
	D.	*21*	*24*	*33*	*30*	*46*	*39*	*15*	*11*	*3*	*6*	*9*	*10*	.	.
	D.★	*24*	*25*	*35*	*34*	*48*	*41*	*14*	*12*	*2*	*8*	*9*	*12*	.	.
Guadeloupe	C.	—	—	—	—	—	.	.	.	.	.	.	.	.	.
Guatemala	C.	.	8	52	.	60	11	8	6	1	6	9	5	9	11
	D.★	*38*	*40*	*16*	*21*	*50*	*2*†	*1*†	*1*†	—	—	—	*1*†	—	—
British Guiana	C.	—	56	—	—	.	—	—	—	*1*	—	—	—	—	.
French Guiana	C.	—	—	—	—	—	.	.	.	.	.	.	.	.	.
Honduras	C.	15	8	.	.	3	.	.	.	—	2	9	8	1	—
British Honduras	C.	51	83	8	57	88	2	.	.	.	.	4	—	—	—
Jamaica	C.	—	—	—	—	—	—	—	—	—	—	—	.	.	—
Martinque	C.	—	3	—	—	—	.	.	.	.	.	.	.	.	.
Mexico	C.	.	.	.	.	.	.	.	.	.	.	3,516	1,718	600	1,123
	D.★	*9,430*	*5.205*	*4,651*	*3,538*	*3,343*	*2,205*	*1,341*	*2,529*	*4,115*	*4,011*	*2,350*	*1.054*	*234*†	.
Nicaragua	C.	.	.	.	1	6	—	43	.	—	6	1	148	3	.
	D.	.	.	.	—	—	—	*15*	5	—	—	—	*3*	*3*	*1*
Panama	C.	.	.	.	.	.	—	—	4	1	1	2	—	—	1
Panama Canal Zone *e*	C.	—	—	—	4	—	—	—	11	1	—	—	—	—	—
	D.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Paraguay	C.	—	14	6	11	.	.	.	8	.	.	.	.	124	807
Peru	C.	502	444	248	.	97	173	371	3,131	2,499	1,826	296	292	699	521
	D.★	.	.	.	.	.	.	.	*2,268*	*3,411f*	*4,069f*	*897*	*404*	.	.
Puerto Rico	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	.
Dominican Republic	C.	2	.	.	.	.	—	—	2	—	—	—	—	—	.
	D.	*1*	—	*4*	—	*2*	—	—	—	—	—	—	—	—	.
St. Lucia	C.	.	.	.	.	—	—	—	—	—	2	—	—	—	—
Salvador	C.	.	484	246	10	19	1	—	—	—	—	—	—	—	.
	D.★	.	*102*	*32*	*10*	2	*3*	*1*	—	*1*	—	—	—	—	.
Trinidad and Tobago	C.	—	—	—	—	—	—	—	—	.	.	.	.	.	.
Uruguay	C.	8	2	53	72	29	7	1	1	—	—	—	104	40	316
	D.★	—	—	*1*	*9*	*1*	—	—	—	—	.	.	.	.	.
Venezuela	C.	.	.	.	.	.	124	564	265	259	610	599	878	1,081	> 4,973
	D.★	*2*	*3*	*70*	*105*	*256*	*148*	*19*	*9*	*11*	.	*21*†	*13*†	*16*†	> *86*†
Asia															
Aden	C.	2	3	—	—	—	.	.	.	.	.	.	7	3	—*q*
	D.	.	.	.	.	.	.	.	.	.	.	.	.	*2*	—*q*
Sa'udi Arabia	C.	306	187	43	8	1	.	.	.	.	.	.	.	.	.
	D.	*214*	*152*	*34*	*6*	*0*	.	.	.	.	.	.	.	.	.
Burma	C.	5,270	4,764	5,155	5,713	1,956	> 702	8,739	> 5,593	.	.	.	6,778	3,941	2,894*q*
	D.★	*1,601*	*1,262*	*1,354*	*1,370*	*254*†	> *131*†	*3,567*†	> *1,124*†	.	.	.	*1,281*†	*1,309*†	†*1,190q*
Burma Federated States	C.	1,285	210	419	652	327	.	.	.	.	.	.	.	.	.
	D.	*182*	*32*	*86*	*59*	*50*	.	.	.	.	.	.	.	.	.
Ceylon	C.	72	115	3	2	—	1	—	167	1	135	124	691	442	1*q*
	D.	*10*	*20*	*4*	—	—	>—	—	*27*	*2*	*21*	*21*	*108*	*75*	—*q*

TABLE 2—*continued*

Countries		1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
China	C.	.	.	.	.	.	2,786	2,546	12,646	9,772	6,450	5,573	5,338	20,562	> 15,832
	D.	.	.	.	.	.	*437*	*288*	*1,996*	*1,142*	*944*	*724*	*671*	*2,593*	> *2,989*
Shanghai *g*	C.	466	41	245	420	1,621	.	.	.	.	.	.	126	687	2,139*q*
	D.	*190*	*9*	*78*	*145*	*554*	.	.	.	.	.	.	*51*	*113*	*445q*
Chinese Eastern	C.	7	.	.	.	.	.	.	.	.	.	.	.	.	.
Railway Zone	D.	*0*	.	.	.	.	.	.	.	.	.	.	.	.	.
South Manchurian	C.	593	.	.	.	.	.	.	.	.	.	.	.	.	.
Railway Zone	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Cyprus	C.	—	—	—	—	—	—	—	—	—	—	3	—	1	—
Korea	C.	450	1,273	1,400	204	39	.	.	.	.	.	.	.	20,574*h*	> 155*h*
	D.	*135*	*324*	*371*	*44*	*10*	.	.	.	.	.	.	.	.	.
Straits Settlements *j*	C.	6	65	*1i*	*1i*	2	1	1	1	.	.	.	.	79	54*q*
	D.	*1*	*21*	—	*1i*	—	—	—	—	.	.	.	.	*25*	*16q*
French Settlements in	C.	1,736	1,124	578	7	22	68	62	50	.	.	.	.	.	12*q*
India	D.	*1,056*	*271*	*719*	*3*	*7*	*35*	*28*	*17*	.	.	.	.	.	*1q*
Formosa	C.	5	2	2	—	—	.	.	.	.	.	.	.	(1,588)*k*	(4,956)*k*
	D.	—	*1*	—	.	.	.	.	.	.	.	.	.	(*324*)*k*	(*1,623*)*k*
Hejaz	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Hong Kong	C.	153	61	21	123	2,276	195	332	7	.	.	.	> 1	1,965	252*q*
	D.	*104*	*44*	*16*	*94*	*1,833*	*153*	*269*	*6*	.	.	.	> —	*1,281*	*149q*
India *l*	C.	261,242	280,881	217,700	105,157	89,346	133,426	187,946	143,202	76,819	136,633	327,586	287,927	145,604	68,719
	D.	*59,281*	*61,650*	*54,643*	*26,481*	*22,027*	*31,295*	*42,473*	*39,916*	*15,433*	*32,834*	*88,984*	*67,260*	*33,496*	*17,127*
British India	D.★	*82,327*	*89,441*	*103,451*	*54,810*	*39,844*	*48,103*	*72,876*	*59,307*	*27,137*	*52,374*	*216,538*	*136,953*	.	.
Indian States:		.	.	.	.	.	.	*11,227*	*10,059*	*7,680*	*14,205*	*14,311*	.	.	.
Baroda	D.★	*171*	*1,542*	*761*	*228*	*148*	.	*1,257*	*157*	*116*	*83*	*139*	.	.	.
Hyderabad	D.★	*9,824*	*7,655*	*1,085*	*250*	*161*	.	*2,759*	*2,012*	*1,765*	*2,342*	*1,592*	.	.	.
Jammu and Kashmir	D.★	*223*	—	*31*	*185*	*62*	.	.	*14*	—	*2*	.	.	.	.
Mysore	D.★	*4,521*	*10,067*	*4,973*	*1,095*	*789*	.	*1,235*	*1,456*	*3,699*	*7,730*	*2,681*	.	.	.
Rajputana	D.★	*2,195*	*3,331*	*1,777*	*950*	*1,229*	.	*421*	*29*	*16*	*224*	*203*	.	.	.
Portuguese India	C.	298	341	45	45	73	42	138	> 92	.	.	.	.	52	12
	D.	*27*	*27*	*2*	*4*	*4*	*5*	*21*	> *5*	.	.	.	.	.	.
Netherlands Indies:															
Java and Madura	C.	4	10	1	1	9	1	—	.	.	.	.	.		
	D.	—	—	*1*	*1*	*2*	—	—	.	.	.	.	.	3	—
Outer Provinces *m*	C.	5	33	79	0	3	—	1	.	.	.	.	.	.	.
	D.	.	.	.	.	.	—	—	.	.	.	.	.		
French Indo-China	C.	4,598	3,655	1,872	3,053	7,403	4,772	1,884	1,272	4,315	5,060	> 1,668	.	> 2,525	5,092
	D.	*622*	*506*	*235*	*685*	*1,370*	*928*	*454*	*260*	*833*	*1,129*	> *383*	.	> *918*	*1,981*
Iraq	C.	387	264	198	28	39	112	1,058	> 2,098	848	265	138	90	18	> 64
	D.	*60*	*80*	*45*	*2*	*10*	*19*	*121*	> *275*	*83*	*41*	*12*	*16*	*3*	> *16*
Iran	C.	203	91	84	34	25	188	3010	42	355	1,163	1,341	266	102	850*q*
	D.	*42*	*29*	*24*	—	*6*	*177*	*370*	*40*	*178*	*509*	*240*	*47*	*25*	*241q*

Japan	C.	320	113	178	90	60	290	297	.	.	.	.	1,719	17,800	391
	D.*	35	16	20	6	.	.	.	.	.	.	.	.	> 2,819†	38†
Kwantung	C.	760	90	.	.	.	.	.	.	.	.	.	.	.	.
Kwangchow-Wan	C.	—	—	—	199	95	.	.	.	.	.	.	.	.	.
	D.	.	—	—	57	59	.	.	.	.	.	.	.	.	.
Macao	C.	87	150	—	2	10	3	482	8	.	.	.	.	.	.
	D.	83	131	—	2	8	.	431	8	.	.	.	.	.	.
Federated Malay	C.	—	2	—	—	—	.	.	.	.	.	.			
States	D.	—	1	—	—	—	.	.	.	.	.	.	.	> 3,066	4,600q
Non-Federated Malay	C.	—	57	41	23	—	.	.	.	.	.	.	.	> 557	1,000q
States	D.	—	9	21	4	—	.	.	.	.	.	.			
Oman	C.	5	755	241	.	.	.	.	.	.	.	.	.	.	.
	D.	—	89	.	.	.	.	.	.	.	.	.	.	.	.
Pakistan	C.	.	.	.	.	.	.	.	.	.	.	.	. . .	.	4,282
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	824
Palestine	C.	30	7	—	—	—	—	—	—	10	31	155	—	1	—
	D.	7	4	—	—	—	—	—	—	1	9	28	—	—	—
Philippines	C.	—	—	—	—	21	.	.	.	.	.	.	.	.	.
	D.	—	—	—	—	11	.	.	.	.	.	.	.	.	.
Siam	C.	152	34	2	51	294	> 50	> 219	> 397	.	.	.	34,970	26,265	1,397q
	D.	29	4	—	11	83	> 51	> 94	> 102	.	.	.	7,728	6,966	318q
Syria	C.	} 1,011	48	1	—	—	1	1	> 1	.	.	.	14	9	11q
Lebanon	C.												—	—	14q
Timor	C.	.	.	.	.	.	.	.	.	.	.	.	.	.	32q
Trans-Jordan	C.	4	—	—	—	—	—	—	—	41	85	6	—	—	—q
	D.	—	—	—	—	—	—	—	—	.	.	.	.	—	—q
U.S.S.R.:															
Transcaucasia	C.	596	146	33	.	.	.	.	.	.	.	.	.	.	.
Uzbekistan	C.	211	118	11	.	.	.	.	.	.	.	.	.	.	.
Turkmenistan	C.	492	41	6	.	.	.	.	.	.	.	.	.	.	.
Tajiskistan	C.	580	265	35	.	.	.	.	.	.	.	.	.	.	.
Other Territories in Asia	C.	945	263	51	.	.	.	.	.	.	.	.	.	.	.
Europe															
Albania	C.	2	1	—	—	—	.	.	.	.	.	.	.	.	.
Germany ("Altreich")	C.	—	1	—	—	—	—	—	—	1	1	—	.	.	.
	D.*	—	—	—	—	—	—	—	—	—	1†	—	.	.	.
United States Zone	C.	.	.	.	.	.	.	.	.	.	.	.	6	2	7q
British Zone	C.	.	.	.	.	.	.	.	.	.	.	.	2	—	—
Austria	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	.
	D.*	—	—	—	—	—	.	.	.	.	.	.	—	—	.
Belgium	C.	—	—	—	—	—	—	—	—	—	1	—	—	—	29q
	D.*	—	—	—	—	—	—	—	—	—	—	—	—	5	.
Bulgaria	C.	—	—	—	—	—	4	—	—	—	—	—	—	—	—
Denmark	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Danzig	C.	—	—	—	—	—	.	.	.	.	.	.	.	.	.
Spain r	C.	688	297	.	.	.	> 841	1,878	678	371	210	128	33	44	> 34
	D.*	5	3	2	6	6	609	977	176	31	—	3	2	.	.
Estonia	C.	.	.	.	.	.	—	.	.	.	.	.	.	.	.
	D.*	8	5	5	3	1	.	.	.	.	.	.	.	.	.

TABLE 2—*continued*

Countries		1934	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
Finland	C.	—	2	38	2	—	—	—	—	>—	—	>—	—	—	—
	D.*	—	*1*	*7*	*1*	—	—	—	*1*	—	—	—	.	.	.
France *s*	C.	199	428	273	5	2	5	5*t*	8*t*	67*t*	5*u*	4	4	10	52
	D.*	*19*	*15*	*10*	.	.	.	*1t*	*1t*	*6t*	*1u*	.	.	.	5†
Gibraltar	C.	—	1*i*	—	—	1*i*	—	1*i*	—	—	—	30	.	—	.
Greece	C.	10	9	2	3	—	—	.	.	.	831	329	—	2	—
	D.	—	—	.	.	.	.	.	.	.	*178*	*61*	—	—	—
	D.*	*20*	*9*	*10*	*7*	*8*	.	.	.	.	.	.	.	.	.
Hungary	C.	.	.	.	.	.	—	—	.	—	—	—	.	—	—
	D.	.	—	—	—	—	—	—	—	—	—	—	—	—	—
	D.*	—	—	—	—	—	—	.	.	.	.	.	.	.	.
Ireland (Eire)	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Italy	C.	—	—	—	—	—	4	—	—	.	.	2,878	2,831	772	44
	D.*	*3*	*1*	—	*1*	—	*1*	—	*1*	*2*	.	.	.	*25*	.
Latvia	C.	—	—	—	—	2	—	—	.	.	.	.	.	.	.
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Lithuania	C.	1	6	1	.	.	.	.	.	.	.	.	.	.	.
	D.*	—	*1*	*1*	*3*	*4*	—	—	.	.	.	.	.	.	.
Luxemburg	C.	—	—	—	—	—	—	.	.	.	.	.	2	—	3
Malta	C.	—	—	—	—	—	—	—	—	—	—	—	—	5	—
	D.*	—	—	—	—	—	—	—	—	—	—	—	—	*1*	—
Norway	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Netherlands	C.	—	—	—	—	—	—	—	—	—	—	2	—	—	—
	D.*	—	—	—	*1*	—	—	—	—	—	—	—	—	*1*	.
Poland	C.	5	4	—	1	—	—	—	.	.	.	.	—	—	—
	D.	—	*2*	—	—	.	.	.	.	.	.	.	.	.	.
Portugal:															
Mainland	C.	1,016	762	836	623	706	1,369	771	464	>352	.	.	.	.	.
	D.	.	.	.	.	*53*	*105*	*45*	*53*	*41*	.	.	.	.	.
	D.*	*220*	*210*	*157*	*105*	*171*	*266*	*91*	*85*	*119*	*45*	*74*	*46*	*100*	*50*
Azores and Madeira	D.*	*1*	*2*	—	—	*1*	—	*1*	—	—	—	—	—	—	*1*
Roumania	C.	7	—	3	15	55	—	1	—	—	—	—	—	—	—
	D.	*1*	—	—	—	—	—	—	—	—	—	—	—	—	—
	D.*	*17*	*6*	*6*	*4*	*1*	*1*	.	.	.	.	.	.	.	.
United Kingdom:															
England and Wales	C.	179	1	12	4	18	1	2	—	7	—	16	5	54	94*q*
	D.*	*6*	—	—	—	*3*	—	—	—	—	—	*3*	—	—	—
Scotland	C.	—	—	—	—	1	—	—	—	116	1	—	3	11	—
	D.*	—	—	—	—	—	—	—	—	*25*	—	—	—	.	.
Northern Ireland	C.	—	—	—	—	—	—	—	—	1*i*	—	—	—	—	—
Sweden	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	D.*	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Switzerland	C.	—	—	—	—	—	1	—	—	—	—	—	.	.	.
	D.*	—	—	—	—	—	—	—	—	—	—	—	.	.	1*i*

Czechoslovakia	C.	—	—	—	—	—	—	1	—	—	—	—	—	—	—	
	D.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
	D.*	—	—	—	—	—	—	—	—	—	.	.	.	.	.	
Turkey	C.	93	106	69	36	641	431	544	7	1,871	12,400	6,054	307	13		2
	D.	*17*	*15*	*2*	*2*	*167*	*74*	*74*	*2*	*174*	*1,380*	*669*	*34*	*1*		*1*
U.S.S.R.:																
Ukraine	C.	76	4	—	.	.	.	.	.	.	.	.	.	.	.	
White Russia	C.	112	12	—	.	.	.	.	.	.	.	.	.	.	.	
Other Territories in Europe	C.	2,780	1,135	79	.	.	.	.	.	.	.	.	.	.	.	
Railways and waterways	C.	102	18	8	.	.	.	.	.	.	.	.	.	.	.	
Yugoslavia	C.	—	—	—	—	—	—	1	>—	.	.	.	.	2	—	
	D.	—	—	—	—	.	.	*1*	.	.	.	.	.	.	.	
Oceania																
Australia	C.	—	—	—	—	—	—	—	—	—	—	—	—	—	.	
	D.	—	—	—	—	*1*	—	—	—	—	—	—	—	—	—	
French Settlements in Oceania	C.	.	.	.	.	.	12	.	.	.	.	.	.	.	.	
	D.	.	.	.	.	.	*3*	.	.	.	.	.	.	.	.	
Hawaii	C.	.	.	.	.	.	—	1	—	—	—	—	—	1[i]	—	
New Zealand	C.	.	.	.	.	.	—	—	—	—	—	—	—	—	—	

NOTES

† Figures recorded by the Health Authorities.
★ Figures recorded by the Central Statistical Office.
a Widespread epidemic, total number of cases unknown.
b Exclusive of Yukon and the North West Territories and, from 1925 to 1929, the Prince Edward Island.
c Variola minor and major.
d From 1923 to 1934, variable number of States.
e Inclusive of the cities of Panama and Colon.
f Year ending 30 June.
g From 1920 to 1925, International Settlement only; 1926–1928, International and French Settlements.
h South Korea only.
i Imported cases.
j 1946 and 1947, Singapore (City) only.
k Included under China
l Aggregate of reporting British Provinces and Indian States; inclusive of Burma up to 1936.
m From 1925 to 1929, principal ports only.
n Year ending 21 March.
o Towns only.
p Siamese civilian year beginning 1 April.
q 53 weeks.
r From 1932 to 1938, inclusive of Spanish Morocco.
s Up to 1936, inclusive of cases of chickenpox.
t 87 departments.
u 86 departments.

Note

Symbols used in the tables:

C. Cases.
D. Deaths.
. No data available.
— Nil or less than half the final digit shown.
> Incomplete figures.

APPENDIX III

(From *Epidemiological and Vital Statistics Report*, 1959, Vol. 12, No 1)

SMALLPOX, NUMBER OF CASES AND DEATHS, 1953–1957

Compared with the Average for 1934–1938

A — Alastrim or variola minor
M — Variola major only
B — Variola major and variola minor

Country		Yearly average 1934–38	Cases 1953	1954	1955	1956	1957	Yearly average 1934–38	Deaths 1953	1954	1955	1956	1957
AFRICA													
French Equatorial Africa		198	1,607	669	315	57	57	...	203	104	57	2	2
Spanish West Africa		...	—	—	—	+	+	...	—	—	—	+	+
French West Africa		3,191	4,380	3,869	3,983	4,855	12,873	365	261	261	255	293	962
Algeria [1]	B	33	56	67	73	18	8	...	...	...	...	...	...
Angola	M	347	42	135	82	26	—	24	1	3	2	—	—
	A	88	96	—	40	87	11		—	—	1	—	—
Basutoland		—	—	—	—	—	—	—	—	—	—	—	—
Bechuanaland	B	3	34	4	—	—	[2] 111	—	—	—	—	—	[2] 2
Cameroons (French)	B	391	63	177	42	42	4	79	3	6	3	9	—
Belgian Congo	M	2,872	274	479	518	970	240	55	29	96	115	157	47
	A		4,427	4,742	5,703	3,693	1,792		43	75	35	63	7
Ethiopia-Eritrea, Fed. of:													
Eritrea		[3] 129	—	—	—	555	403	...	—	—	—	14	10
Ethiopia		...	188	378	282			...	1	3	2		
Gambia	B	29	226	107	31	15	33	5	6	1	3	—	—
Ghana [1] (Former Gold Coast)		55	282	36	125	259	★ 184	7	43	2	19	61	★ 15
Spanish Guinea	A	...	—	2	—	—	—	...	—	—	—	—	—
Portuguese Guinea	M	27	153	124	56	4	43	—	16	9	10	—	—
	A		21	38	2	—	106		1	—	—	—	—
Kenya		383	—	—	61	A 396	A 806	...	—	—	1	1	1
Morocco: Former French Protectorate	B	37	—	—	2	—	2	...	...	...	...	...	...
Mozambique	B	459	390	28	31	94	...	6	—	1	1	—	...
of which	M	...	4	3	3	4	—	...	—	—	—	—	—
	A	...	290	22	28	90	...	...	—	1	1	—	...

Nigeria (Incl. Brit. Cameroons)		6,384	[5] 3,258	6,372	5,828	4,614	9,733	1,337	[5] 427	710	751	588	1,350
Uganda	B	...	341	199	101	231	481	1	2	2	2	8	4
United Arab Republic: Province of Egypt		303	—	3	—	—	1	54	1	1	—	—	—
Rhodesia-Nyasaland, Federation of:													
Nyasaland		255	6	5	28	248	315	[3] 64	—	—	—	6	1
N. Rhodesia		47	A 693	1,024	3,538	576	565	1	6	9	501	52	74
S. Rhodesia		434	11	1	157	150	35	2	—	—	11	3	1
Ruanda Urundi	M	—	—	—	3	—	—	—	—	—	—	—	—
	A	72	219	234	110	58	34	1	1	1	—	—	1
Sierra Leone		1,014	12	5	49	946	4,845	116	—	—	3	19	228
Somaliland (British Protectorate)		98	A 240	A 818	—	—	3	—	—	—	—	—	—
Somaliland (Italian)		—	—	A 737	A 391	A 84	+	...	—	—	+	+	+
Sudan		340	3,030	4,200	1,427	438	285	70	413	+	284	55	32
Swaziland		...	—	—	—	A 1	—	—	—	—	—	—	—
Tanganyika		1,024	1,200	928	542	605	856	27	54	28	15	21	38
Tangier		—	—	—	—	—	+	...	—	—	—	—	+
Togoland (French)		17	228	226	2	6	* 11	...	14	3	—	—	* 2
Tunisia		6	7	1	—	2	—	...	...	...	...	...	...
Union of South Africa		[6] 152	14	7	27	4	—	[6] 3	—	1	—	—	+
Zanzibar		—	—	—	—	A 52	1	—	—	—	—	—	+
AMERICA													
Alaska		3	—	—	—	+	+	...	—	—	—	+	+
Argentina		[3] 174	306	251	55	86	335	[3] 65	—	31	3	5	+
Bolivia		* 549	429	624	372	481	1,310	...	201	+	+	+	+
Brazil [7, 8]	B	...	923	1,035	2,580	2,385	1,014	...	9	24	45	44	28
Canada [9]		58	—	—	—	—	—	3	—	—	—	—	+
Chile		2	A 9	—	—	—	—	1	2	4	+	+	+
Colombia [7]	B	...	5,526	7,203	3,404	2,572	2,103	[3] 402	408	282	206	157	226
Ecuador	B	161	708	2,516	1,831	669	913	[3] 22	...	267	219	+	+
United States		9,555	4	[10] 9	[10] 2	—	—	33	1	—	—	—	+
Guatemala		...	1	—	—	—	—	33	...	2	+	+	+
British Honduras	B	57	—	—	—	—	—	...	—	—	—	—	+
Mexico		...	...	...	...	...	...	5,233	77	47	15	+	+
Paraguay		[3] 10	[7] 770	[7] 207	[7] 57	132	103	...	—	—	1	+	+
Peru [7]		257	172	115	—	—	—	...	...	...	...	...	...
El Salvador		148	—	—	—	—	—	[3] 25	—	—	1	—	—
Uruguay		33	A 7	A 1	A 43	42	A 2	[3] 2	—	—	1	—	—
Venezuela		...	72	13	2	4	—	87	1	1	+	—	+
ASIA													
Aden Colony		1	—	A 66	[1] 1	—	13	—	—	—	—	—	2
Afghanistan		...	1,813	1,725	1,345	1,002	239	...	28	61	54	5	1
Saudi Arabia *		109	162	5	1	* 9	* 65	81	42	—	1	+	+
Bahrain		...	—	—	A 1	62	7	...	—	—	...	10	2
Burma		5,150	164	216	1,675	[12] 4,223	[12] 2,739	1,250	18	32	319	[12] 1,495	[12] 759
Cambodia		...	1,788	435	485	525	111	...	376	107	145	70	12

Country	Yearly average 1934–38	Cases					Yearly average 1934–38	Deaths				
		1953	1954	1955	1956	1957		1953	1954	1955	1956	1957
Asia—*continued*												
Ceylon	38	2	1	—	—	19	7	1	—	—	—	7
China:												
Taiwan	2	14	9	—	—	—	—	—	1	—	—	—
South Korea	673	3,349	781	* 2	* 9	9	177	571	122	* —	* —	1
Hong Kong	527	—	—	—	—	—	413	—	—	—	—	—
India [13]												
Total	...	36,857	46,828	41,934	[14] 45,166	[15] 78,896	...	32,771	37,254	31,702	*[14] 16,670	[15] 23,121
of which:												
Ajmer	...	18	199	122	[16] 6		...	153	357	172	61	
Andhra	...	[19] 240	3,154	3,681	7,997		...	2,195	1,471	1,278	2,240	
Assam	...	119	55	14	197		...	237	[18] 27	[18] 58	125	
West Bengal	...	1,051	2,223	1,060	2,581		...	513	850	502	1,185	
Bhopal	...	61	877	1,503	[16] 620		...	61	236	451	[17] 150	
Bihar	...	2,235	1,809	1,994	3,141		...	2,178	2,719	3,922	[18] 851	
Bombay	...	6,184	10,241	7,138	5,521		...	2,112	3,048	2,419	[18] 1,036	
Coorg	...	17	50	107	[16] —		...	23	74	30	[16] —	
Delhi	...	426	133	105	411		...	154	39	40	129	
Hyderabad	...	353	159	212	[16] 513		...	217	233	[18] 65	[17] 179	
Himachal Pradesh	...	90	* 28	11	13		...	31	3	2	3	
Jammu and Kashmir	...	131	434	287	114		...	—	[18] 107	[18] 54	[18] 24	
Madhya Bharat	...	676	1,193	1,076	[16] 678		...	407	2,745	1,240	[17] 192	
Madhya Pradesh	...	1,140	4,903	9,851	10,583		...	1,539	3,356	2,319	[18] 1,505	
Madras	...	6,750	4,483	2,026	3,418		...	2,733	1,711	862	1,129	
Manipur	...	11	5	—	12		...	2	1	—	3	
Mysore	...	1,803	1,133	693	612		...	1,140	1,022	422	532	
Orissa	...	3,338	3,515	2,149	1,657		...	1,781	879	389	[18] 102	
Punjab	...	2,111	532	415	290		...	609	221	197	84	
Pondicherry	...	.	+	305	1,509		...	.	28	184	263	
Rajasthan	...	2,410	3,934	2,313	2,435		...	889	636	1,181	657	
Saurashtra	...	1,273	365	488	[16] 253		...	618	202	335	[17] 83	
Travancore-Cochin	...	1,478	1,663	114	593		...	522	695	31	233	
Tripura	...	3	2	27	41		...	—	—	—	7	
Patiala and East Punjab States Union	...	1,784	422	681	[16] 45		...	907	103	93	103	
Uttar Pradesh	...	2,822	4,539	4,383	1,848		...	13,625	16,405	15,262	5,742	
Vindhya Pradesh	...	333	757	1,179	[16] 78		...	125	86	[18] 194	[17] 12	
Portuguese India	160	12	13	9	1	42	13	10	12	1	—	7
Indonesia	...	2,584	1,878	1,377	2,817	1,550	...	363	277	460	2,078	320
Iraq	183	[12] 251	[12] 27	72	2,173	1,924	39	37	—	5	281	222
Iran	87	148	90	542	1,616	1,008	20	1	—	48	175	42
Japan	152	6	2	1	—	—	17	—	—	—	—	—
Qatar	...	...	...	...	4	2	...	...	...	...	—	1

Kuwait		...	...	...	...	[12] 8	23	...	...	...	...	—	8
Laos		...	15	—	—	—	—	...	30	—	—	—	—
Lebanon		...	—	—	—	84	108	...	—	—	—	46	
Malaya, Federation of		...	[12] 5	—	—	—	—	...	—	—	—	—	—
Muscat and Oman		...	...	...	...	22	* 4	...	...	...	...	1	* 2
Trucial Oman		...	...	...	...	3	5	...	...	...	...	1	1
Pakistan [13]													
Total		...	5,065	2,568	3,261	5,323	25,770	...	3,644	[18] 875	[18] 1,360	[18] 2,130	[18] 11,203
of which:													
Karachi Area		...	156	144	32	41	851	...	39	[18] 42	[18] 4	[18] 10	[18] 177
Parkistan, West		...	3,871	1,978	1,351	112	173	...	2,817	[18] 645	[18] 377	[18] 19	[18] 33
Pakistan, East		...	1,038	446	1,879	5,170	24,746	...	788	188	979	[18] 2,101	[18] 10,993
United Arab Republic:													
Province of Syria		...	3	7	—	—	+	...	2	—	1	8	3
Ryu-Kyu		...	—	—	1	—	+	...	—	—	1	—	+
Thailand		109	44	20	117	4	3	28	—	—	2	—	—
Timor		...	—	—	—	1	1	...	—	—	—	—	—
Turkey		189	—	—	—	—	128	41	—	—	—	—	7
Viet-Nam [11]		...	1,582	3,588	923	256	83	...	704	1,518	200	56	35
EUROPE													
Germany:													
Federal Republic		—	—	—	—	—	[i] 1	—	—	—	—	—	+
Spain		[3] 705	1	2	—	—	—	[3] 5	—	—	—	—	—
France		6	—	15	85	—	—	—	—	—	18	—	—
Greece	B	5	—	—	—	—	—	11	—	—	4	2	1
Italy		—	—	—	—	—	A 7	1	—	—	—	+	+
Netherlands	A	—	—	40	—	—	—	—	—	—	—	—	—
Portugal:													
Mainland	M	851	7	—	—	—	—	173	1	—	—	—	—
	A		1	—	—	—	—		—	—	—	—	—
Azores and Madeira	M	...	1	—	—	—	+	1	—	—	—	—	+
Islands	A	...	—	—	—	—	+		—	—	—	—	+
United Kingdom:													
England and Wales	M	43	30	—	—	—	4	2	8	—	—	—	2
OCEANIA													
Australia		—	—	1	—	—	—	—	—	—	—	—	—

NOTES

[i] Imported case.

[1] Including chickenpox.

[2] Eleven months.

[3] Average for the following years: *Eritrea*, cases: 1933–37; *Nyasaland*, deaths: 1932–36; *Argentina*, cases: 1936–39, deaths: 1934–36; *Colombia*, deaths: 1935–36, 1938; *Ecuador*, deaths: 1936–40; *Paraguay*, cases: 1935–37; *El Salvador*, deaths: 1935–39; *Spain*, cases and deaths: 1931–35.

[4] Including Togoland under British administration.

[5] Data for the period from 1.IV to 31.III.

[6] Years ending 30 June.

[7] Reporting area of which the population, with regard to the population as a whole, is estimated as follows:

		1953	*1954*	*1955*	*1956*
Brazil: F.D. and State capitals	Cases	14·8%	14·9%	15·4%	11·2%
	Deaths	15·6%	15·7%	15·7%	15·8%
Colombia	Cases	81·1%	88·2%	87·5%	91·8%
Paraguay	Cases	88·4%	88·2%	*a* 45·8%	...
Peru	Cases	46·8%	48·8%	49·4%	50·1%

a This reduction is due to a change in the definition of the reporting area.

[8] F.D. and State capitals except: Salvador, 1953 and 1954; Niteroi, 1955.
[9] Excluding Northwest Territories and, prior to 1955, Yukon.
[10] These cases do not fulfil the generally accepted criteria for a diagnosis of smallpox.
[11] From July 1954, excluding North Viet Nam.
[12] Burma 1956: including 197 imported cases of which 82 deaths
„ 1957: „ 44 „ „ „ „ 10 „
Iraq 1953: „ 24 „ „ „
„ 1954: „ 4 „ „
Kuwait 1956: „ 1 „ „
Malaya 1953: „ 4 „ „

[13] Data relating to *cases* of smallpox in India and Pakistan are only given for information and must be considered as very imperfect.
[14] Including 141 cases and 42 deaths in the new Kerala State.
[15] The available data for 1957 according to the new territorial partition that came into force on 1 November 1956 are as follows:

	Cases	*Deaths*
India:		
Total	* 78,896	* 23,121
of which:		
Andaman and Nicobar, Islands	+	+
Andhra Pradesh	9,444	1,848
Assam	539	132
West Bengal	17,649	8,497
Bihar	3,134	851
Bombay	13,064	2,437
Delhi	558	145
Himachal Pradesh	58	9
Jammu and Kashmir	21	1
Kerala	1,371	517
Laccadive, Minicoy and Amindivi, Islands	+	+
Madhya Pradesh	4,155	791
Madras	10,787	3,032
Manipur	33	6
Mysore	3,048	868
Orissa	7,172	1,543
Pondicherry	449	264
Punjab	386	76
Rajasthan	3,438	872
Tripura	117	22
Uttar Pradesh	3,473	1,210

[16] These provisional data refer only to the first ten months of 1956 as this State has been suppressed. From November 1956, figures relating to this territory are included in the data of the State with which it has been incorporated.
[17] Provisional figures covering only ten months; final data, which may be very different, are not yet available.
[18] Provisional figures; final data may be very different.
[19] This figure refers only to the end of 1953 as this State came into being on 1 October 1953.

* Preliminary approximate.
... Data not available, estimated.
\+ Data not yet available, may be later.
— Nil or negligible magnitude.
x Unofficial data.
r Revised data.

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