

REPORT

OF THE

DIRECTOR OF THE HOSPITAL

TO THE CORPORATION OF THE

ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

OCTOBER, 1918.

The following report was prepared by the Director of the Hospital, Dr. J. H. P. ...

The report covers the period from ... to ... and includes a summary of the work done during the year.

The work of the Hospital during the year has been ... and the results are ...

The following table shows the number of patients treated during the year:

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The total number of patients treated during the year was ...

The following table shows the number of operations performed during the year:

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The total number of operations performed during the year was ...

The following table shows the number of deaths during the year:

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The total number of deaths during the year was ...

The following table shows the number of discharges during the year:

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The total number of discharges during the year was ...

The following table shows the number of admissions during the year:

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The total number of admissions during the year was ...

The following table shows the number of patients who died during the year:

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The total number of patients who died during the year was ...

The following table shows the number of patients who were discharged during the year:

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The total number of patients who were discharged during the year was ...

The following table shows the number of patients who were admitted during the year:

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The total number of patients who were admitted during the year was ...

ANNUAL REPORT OF THE DIRECTOR OF THE HOSPITAL
OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH,

October 1918.

To the Members of the Corporation of
The Rockefeller Institute for Medical Research:

Gentlemen:

In my report of one year ago I stated that a large number of the members of the hospital staff had joined the medical corps of the army and many of them had been ordered elsewhere. This exodus has continued, and more of the staff members have gone into the service, until now, Dr. Van Slyke and the Director are the only members not in uniform. The hospital has also received a quasi-military character through its designation as an auxiliary hospital, and it has now seemed wise for the Director, as well as for Dr. Van Slyke, to apply for commissions. This has been done, and within a very short time the entire staff will consist of army officers. The Director hopes that, for the present at least, he will be permitted by the Surgeon General to remain at the hospital and to continue its direction.

In January Dr. Cohn entered the service and in March was ordered to France where he has been acting as a consultant in cardio-

vascular diseases. In May Dr. Chickering, the Resident Physician, was ordered to Camp Jackson to carry on instruction of medical officers in the diagnosis and treatment of pneumonia. Groups of officers have been ordered there from time to time, and Dr. Chickering's work, which is still in progress, has been of much value. His departure left us without any resident physician who had had any considerable experience in the work of our hospital, and to meet the emergency Dr. Stadie, who entered the hospital in January to assist in the studies on syphilis, was made acting resident physician. In spite of the extreme depletion of the staff, it has been possible to continue our activities and care for a considerable number of patients. This has been rendered possible by the army sending to us a small number of officers to be trained in the diagnosis and treatment of pneumonia and detailing to the hospital several men to assist in the investigation being made of the new drug for the treatment of syphilis.

In May a Board for the Investigation of Respiratory Diseases in the Army was appointed by the Secretary of War, and Dr. Cole was made a member of this Board. This has necessitated considerable absence from the hospital due to frequent trips to Washington, and to an extended trip to camps in the west in May and June, and lately a trip to southern camps, which occupied about three weeks. This, with the trip to Texas lasting two months, of which mention will be made below, has made it impossible for the Director to give the same continuous personal attention to the hospital as has been the case in preceding years.

Instruction for Army Officers in the Institute and Hospital.

During the entire year courses in bacteriology for army medical officers have been given in the Institute. The instruction regarding the bacteria concerned in pneumonia has been given by members of the hospital

staff. During one week of each month, this teaching work has occupied a large part of the time of Dr. Dochez and of Dr. Avery. They have also been assisted in this work by Dr. Ernest Stillman. Before Dr. Chickering's departure for Camp Jackson, he had charge of the instruction concerning the typhoid bacillus.

On April first, a laboratory course of instruction in medical chemistry for chemists in the Sanitary Corps was organized by Dr. Van Slyke, and has been given in the hospital chemical laboratory. Each month about twenty men have been ordered here and have received instruction in the methods of medical chemistry. This has made it necessary to turn over a considerable portion of the laboratory space to this work. The work has been under the immediate direction of Dr. Van Slyke with the assistance of Capt. Robinson, who was ordered here for this purpose.

Last autumn, acting upon the authority of the Board of Scientific Directors, the Director of the Hospital invited the Surgeon General of the Army to send to the hospital "a limited number of medical officers to assist in the treatment of patients with pneumonia, in order that the officers could become thoroughly familiar with the methods of treatment employed here". The Surgeon General has responded to this invitation by sending officers to the hospital from time to time for various lengths of residence. Up to the present, 27 officers have been detailed here. Some have remained for only a couple of weeks, most of them for periods of from one to three months. These officers have lived in the hospital and have taken the places of the hospital internes who have entered the service. This arrangement has permitted us to care for a considerable number of patients with pneumonia, which care would otherwise have been impossible. On the other hand, it is believed that this service has been of very great advantage to the army. It

has been a source of gratification on visiting the army hospitals to find that the officers trained here, even though this training was only very short and fragmentary, are being relied upon to direct and organize the care and treatment of the patients suffering from pneumonia.

The problem of determining accurately the etiologic agent concerned in cases of pneumonia in the army hospitals has proved a difficult matter in spite of the fact that large numbers of men have been trained in this work in the bacteriological courses being given in the Institute laboratories. The chief reason for this difficulty has been that the trained men have been shifted about from place to place, and from one kind of work to another, and very large numbers of these men have been sent overseas. The only feasible plan to make this work satisfactory seems to be to train especially for this work women who can be kept permanently in the camp hospital laboratories. With the authority of the Board of Scientific Directors, we have agreed to train women especially for this service, and arrangements have been made to send here at once ten women for such training. For this purpose we shall use the laboratory previously occupied by the laboratory for the study of cardiac pathology and physiology.

Clinical Studies.

During the past year, the facilities of the hospital wards have been employed almost entirely in the care of patients suffering from pneumonia and of those suffering from syphilis. A large number of the patients treated have been soldiers sent in from nearby camps. Certain difficulties have arisen in the control of these soldiers, though these difficulties have not appeared to be serious. However, it has been felt by the army authorities that these difficulties could best be overcome by giving the hospital a purely nominal army status. This has been done by the army by designating the hospital U. S. Army Auxiliary Hospital No. 1 and by giving Capt. Edgar Stillman, a

member of our staff, the designation Commanding Officer. Capt. Stillman then reports weekly to the Chief Surgeon of the Port of Embarkation the condition of the soldiers being treated and informs him of the number of beds available for patients. A lieutenant to act as adjutant has also been detailed to the hospital to look after the records of the men. This entails no added obligations on the part of the hospital and will probably enable us to be of still greater service in the way of caring for sick soldiers.

Clinical Studies Concerning Pneumonia.

In the report to the Scientific Directors for the meeting of January 19th, I drew attention to the fact that among the cases of pneumonia in soldiers treated in the hospital, 4 were apparently due to haemolytic streptococci, all of them were associated with empyema and two of them died. An autopsy was obtained in one of these cases. "The lungs in this case showed an irregularly distributed patchy pneumonic process, the areas bearing some relation to the bronchi, but the entire picture, however, not being a characteristic broncho-pneumonia. In certain places small areas were seen where the entire lung tissue failed to stain. In other words, there was beginning necrosis or abscess formation."

During the autumn and early winter, pneumonia had been very prevalent in the camps, especially pneumonia in association with measles which was prevailing to a very great extent. On December 4th Capt. Dochez of our staff had been ordered to Camp Bowie, Fort Worth, Texas, to assist in investigating the pneumonia epidemic there. He was joined there by Dr. Jobling, and together they carried on certain studies concerning the etiology and pathology of the cases of pneumonia. They found a large number of cases of lobar pneumonia associated with the presence of pneumococci, but in addition they discovered a very large number of cases of broncho-pneumonia or atypical

lobar pneumonia, many of them associated with or following measles. Autopsies were performed in 27 such cases, and in 22 of them empyema was present. Bacteriological examination of 16 of the empyema fluids showed the presence of a haemolytic streptococcus in 13 of them. The pathology of the pulmonary lesions was not exhaustively studied.

These observations taken in connection with our own indicated that the pneumonia prevailing in the camps was not all of the typical lobar pneumonia, but that, as I stated in my report of January 19th, "two kinds of pneumonia existed; first, typical lobar pneumonia due to pneumococci of the various types, and second, atypical or broncho-pneumonia due to streptococci and possibly also to pneumococci". In this report I outlined the problems which demanded solution. I consequently brought the matter to the attention of Col. Russell and Col. Longcope of the Surgeon General's Office and requested that in order to solve these problems I be permitted to organize a group of investigators to study the matter intensively in one camp. Permission was granted for this and Dr. MacCallum of Baltimore was persuaded to join the party, since it seemed most important that careful pathologic studies be made on the cases suffering from the atypical disease.

A commission was organized consisting of Dr. Cole, Dr. Avery and Capt. Dochez of this hospital, Dr. MacCallum and Lieut. von Glahn of the Johns Hopkins University, Lieut. Blake, formerly of this hospital, Capt. Kinsella, and Lieuts. Rivers, John and Stevens.

It was decided to carry on the study at the Base Hospital, Fort Sam Houston, San Antonio, Texas. In the prosecution of this work the Director was absent from his regular hospital duties from January the 28th to March the 25th.

The preliminary survey of the cases in the base hospital made it evident that all the cases were not of the same variety and that

our present knowledge did not permit a ready differentiation of the cases of the different kinds. An extensive statistical study was therefore out of the question and therefore a very careful clinical, bacteriological and pathological study of a limited number of cases was undertaken. The following is a copy of the conclusions from my report to the Surgeon General.

Discussions and Conclusions.

"The studies indicate that the cases of pneumonia at the Base Hospital, Fort Sam Houston, are chiefly of two varieties: first, acute lobar pneumonia, which does not differ essentially from that which occurs elsewhere; and second, broncho-pneumonia, which in most cases, at present at least, follows measles.

"The pulmonary lesions in most cases of this type of broncho-pneumonia are characteristic and specific and have been studied and described by Dr. MacCallum. The etiologic agent in all the cases studied by us has been *Streptococcus haemolyticus*. There is no evidence presented by this work that indicates that pneumococcus causes the lesions and symptoms of this condition. Pneumonia following measles may be due to pneumococci, but the pulmonary lesion is then of the lobar variety. This complication of measles, however, is comparatively rare. Cases may occur in which both types of infection and both types of lesions are present. The sequence of events in such cases is difficult to determine and is probably not always the same.

"*Streptococcus* infections following lobar pneumonia occur with considerable frequency in this hospital. Broncho-pneumonia similar to that following measles may also probably occur as a sequel of acute lobar pneumonia, though the evidence for this is not conclusive. Whether in the cases of streptococcus empyema, complicating lobar pneumonia, pulmonary lesions due to the streptococci are always present or not, has not been determined.

"The mortality in the cases of broncho-pneumonia is very high; that of uncomplicated lobar pneumonia is low. Practically all the fatal cases of broncho-pneumonia are complicated by empyema. The incidence of empyema among the uncomplicated cases of lobar pneumonia does not seem to be extremely high.

"The number of measles cases infected with haemolytic streptococci on admission to the hospital is not large. The majority of the patients with measles acquire this organism during their stay in the hospital. The chance of developing post-measles streptococcus infections is therefore increased by residence in this hospital.

"A very large number of the patients in this hospital suffering from acute lobar pneumonia have haemolytic streptococci in their throats. We have no direct evidence that they acquire these bacteria in the hospital, but the presumptive evidence indicates that many of them do so.

"The work indicates that the high incidence of pneumonia in this hospital, and the resulting high mortality, has been due, to some extent at least, to infection occurring within the hospital itself. The conditions are not unlike those surrounding puerperal fever and surgical wound infections. While in measles, raw surfaces do not exist on which infection can occur, this disease renders the respiratory mucous membrane especially vulnerable to infection with streptococci. Possibly in other diseases, as scarlet fever and even lobar pneumonia, similar conditions exist. When infection is once started in a ward in which the patients are closely associated, the streptococci become widely distributed; they probably gain in virulence with repeated transfer through the human subject, and serious and widespread infection results.

"Probably the conditions in this hospital are not unique. It is possible that the widespread incidence of fatal pneumonia in the other army hospitals may have a similar explanation."

Our studies in Texas indicated the important part which empyema played in the mortality from the streptococcus pneumonia and we strongly urged upon the officers at the Surgeon General's office the importance of further study of this complication, especially with a view of devising improved methods of treatment.

The results of our study in Texas were rapidly confirmed by observations in other camps. The nature of this serious malady is now fairly well understood. There remain, however, many problems awaiting solution before satisfactory procedures for prevention and treatment can be carried out. Many of these problems were considered in a conference of bacteriologists and clinicians held at the Department of Animal Pathology of The Rockefeller Institute at Princeton on June first. The study of certain of the questions demanding early solution has been undertaken by Major Dochez, Captain Avery and Lieut. Stillman at this hospital, and the results so far obtained are described below.

Very recently a new form of pneumonia has appeared in the army camps and to a less extent among the civilian population. Last spring reports appeared in the newspapers of the appearance in European countries of an epidemic of acute respiratory disease resembling influenza. This disease has prevailed to a considerable extent in the armies abroad. The exact extent and severity of the disease there cannot be determined from the reports so far published. In certain localities at least it occurred as a serious disease. There seems as yet to be no unanimity of opinion by foreign observers as to the etiology, though certain observers have indicated their opinion that it is due to the Influenza Bacillus of Pfeiffer, and they believe the disease to be identical with that occurring in epidemic form in 1890-91. The disease has now appeared with great suddenness and severity in certain of our army camps.

As a member of the Board for the Investigation of Respiratory Diseases in the Army, the Director was last week called to Camp Devens, Massachusetts, for consultation. In this camp within two weeks there have occurred over 12,000 cases, in a considerable number of which pneumonia was present and with a large number of deaths, reaching on some days over 80 per day. Judging from a few autopsies seen by the writer, it is evident that we now have to deal with another distinct form of pneumonia. Pneumococci and streptococci are present in these cases, but it seems certain that they are not the primary etiologic agents concerned in this disease. At the time of my visit influenza bacilli had not been isolated in any considerable number of cases, but Capt. Avery of our staff, whom I called upon to assist me, succeeded in demonstrating the presence of these organisms in a considerable proportion of the cases examined.

Patients suffering from this disease are now being admitted to the Hospital of The Rockefeller Institute, and from most of them it has been possible to isolate the influenza bacillus. It is believed to be important that a considerable part of the resources of this hospital for so long as may be necessary be devoted to a study of this disease. Dr. Avery is already busily engaged in attempts to improve the methods for demonstration of influenza bacilli in the sputum of such cases. It is also important that immunological studies be at once undertaken, and this will be done by Dr. Dochez as soon as he himself recovers from an attack of the disease from which he is now suffering.

During the past year, 311 cases of pneumonia have been treated in this hospital. This is by far the largest number of pneumonia cases treated in this hospital in any one year since its opening. Of the patients treated 146 were soldiers and 165 were civilians. Of the cases undoubtedly due to pneumococci, 34 per cent were Type I, 32 per cent Type II, 6 per cent Type III, and 28 per cent Type IV. Forty-four cases were due to Streptococcus haemolyticus. Of the 84 cases due to Type I, 8 died - a mortality of 9.5 per cent. Of the Type II cases, 9 died - a mortality of 23 per cent; of the Type III cases, 4 died - 28 per cent; of the Type IV cases, 5 died - 7.8 per cent. As in our previous experience, the mortality due to pneumococci of Type I was low. The total mortality also was low. This was undoubtedly due in part at least to the low mortality of Type I cases, most of which were treated with serum, as will be mentioned below. Of the 44 cases due to Streptococcus haemolyticus, 30 were complicated with empyema. Fifteen of the Streptococcus haemolyticus cases died - a mortality of 34 per cent. Of the cases complicated by empyema, 28 were operated upon and 10 died - a mortality of 35 per cent. Two of the empyema cases were not operated upon and both died.

Serum Treatment.

As stated above, the mortality in cases due to Type I, 9.5 per cent, was very low as compared with our experience before we began the treatment of cases with serum. Two of the fatal cases were patients admitted very late to the hospital - too late for serum treatment. If we omit these two cases in which serum treatment could not be carried out, the mortality was 7.3 per cent, which is a most satisfactory result. It seems that there can be little doubt that the excellent results obtained by the treatment of this type of case has been largely due to the proper administration of

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antipneumococcicserum.

The results of serum treatment in the army, as far as reported, have been quite uniformly satisfactory. It must be stated, however, that in most camps it has been difficult or impossible to carry out the serum treatment in the manner in which we have advised. In certain camps no attempt has been made to treat only the Type I cases, and all cases, due to whatever type of organism, have had serum administered to them. In a few camps, however, notably at Camp Upton and Camp Jackson, very accurate determinations of the type of infecting organism were made, and the serum was properly administered. In both these camps the mortality in the cases due to Type I infection was very low. It is hoped that during the coming winter satisfactory employment of the serum may be made in a larger number of the camps.

Treatment of Cases with Empyema Due to Streptococcus haemolyticus.

The results of operative treatment of these cases will be discussed in the report from the War Demonstration Hospital. The diagnosis of empyema was made early in all cases, and the surgeon was at once called in consultation. In most of the cases operation was performed within a short time after the discovery of the purulent exudate, but in some of the cases, repeated aspiration was performed before operation. The number of such cases, however, is not sufficient for us to draw any conclusions as to the relative value of the two methods. The mortality in the cases of empyema due to streptococcus was high, but not so high as that observed in many of the camps. During the period when the largest number of these cases occurred, the Director was away, and no special study directed toward demonstrating the advantage of delay in operation was made.

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Studies by Dr. Dochez and Dr. Avery Concerning Streptococcus

Haemolyticus.

The problem assigned to us was the biology of this organism, having particularly in view the character of its immune reactions. Much work has previously been devoted to this problem, but there are still a number of questions to be answered. A most important question is whether there exists unity or diversity among the strains of Streptococcus haemolyticus known to be pathogenic for human beings. An attempt to answer this question has been made by making use of the methods previously employed in the study of the biology of pneumococcus.

A large number of strains of *S. haemolyticus* were obtained from pathological lesions in human beings, the majority of strains being from patients suffering from broncho-pneumonia, and a lesser number from infectious processes in other parts of the body. The organisms were studied with regard to the following points: The general biological reactions which would justify their being classed as *S. haemolyticus*; their virulence for the ordinary laboratory animals; the production of active immunity in animals to these organisms; the production of protective immune sera; the determination of the identity or diversity of different strains by the protective reaction in animals; the relationship of the agglutination reaction to the protective reaction.

I. Cultural and fermentative reactions.

The cultural and fermentative reactions of all the strains studied were such as to justify their being included within the group *S. haemolyticus* or *S. pyogenes*, whichever nomenclature is preferred. All the organisms were round, gram positive chain cocci with the characteristic cultural characters of *S. haemolyticus*. All were bile insoluble, and all hemolyzed

red blood cells both when grown as superficial colonies on blood agar plates and when a twenty-four hour broth culture was added to a five per cent suspension of red cells. The sugar fermentations of all the strains were also tested and in general they corresponded to those already described for *S. haemolyticus*. Most strains fermented lactose and 20 per cent of the strains fermented mannit. The capacity to ferment these latter sugars, however, did not seem to be related to any other fundamental biological differences and could not serve as a basis of final classification.

II. Virulence for laboratory animals.

The virulence of most of the strains for white mice, rats, rabbits and guinea pigs was found to be low, using pneumococcus as a standard of comparison. The virulence could not be raised to a high point for either rabbits or guinea pigs. The organisms were somewhat more virulent for rabbits than for guinea pigs. The virulence could be raised to a higher point for white rats. By repeated passages through a series of white rats, it was possible to raise the virulence of a number of the strains to a very high point for white mice, so that in a considerable number of instances a dose of 0.00000001 cc. of an 18 hour broth culture was sufficient to kill the animals in twenty-four hours. This high degree of virulence is necessary in order to titer satisfactorily the protective value of immune sera in experiments to test cross immunity between different strains.

III. Active immunisation.

In the experiments to test active immunity, three types of animal were used, white mice, white rats and rabbits. The experiments with mice and rats were unsatisfactory, no active immunity being observed after repeated inoculation of killed organisms. In rabbits, however, sufficient immunity was obtained after three inoculations of killed organisms to enable the animals to withstand ten times a certain lethal dose of living virulent streptococci.

IV. The development of protective immune sera.

In the effort to produce an immune serum which would afford passive protection to animals against *S. haemolyticus*, rabbits, sheep, dogs and one horse were used for purposes of immunization. All of these animals, with the exception of the horse, gave good protective sera. The animals were immunized by injecting first heat-killed and then living cultures intravenously. The intravenous administration of living cultures had to be abandoned because of the localization of the living organisms in joints and other parts of the body. The subcutaneous route was then substituted for the intravenous. The immune sera were considered sufficiently potent for use when 0.5 cc. given intraperitoneally in white mice afforded protection against 0.001 cc. of a broth culture that killed the animals in doses of from 0.000001 cc. to 0.00000001 cc. in twenty-four hours. For the successful performance of the test, the serum must be given intraperitoneally at least eight hours before the administration of the infecting dose of streptococcus.

V. Diversity of strains of *Streptococcus haemolyticus*.

Use of the above sera has demonstrated that strains of *S. haemolyticus* are diverse in their immunologic reactions and do not constitute a unit group. Furthermore close immunologic relationship can be demonstrated between certain strains and the evidence obtained up to the present points to the existence of types of haemolytic streptococci just as there are types of pneumococci and meningococci. At least four such types have been identified so far. In general there seems to be a separation between what may be classed as the respiratory strains and the septicæmic strains, including in the latter group strains from septicæmia, cellulitis, erysipelas, puerperal sepsis, etc. Where the point of contact is between these two groups has not yet been determined.

VI. Agglutination reactions.

Great difficulty was experienced at first in the obtaining of satisfactory agglutination reactions. With the very highly active immune serum which we now possess more satisfactory agglutination reactions are being obtained, especially when the reaction is carried out at 55° C., and when the dilutions are made in broth rather than in salt solution. As far as the work has progressed, the agglutination reactions correspond with the protective reactions.

Prophylactic Vaccination.

A few experiments have been carried out with a view of studying methods of prophylactic vaccination. It was found that mixtures of gelatin and agar can be prepared which melt at 40° C. These have been used as a vehicle for the suspension of bacterial vaccines. Such vaccines when injected subcutaneously in animals give a good immunity and also produce a mild local reaction. This method will have to be tried out in human beings in order to judge its general usefulness.

Differentiation of Streptococci from Human and Bovine Sources.

With the assistance of Dr. Cullen, Dr. Avery has investigated the limiting hydrogen ion concentration in cultures of Streptococcus haemolyticus isolated from human and bovine sources. Many investigators, especially Clark and Lubs, have shown clearly and conclusively that the final hydrogen ion concentration of a culture is a definite biological constant, but that the titratable acidity is variable, depending on the buffer action of the salts and protein, as well as on the acid produced. This fact, not yet universally accepted by bacteriologists, has been strikingly demonstrated by Ayers, who finds that certain cultures may actually show "negative acid" upon titration, although the hydrogen ion concentration has increased.

Approximately 125 strains of S. haemolyticus from human sources have been studied and compared with about 50 strains of this organism of bovine origin isolated from mastitis in cows, from milk and from cheese. The latter were authentic strains, some of which were obtained from the Department of Animal Pathology and others isolated directly by us. The hydrogen ion concentrations were all made by the colorimetric method. A definite and distinct difference has been found between the bovine and human types of this organism in the final hydrogen ion concentration of cultures grown in dextrose broth. Using methyl red as an indicator, cultures of bovine origin isolated from milk, mastitis and cheese have consistently shown a pH of 4.5, while those of human source have a pH of 5.1. Cultures with the more acid reaction exhibit a definite claret-red color, while those with a reaction of 5.0 to 5.2 show only a faint salmon tint. Using this colorimetric method, 90 to 95 per cent of all known strains have reacted true to type - the others forming an intermediary group in which the "methyl red reaction" fails in absolute classification.

By the use of medicinal methylene blue, a further differentiation has been found between the human and bovine strains on the one hand and

cultures of haemolytic streptococci isolated from cheese, on the other. The former, the more pathogenic group of human and bovine types, fail to grow on agar plates containing a dilution of dye 1:20,000, while the latter, the more vegetative cheese varieties, grow luxuriantly. Haemolytic streptococci, with the exception of these last named organisms, are extremely sensitive to methylene blue, even in dilutions as high as 1:500,000.

The possible chemotherapeutic significance of this observation has been considered, but further study is required before any conclusions may be drawn.

Persistence in the Human Throat of Haemolytic Streptococci
derived from Milk and Cheese.

Certain investigators have raised the question as to whether the streptococci responsible for acute respiratory disease in man may not be acquired by eating cheese and drinking milk. The studies of Drs. Dochez and Avery, and others have demonstrated conclusively that the streptococci found in pneumonia in man are not identical with the haemolytic streptococci commonly found in milk and cheese.

The epidemiological conclusions concerning this form of pneumonia, however, have been based largely on culture made from the pharynxes of healthy human beings as well as from the throat of patients suffering from the disease itself.

The question has arisen whether these conclusions may not be vitiated by the persistence in the throat, for a limited time at least, of haemolytic streptococci which were present in cheese or milk which had been ingested.

To test this question Dr. Ernest Stillman has made cultures from the throats of individuals a short time following the ingestion of milk and cheese known to contain haemolytic streptococci of the bovine type. Cultures from the same throats, made before taking the milk or cheese, had been shown to be free from haemolytic streptococci. The experiments made with milk, which have been frequently repeated, have shown that within an hour following the ingestion of the milk, even though the latter contained large numbers of streptococci, no haemolytic streptococcus colonies can be demonstrated on the surface of the plates inoculated by swabs in the ordinary way. The reason for this is probably two fold. First, by natural processes the pharynx is probably very quickly rendered clean of any milk particles, and second, the haemolytic streptococci in milk have

a relatively slight power to produce haemolysis when only isolated colonies occur on the surface of blood agar. It is not likely, therefore, that errors may arise from the presence of milk streptococci in the human throat.

As regards the cheese streptococci, however, there is a greater possibility that they may give rise to error in epidemiological studies. The greatest length of time that these streptococci may be found following the ingestion of cheese has not yet been determined, but certainly for several hours. In the first place these organisms are more actively haemolytic, when grown on the surface of blood agar, than are milk strains; and secondly, the throat probably rids itself of the particles of cheese with less readiness than it does of the milk. The possibility of error due to this cause should, therefore, be kept in mind in studying carriers, but it is not likely that any considerable confusion has arisen from this source in the past.

Antipneumococcus Vaccination.

In the annual report one year ago, attention was called to the possibility of employing prophylactic vaccination in the prevention of pneumonia in the Army, and it was stated that studies concerning this method were being made by Dr. Chickering. The results of these studies, as well as numerous studies made by Dr. Cole in the production of immunity in animals, as well as the studies carried out by Dr. Lister in South Africa indicated strongly that prophylactic vaccination in man against pneumococci of Types I, II, and III would be very likely to yield favorable results. This matter was brought to the attention of Colonel Russell of the Surgeon General's Office, and Captain Austin was ordered to the Hospital to carry on investigations concerning the technique of manufacture of vaccine. Miss Pauli was employed by the Institute to assist in this work. By the use of a special form of centrifuge, it was found possible to prepare large

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amounts of vaccine without difficulty, and tests were made on various members of the Staff to determine the most suitable dosage, etc. With the cooperation of Major Cecil of Camp Upton, a large number of soldiers at that camp (about 12,000) were then given prophylactic injections. The men remained in the camp only for two to three months following the injections and were then transferred overseas. During this period, however, not a case of pneumonia due to the types of pneumococci used for the inoculation occurred among the inoculated men, while a considerable number of such cases occurred among the men not inoculated. Attempts were made to obtain records of the occurrence of pneumonia in these men following their transfer to France, and a grant of money was generously made by the Directors for this purpose, but for military reasons it has been impossible to carry out this intention. The results, however, have been felt to be sufficiently promising to justify the employment of this method on a larger scale.

The work has been taken over by the Army, and the vaccine is being prepared on a large scale at the Army Medical School. By making an emulsion of the bacteria in oil instead of in salt solution, it is believed that one inoculation will suffice, instead of using three injections as was formerly done. Large numbers of soldiers are now being inoculated by Drs. Cecil and Vaughan at Camp Jackson, and by Dr. Austin at Camp Dix.

Rapid Method of Etiologic Diagnosis in Cases of

Pneumonia due to Pneumococci.

During the year Dr. Avery has developed a method whereby the types of pneumococci present in sputum can be determined within five hours in many cases without employing mice for this purpose. By inoculating the sputum in one per cent glucose broth containing five per cent of blood, a rapid growth of pneumococci occurs, while other organisms present

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do not multiply to any great extent. After the blood cells and bacteria are removed by centrifugalization, the type of pneumococcus which has grown may be determined by the demonstration of the specific precipitins in the supernatant fluid. This method, while not applicable in all cases, has proved of great value in the camps, especially when mice were not available.

Use of Masks in Preventing Infection in

Respiratory Diseases.

During the past winter gauze masks have been employed in a number of camps for the purpose of preventing the transference of the bacteria causing pneumonia from the persons suffering from the disease to healthy persons. The use of masks is based on the well-known experiments of Pflügge concerning droplet infection. No careful experiments, however, have yet been made to determine the efficiency of the masks employed in this country. Consequently, it was thought advisable to have Capt. Doust and Lieut. Lyon, Army Officers sent here for instruction, investigate this subject. They have repeated the experiments concerning droplet infection, employing masks prepared in different ways, and have devised a mask which has been shown by experiment to be efficient. They have also shown that many of the masks now being employed are of little or no value. The results of this study will be published immediately and will undoubtedly be of much practical value.

Chemical Studies.

During the year Dr. Goto, a volunteer assistant, has, under Dr. Van Slyke's direction, carried on a study concerning the location of the reserves of mineral alkali which are drawn upon in acidosis. He has also made an interesting study of renal diabetes, and has also devised a method for determining carbonate in mineral analyses.

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Dr. Dernby of Sweden, a voluntary assistant, has studied with Dr. Avery the effect of the reaction of culture media on the growth of pneumococci. Under Dr. Van Slyke's direction he has also studied the autolytic enzymes of the tissues.

Diabetes.

Dr. Allen has completed his studies in the Hospital concerning diabetes, and the clinical report of his work is now in process of publication by the Institute as a Monograph. Dr. Allen has entered the medical service of the Army and has been assigned to the hospital at Lakewood to undertake the care of soldiers suffering from diabetes.

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Clinical Studies Concerning the Use of A 189 in the Treatment
of Syphilis.

In the fall of 1917, plans were made to test clinically in the hospital the arsenical preparation, A 189, which, out of a considerable number synthesized by Dr. Jacobs and tested on animals by Drs. Brown and Pearce, had been selected as the most promising for the cure of human syphilis. After several conferences between members of the staff of the hospital and the laboratories, it was agreed that the hospital undertake the problem of working out the clinical application of the drug. The responsibility and expense of this work was to be borne by the hospital, with the exception of the preparation and standardization of the drug.

Original Plan of Investigation.

The original plan of investigation was to take patients with active, primary and secondary lesions, as well as positive Wassermanns, in order that the effect of the drug on both the lesion and the blood reaction might be ascertained. The patients were to be chosen from those who had had no previous treatment. As the drug, if successful, promised to have great military importance, arrangements were made with the officials at the Port of Embarkation, whereby soldiers suffering from syphilis were transferred to this hospital as patients, where Dr. Stillman, and later Dr. Stadie, accepted commissions in the Medical Department of the Army. The work was begun in January 1918 by Drs. Stillman, Van Slyke and Cohn. It was planned that Dr. Stillman should study the therapeutic effect on the Wassermann reaction and the effect of the drug on active manifestation; that Dr. Van Slyke should study the mode in which the drug was excreted and retained; and that Dr. Cohn should control the electrographic behavior of the heart during and after administration.

On the first of March, Dr. W. C. Stadie from the Presbyterian Hospital was added to the staff, and has divided the clinical work with Dr. Stillman and cooperated with Dr. Van Slyke on the problem of arsenic excretion

and distribution in the tissues.

During the present month, Colonel Russell has detailed to us two additional men, Dr. Fortune, formerly of the Presbyterian Hospital, and Dr. Klauder, who had been for a considerable time treating syphilitic patients at Camp Upton. Occasionally Dr. Fordyce has examined the patients and has assisted with advice. Drs. Brown and Pearce have been regularly consulted in connection with the plans made for administration of the drug. Suggestions which they have made, based on their animal experiments, have been utilized.

The following points have been investigated. They have not been taken up chronologically in the order in which they are given here, as several points were, during most of the time, simultaneously under investigation.

1. At what dosage must the drug be given to produce therapeutic results?

It was found that the injection of dosage of 7 mg. of drug per kilo body weight once a week resulted in the disappearance of the external lesions within an average period of 9 days, and a negative Wassermann on an average number of 47 days. Some patients cleared up much more rapidly than others, while some required extensive treatment. In no case, except those in which treatment was stopped for reasons other than failure to tolerate the drug, did we fail to finally obtain a negative Wassermann reaction. As the soldiers who were patients could not be kept from their military duties for an indefinite period, the negative Wassermann reaction, when obtained consistently and rapidly, was taken as indicating the end of the treatment.

We have not, therefore, as yet, and in the immediate future may not have, data as to the frequency of recurrence, although it is hoped that the follow-up histories may be obtained on at least part of our discharged patients. They have all been instructed to return to us on their return to New

York. It is probable that a considerable number of navy men may be thus kept under observation.

2. For the given rate of administration, the question was raised as to whether a cure could be effected more quickly when the drug was dissolved in 2 1/4 molecules than when it was dissolved in 1 molecule. The animal experiments of Drs. Brown and Pearce had indicated that only 1/2 to 1/3 as much drug was required for a cure when a larger amount of alkali was used. Our results have shown no differences whatever in the therapeutic effect, whether the drug was dissolved in 2 1/4 or 1 molecule of alkali.

Of sixteen cases treated with 1 molecule of alkali, the average time required for negative Wassermann was 42 days. Of nineteen cases treated with 2 1/4 molecules, the average time was 47 days.

3. The question was also raised as to whether the administration of the drug with excessive alkali, namely 2 1/4 molecules, diminishes the toxic effect in man. The following toxic effects were noted for a record when they occurred in the cases under each mode of treatment: Thrombosis, abdominal pain, fever, chill, headache, nausea, vomiting, appearance of albumin or casts. Of these there was no marked differences in the two series except in thrombosis.

The caustic effect of alkali, when 2 1/4 molecules were used, resulted in thrombosis after 21 per cent of the injections, while, when only 1 molecule of alkali was used, thrombosis occurred following only 1.5 per cent of the injections. The other effects may be noted by reference to the table below.

Table I.

Relative therapeutic effects of A 189 dissolved in 1 and in 2 1/4 molecules of NaOH.

	<u>1 mol.</u>	<u>2 1/4 mols.</u>
No. cases treated with open lesions.	21.	25.
Average no. days until lesions healed.	7.8	10.9
No. cases treated with positive W. R.	16	19
Average no. days until W. R. became negative	42	47

Table II.

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Relative toxic effects of A 189 dissolved in 1 and 2 1/4 molecules of NaOH.

	1 mol.	2 1/4 mols.
Total no. cases treated. (1)	34	37
Percentage of cases showing abdominal pain at some stage of treatment.	41 ⁽²⁾	16
Total no. of injections.	197	217
Percentage of injections followed by thrombosis.	1.5	21.0
" " " " " fever.	14.	24.
" " " " " chill.	2.9	17.5
" " " " " headache.	9.2	12.4
" " " " " nausea.	5.8	11.5
" " " " " vomiting.	4.8	6.0
" " " " " albumin or casts.	12.1	25.8

(1) Only 71 of our cases have been treated throughout purely with either 1 or 2 1/4 molecules of alkali. Of the remainder many have been started with 2 1/4 molecules, and during the treatment changed to 1 molecule, because their veins were sensitive to alkali and thrombosis regularly followed the injections. Such cases are not included in the table. If they were, the percentage of thrombosis recorded against the 2/1/4 molecule treatment in Table II would be increased.

(2) The cause of this high percentage of pains is that 21 of the 34 cases on 1 molecule NaOH received the drug at the rate of 10 mg. per kilo every 5 days. None of the 2 1/4 molecule cases received it as rapidly. Among cases receiving the drug at the same rate the percentage of abdominal pains is about the same, whether it is given in 1 or 2 1/4 molecules of NaOH. With the dosage chosen as the optimum, 7 mg. per kilo every 7 days the pains seldom occur with either 1 or 2 1/4 molecules NaOH.

Among these effects the abdominal pain is especially important. It apparently occurs from administering the drug in doses of 10 mg. per kilo too closely together. When the dose mentioned previously of 7 mg. of drug per kilo body weight once per week is given, abdominal cramps are seldom obtained. When the dosage was increased to 10 mg. per kilo body weight every five days, cramps resulted in more than one half of the cases. They were extremely painful, cyclic, and might occur within a few hours or several days after the last injection. In no case, however, did examination of the urine indicate kidney injury, nor could any effect on the heart action be detected by the electrocardiogram even during the attack. All patients having cramps recovered. In no case was there evidence of permanent injury.

4. Maximum rapidity in which the drug can be administered with safety. This point has been considered in paragraphs 1 and 3.

5. Effect on kidney function. Routine examinations of the urine have been carried on twice a week on every patient under observation, and in most cases the kidney function has been also examined once a week by the phenol-sulphonphthalein excretion method and by biweekly determination of the blood urea. Occasionally slight albumin and casts have been encountered, but only in one case was real kidney injury determinable. This patient had received about 7 grams of the drug, and after the last dose suddenly developed anuria. He was treated by Dr. Stadie in the manner utilized for handling patients with bichloride poisoning and recovered completely.

6. Effect of the drug on heart action. Electrocardiograms were taken of the patients during the injection of the drug, and at whatever other times promised to be of interest, especially during and after abdominal pains referred to above. The drug had no effect on the electrocardiogram, but an interesting abnormality was noted in a considerable percentage of the syphilitics who came to us for treatment.

Out of 85 cases observed, 35 showed a split T-wave in the third lead. This phenomenon indicates some aortic involvement. So far as is known, this phenomenon has never before been observed. It was noted that this notch disappeared after the Wassermann became negative. The exact cause of this change is not at present clear, but we hope to continue the study of this phenomenon. It may be of interest to know here that this notching of the T-wave was observed in a convalescing pneumonia patient who, upon examination, showed a four plus Wassermann. Another case was sent in by a doctor from Montclair who found this notch and was unable to explain it. Subsequent examination of the blood showed a four plus Wassermann.

7. Rate of elimination of arsenic administered as A 189. A practical method for the determination of arsenic in the urine and feces was worked out. It was found that about equal amounts of arsenic are eliminated by the kidney and the intestines. Elimination begins immediately after injection and on succeeding days becomes gradually slower. Within three weeks after the most rapid treatment, the elimination has practically ceased.

Similar excretion experiments were performed on rabbits, and their tissues were analyzed at varying periods after the injection of large doses of A 189. The animals also in about three weeks showed approximately complete elimination. It was especially interesting to note that when elimination in the urine stopped, no more arsenic could be found in the tissues. This indicates that the drug is not stored in the tissues, but is completely excreted, and that when it is not given too rapidly, there is probably no danger of accumulative effect.

8. The distribution of arsenic in the tissues of rabbits after the injection of A 189 was studied. It was found that the drug accumulates especially in the liver. The lungs, kidneys, intestines, and muscles contained less arsenic than the liver. The administration of the drug with

3 molecules of alkali as compared with 1 molecule had no effect on either distribution or rate of elimination of the arsenic, except when very massive doses were given. The one exception was noted when the tremendous dose, namely 150 mg. per kilo, was injected. When this dose was given with only 1 molecule of the alkali, large amounts of arsenic were found in the lungs, apparently because the drug was precipitated in the blood and stopped by the capillaries of the lungs. When 3 molecules of alkali were given, this did not occur. It occurred with one molecule only when the above massive test was given, not when doses comparable with those used therapeutically were given. Even when the doses were as high as 50 mg. per kilo or 7 times the therapeutic dose adopted for man, there was no accumulation in the lungs. In such doses the occasional alkali was without any effect on the distribution of the drug on the body.

9. The Wassermann reactions were followed at weekly intervals by at least two laboratories. At first the blood specimens were sent to the Board of Health laboratory and Dr. Jagle. Since then, however, the facilities for performing our own Wassermann reactions were developed, and the results obtained from these laboratories are compared with those of Dr. Jagle's. At present we are relying upon our own Wassermans as the technique was developed to such a point that the results became thoroughly consistent.

10. Dark-field determinations. Lesions are regularly examined for spirochetes by the dark-field. One of the problems at present under investigation concerns the length of time which elapses after the first injection before the spirochetes disappear from the external lesion.

11. Charting the results. Charts were printed in detail tab-
in
ulating concise form, both laboratory and clinical data, bringing out all the above points.

PLANS FOR THE IMMEDIATE FUTURE.

At present the following plan seems to be acceptable: A dosage of about 7 mg. A 189 per kilo body weight weekly is the optimum. It is seldom followed by abdominal pain or other serious effects, and represents a maximum rate of administration. It is possible to inject this amount with only 1 molecule of alkali since larger amounts result in increased percentage of thrombosis without apparent effect in either increasing therapeutic power or decreasing toxicity.

The following problems seem to be the next demanding solution:

1. The optimum concentration for the administration of the drug. Thus far the concentration has been varied from 1:1000 to 1:150 without apparent effect on therapeutic power or toxic action. If the drug is utilized for military purposes on a wide scale, it may be necessary under some conditions to give it a more concentrated form with a syringe if it is given at all. Consequently we are continually increasing concentration in order to diminish the volume of solution injected, in order to determine the greatest concentration which may be given with safety without effecting the therapeutic results.

2. Combination of A 189 with mercury. Since it is generally held that the best results with salvarsan are obtained when the treatment is reinforced with mercury, we are attempting to find whether the same is true with A 189. Consequently a series of cases have been started that are receiving A 189 and simultaneously bichloride and mercury intramuscularly. At present with the data which we already have on hand, the results from these cases should indicate within a few weeks whether the mercury shortens the period required to obtain a negative Wassermann.

3. Comparison with salvarsan. After the appropriate mode of administering A 189 has been ascertained, it appears desirable to compare it in the same wards with salvarsan on a sufficient number of cases to get satisfactory data on which a comparison of the peculiar merits and disadvantages of each drug might be tested.

4. The work thus far has been purposely limited for the most part to primary and secondary cases. It is now being extended to nervous, tertiary, and congenital syphilis.

5. We have been unable to find in the literature or in consulting with syphilologists any accurate data as to the status neuro-residive. It, therefore, seems advisable in our treatment of our primary and secondary cases to do lumbar puncture before, in the middle, and at the end of our treatment in each case, in order that this important question may be settled.

6. It is our purpose to continue the electro-cardiograph study mentioned above in order to clear up the cause of the anomaly noted and also to find out, if possible, whether this may be a rather important diagnostic point in early vascular syphilis.

SUMMARY OF CASES TREATED WITH A 149 JANUARY 1 - OCTOBER 1, 1918.

1.	No. of cases treated	128
2.	" " " discharged Wassermann negative	45
3.	" " " " " positive	25
4.	" " " under observation	57
5.	" " " died	<u>1</u>
		128

In the 25 cases discharged with positive Wassermann reactions, one refused sufficient treatment, twenty were discharged as unsuitable cases for observation, and four were discharged for disciplinary reasons. The one death was in a case who died within four hours of admission, before treatment. The cause of death as revealed by autopsy was due to cardio-vascular failure, resulting probably from diphtheria.