

R E P O R T

O F T H E

DIRECTOR OF THE HOSPITAL.

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T H E R O C K E F E L L E R I N S T I T U T E F O R M E D I C A L R E S E A R C H .

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To the Board of Scientific Directors
of the Rockefeller Institute.

Gentlemen:-

The Director of the Hospital has the honor to submit the following report of the work carried on in the Hospital during the past quarter year.

Since the opening of the Hospital five years ago there has been a steady increase in the number of patients requesting admission to the Hospital for treatment. This has been especially marked during the past months. A hospital several times larger could have been kept filled with patients suitable for the studies being carried on. Our experience more and more indicates, however, that our work is much more productive when the number of patients is kept low. This makes the expense of the Hospital per patient very high, but materially increases the quality of the work.

In November a clinic on pneumonia and diabetes was held at the Hospital. To this were invited physicians who have referred patients to the Hospital. The plan of sending out bulletins from time to time describing the kind of patients which are admitted has been continued. We were gratified that the last Bulletin was copied in the Journal of the American Medical Association, and also in the Bulletin of the New York Board of Health, which I understand is sent to all physicians in the city. This was done without request on our part.

It is evident that the hospital is becoming better known among the people, and the general medical profession, and also that any feeling of distrust which existed in the mind of the public is rapidly disappearing.

Under these circumstances it is possible that the question of obligatory autopsies may now be again seriously considered. When the Hospital opened I considered this inadvisable, but it is now probable that we could ask every patient on admission to the Hospital to sign a permit for an autopsy in case of death. The opinion of the members of the Board on this subject would be welcome.

Cancer: The study of the effect of X-ray on patients with cancer.

It was hoped that the admission of cancer patients might be undertaken

in January first, but delay in obtaining a satisfactory man to care for these patients has rendered this impossible. Several men are now under consideration, and it is hoped to begin admitting these patients very soon.

ACUTE LOBAR PNEUMONIA: During the past quarter the work on pneumonia has proceeded largely along the lines indicated in our previous report.

The number of cases for study has been most satisfactory. From October first to January first 41 cases of pneumonia were admitted. This is to be compared with 25 cases admitted during a similar period last year. Unfortunately for the progress of our main study only seven of the patients have been of Type I. All of these have been treated with serum. One of those cases died, but this was a case admitted only on the 5th day, and treatment could be very inefficiently carried out. Death occurred on the 6th day. A striking fact has been that 8 of the cases have been due to pneumococci of Type III, pneumococcus mucosus, a much larger proportion of cases due to this type than we have previously seen. 13 cases were due to Type II and 11 cases were due to Type IV pneumococcus. The fact that so many of the cases were due to pneumococci of Types II and III explains our high mortality this year, and suggested that the great severity of the pneumonia now occurring in the city at large may be due to the increased frequency of cases due to this type of pneumococci. One of our cases was due to a gram negative bacillus. This organism resembled somewhat Friedlander's bacillus but had no capsules and did not grow in a typical manner on agar. We have previously had other cases due to a similar organism and it seems that this bacterium is a etiologic agent in pneumonia not previously described.

The studies concerning the epidemiology of pneumonia have been continued by Dr Ernest Stillman. He is studying the flora of the mouth in a series of persons without pneumonia, using the persons coming to the dispensary for this purpose, and is also studying the mouth flora of the members of the families of patients, and also of the nurses caring for pneumonia patients. It is planned to continue this study

During the year. The results so far confirm those previously obtained. In the mouths of normal persons the pneumococci present are of Type IV, except in certain instances among the persons closely associated with pneumonia patients, in which case pneumococci of mixed types may be present. In three instances (normal persons) without history of contact, pneumococcus mucosus has been isolated. Dr Avery has now collected about 50 strains of this type of pneumococcus, including those from patients with pneumonia, as well as those from normal mouths, and he is making a thorough study to determine, if possible, whether any constant differences (cultural or immunological) exist between the strains found in disease and those present in health. It is too soon to report on the results obtained.

Dr Dochez is continuing his study of anti-blastic immunity. At present he is attempting to isolate the substances in the serum which are responsible for the inhibition of the bacterial proteolytic and glycolytic action.

Dr Chickering returned on December first from California where he had been working with Dr Gay on the treatment of typhoid fever by intravenous injections of sensitized typhoid vaccines. The work was aided by a grant from this Institute made last autumn. The therapeutic results are interesting and suggestive. One observation made by Dr Chickering seems to be of considerable value, that is that the number of typhoid bacilli in the blood during the course of the disease is of considerable prognostic importance. Apparently the injection of the vaccine is followed by a decrease in the number of bacilli in the blood or they entirely disappear. The work has also confirmed the observation of Gay that such injections are followed by a wave of leucocytosis. The injection of vaccines is usually followed by a severe general reaction and certain of their observations suggest that such reactions may in some secure way be of protective value, even when they are non-specific in character.

The subject is worthy of further study. For the present, Dr Chickering is busily engaged in preparing a supply of bacterial precipitates, as studied last year by Gay and Chickering as it is planned to treat a series of cases due to pneumococcus of Type II with this preparation.

Dr Chesney has almost completed a study of the rate of growth of pneumococci, especially of the phenomenon which has been described as bacterial "lag". In broth cultures there usually first occurs a period in which multiplication is very slow. For a time no multiplication whatever may occur, indeed, as Gillespie has shown when the number inoculated is small there may be no growth at all. Following this latent period a period of maximum rate of multiplication occurs and then again a period of decline. Chesney has shown that the occurrence or degree of latent period, or lag, depends upon the stage of growth of the culture from which the subculture is made. If the former be in the stage of maximum or logarithmic growth, the subculture may show no lag whatever, whereas if the culture be in the early or late stage the lag may be marked. The curves of the first few hours of growth of the sub-culture parallel almost exactly those of the original culture during the same period. If during the period of maximal rate of growth, the culture be placed in the ice box and kept at 0°C, the culture ceases to grow, but on removal from the ice box it will again grow at maximum rate (without lag), even if kept on ice for as long as three days, and subcultures from this same culture kept on ice will also grow at maximum rate, without lag.

Pneumococci of Type IV, when freshly isolated from the human body, show a very marked lag, much greater than pneumococci of Type I or Type II freshly isolated from the human body. The minimum generation time of pneumococci (Types I and II) has been found to be from 25 to 30 minutes.

The idea is entertained that lag is an expression of injury, which view is supported by the experiments so far performed. Attempts have been made to deter-

mine whether cultures showing marked lag are less virulent for mice than those not showing lag, but it has not been possible to secure clean-cut results, as yet.

With Mr Cullen, Dr Chesney has followed the change in H-ion concentration which occur in a culture of pneumococcus during its growth and the experiments done thus far show a striking parallelism between the growth curve and the H-ion concentration curve up to the point where growth ceases. After this point is reached, the H-ion concentration remains constant for days, although the pneumococci decrease in number and autolysis occurs as is evidenced by a partial clearing of the culture. Cultures of both Type I and Type II pneumococci attain the same H-ion concentration, and growth in each case ceases at this particular level of H-ion concentration. It is interesting that at the time at which this level is reached, the culture of pneumococcus Type I shows twice as many organisms per unit volume as does the culture of Type II. This would indicate that the metabolic activity as measured by H-ion concentration, is greater in the case of Pneumococcus Type II than in the case of Pneumococcus Type I.

Dr Moore has been given charge of the preparation of immune serum and is also continuing his study of the action of ethylhydrocuprein. Attempts are being made to produce rapid and effective immunity in horses by the daily injection of small doses of cultures, as was shown last year could be done in rabbits. The preparation of the immune serum for experimental and therapeutic purposes has now grown to be a considerable undertaking. A very large number of clinics, boards of health etc. are now determining types of pneumococci by the methods devised here and almost daily requests are received for serum for such diagnostic and experimental purposes. We are also supplying serum for a few clinics for therapeutic uses. It is impossible at present, however, to do this except in a very limited way. Serum of Type I and Type II is now being prepared, however, by the New York City Board of Health, the New York State Board of Health and the Pennsylvania State

Board of Health so that it is hoped that we shall be relieved of the need of continuing or extending this work. The New York State Board of Health is making preparations to determine the type of infecting agent for physicians in the larger cities of the state. In this way will undoubtedly be obtained observations and statistics of great epidemiological significance.

At present a series of cases due to Pneumococcus of Type II and Type III are being treated by optochin(ethylhydrocuprein). Last spring Dr Moore made a study of the bactericidal effect of the blood serum of rabbits following the administration of optochin. Curves made by plotting the bactericidal power at intervals following the administration of the drug were made. Similar studies were also made on a few normal persons. This study permitted the development of a technique which may now be employed in the study of patients. The number of patients treated is still too few for any conclusion to be drawn as to the therapeutic effect of the drug, but so far the results are promising. In any case, the effect of the drug in increasing the bactericidal power of the serum can be readily demonstrated and repeated doses have a cumulative effect. We have already had a distressing example of the toxic effect of the drug, however. One patient 16 years old, received four doses of the drug 0.5gm. each, over a period of 36 hours. Following this she became completely blind, and the total loss of vision lasted six days. She then became able to distinguish light from darkness and there has followed a gradual improvement. It is at present impossible to say whether or not complete recovery will occur. This seems to be one of the most severe cases of amblyopia which has occurred following the use of this drug. Some cases are now being treated giving very small doses of the drug every two hours, but administering a total amount of 1.5 gm in 24 hours, as it is not likely that any smaller doses can be of any value. It is planned later, in a series of cases to combine the drug with immune serum.

Last year Lister in South Africa published a short paper setting forth that when pneumococci are grown in immune serum they become more susceptible to the action of normal serum as shown by the power of normal serum to cause agglutination and also opsonization. This phenomenon he called piantiication (to fatten for slaughter). He showed also that such organisms become less susceptible to the action of the immune serum. A series of studies have therefore been made by Miss Stricker to investigate this phenomenon, studying pneumococci of various types. It has been found true that when pneumococcus of Type I for instance is grown repeatedly in serum of Type I it may become to a slight extent spontaneously agglutinable with normal serum, but more striking and of greater significance is the fact that it becomes much less agglutinable with the homologous serum, and also now becomes readily agglutinable with serum of Type II. With this change in agglutinability the pneumococci lose their virulence. If such pneumococci were now observed for the first time it would be difficult to at once determine the type. Passage through animals, however, readily brings back their virulence and also makes evident the specific agglutinability, which is always of the same character as that originally present. The change in the organism occurs after five to six passages through broth containing one tenth part of immune serum. Organisms have now been passed through as many as 95 transfers in serum broth over a period of one year. The changed character of the organism may persist for as many as 50 transfers on broth, though, as previously stated, it quickly reverts on animal passage. The interpretation of this phenomenon is at present difficult, and studies are being made by immunization of animals against these changed types etc., in the endeavour to find underlying factors. At the present time the significance in relation to the question of epidemiology and origin of types does not seem to be great. In any case it is entirely different from the so-called transformation of organisms as described by Rosenow.

Diabetes: Only children and adults suffering from the most severe type of this disease are being admitted for study. These cases are under the immediate care of Dr Stillman. Dr Allen's study of this disease has made two radical innovations in the treatment, first, the valuable effect of prolonged fasting has been demonstrated, and second, the important rôle which exercise plays in the treatment has been shown. Moreover, it has become evident that the treatment of the patients after they have become aglycosuric consist in education - teaching them how to live with their restricted functions. This cannot be done by general instructions, but each patient (or if a child, the parent) must take a course of instruction in the diet kitchen, and he must learn to examine his own urine accurately for sugar and diacetic acid.

For the accurate clinical study of diabetes and the proper treatment of the patients it has been necessary to develop a quite elaborate organization of the diet kitchen and clinical laboratory. This has been accomplished largely by the efforts of Dr Stillman and I think it is no more than true and proper to say that this has become a model that is being imitated throughout the country. The methods employed are constantly being demonstrated to very large numbers of visiting physicians. Dr Stillman is getting ready for publication in a monograph a complete description of the methods employed, with full reports of the cases treated for illustration.

At the present time, Dr Allen is giving his time largely to the preparation of his experimental material for publication. With the aid of Miss Wishart he is continuing and finishing some necessarily long and tedious experiments.

Dr Fitz has made some studies on the question of renal function in patients with diabetes, especially with reference to the disturbed salt metabolism frequently present. He is now, under Dr Van Slyke's direction, working on methods for the determination of the abnormal organic acids in the blood and urine for the purpose of determining if possible the laws governing their excretion.

Dr Palmer has carried on a series of studies concerning the concentration of sugar in the tissues. Although much work on the fate of glucose in the animal organism has been reported, little attention has been given to the concentration of this substance in the tissues. The purpose of this investigation is to determine the amount of glucose in the tissues under varying conditions (normal and diabetic animals, hyperglycaemia artificially produced) with the view of throwing further light on the utilization of sugar in normal and abnormal carbohydrate metabolism. It was necessary to develop a suitable method of investigation, which has been accomplished. (Up to the present 26 dogs, 18 of which were normal and 8 in various stages of diabetes, as well as 16 rabbits and 1 monkey have been used). In several instances the concentration of glucose in 20 different tissues has been determined. The results thus far are as follows. The concentration of sugar in the various tissues, though considerably lower, varies directly with the concentration in the blood. There seems to be little difference in this respect between normal and diabetic animals.

Acidosis - Dr. Van Slyke, Mr. Cullen and Dr. Stillman have carried on an extensive study concerning acidosis in diabetes. As mentioned in a previous report, Dr. Van Slyke has devised an accurate but simple method for the study of CO₂ capacity of the blood, which seems to be the best clinical method available. The use of some such method is of great importance where the method of prolonged fasting is being employed. This and other methods for determining acidosis have been used in the study made here. From this study Dr. Stillman has been able to separate the cases of diabetes into four types as regards acidosis.

1. Cases with only slight tendency to form abnormal acids, either on fasting or on a diet. Little or no excretion of acetone bodies. No tendency for plasma bicarbonate to fall. Cases of this type are usually mild.

(2) Cases with a tendency to acute acidosis on fasting. Patients may begin the treatment in apparently fairly good condition, but the plasma bicarbonate falls rapidly when the fast is instituted, and may result fatally if acidosis is not detected and checked (by feeding) in time. Since the present method of plasma bicarbonate determination has been employed for detecting acidosis, patients of this type have without exception been detected and successfully treated. A peculiarity of such cases is that at the second or third attempt to make the urine sugar-free by fasting no acidosis may occur.

(3) Cases showing acute acidosis, curable by fasting. This type shows a behaviour exactly opposite to that of type 2. A patient entering the hospital in a condition of serious acidosis, with plasma bicarbonate at half the normal level and with physical and mental symptoms of impending coma, may as the result of fasting and moderate carbonate dosage, or even without carbonate, clear up so rapidly that in two or three days' time both the blood tests and the clinical signs are normal. Such patients put on a rational diet then tend to remain free of acidosis.

(4) Cases showing chronic acidosis. These patients even after long treatments show subnormal plasma bicarbonate and hypernormal ammonia excretion. They form acids in abnormal amounts and eliminate them less efficiently than do normal individuals. These cases are in an unstable condition, and are the most difficult of all to treat satisfactorily. Eventually, however, some of them appear to graduate into the milder type described under (1).

Nephritis. Dr McLean is continuing the clinical study of nephritis, employing the numerical laws governing the excretion of urea and sodium chloride. In the individual case one of the excretory functions is frequently affected while the others remain normal. Urea excretion function apparently depends on kidney factors alone, but conditions regulating salt excretion function are more complex and apparently are largely extra-renal. The cases of nephritis so far studied have been mainly cases

with advanced functional change, especially those liable to uremia, and also cases with edema. In addition, cases of primary hypertension without apparent kidney functional changes are being studied.

Studies are also being made of the effect of differences in nitrogen intake (very large amounts, as well as very small amounts) on the index of excretion. Such changes in intake apparently cause no change whatever on the index of urea excretion.

Heart disease: Dr Cohn and Dr Jamieson.

By preference patients suffering from auricular fibrillation and oedema are being admitted. In these patients the effect of digitalis on heart-rate, kidney function, blood pressure, fever (when this is present) and on the electrocardiogram is being studied. Blood pressure in patients with fibrillation is being studied by recording the percentage of total beats that reach the wrist with different levels of external pressure. From these records curves are being made which are believed to give a more satisfactory account of the effect of digitalis on blood pressure than do figures composed of averages.

The time when the clinical effect of digitalis becomes evident is being compared with the time when alteration in the T wave occurs. Studies are also being made to decide whether a larger dose of digitalis given in a short time has the same effect on the electrocardiogram as a small dose given over longer periods.

The action of digitalis in 108 cases of pneumonia in respect to changes in the T wave and in conduction time has been studied. 58 cases that took no digitalis served as controls. 50 cases took digitalis. Of these only 40 were available for study, the others not having had an amount of digitalis sufficient to influence the curve. Of the 40 available cases that took digitalis, 37 were studied. Briefly stated, the observations showed that in the absence of digitalis 90.3 per cent of the cases showed no changes in the electrocardiogram while of those who took the drug, 90.3 per cent showed change of one sort or another. These figures show that digitalis

produces an effect even during the febrile period in pneumonia.

As to whether the drug is beneficial in pneumonia the observations offer no precise information. We can, however, draw some deduction from the following facts: in examining 126 cases (those (108) already mentioned, together with 18 other cases not included in them for certain reasons), 12 cases (9.5%) developed either fibrillation or flutter. 9 recovered from the irregularity; 1 left the hospital with it; 2 died while it was still present. When the irregularity began 4 cases had had digitalis; the others had had very small doses which could not be regarded as the cause of the irregularity. If the irregularity existed and lasted sufficiently long, digitalis was able to reduce the heart rate by blocking auricular impulses, just as it does under ordinary conditions. In these cases showing these irregularities therefore the beneficial action of the drug is very evident.

We are continuing the study of the action of digitalis in fever with the view of obtaining an effect more rapidly than has been possible by the use of the doses previously employed, namely 0.4 gram per day by mouth. Digitalis is now being employed in doses of 1.0 gram or more by mouth in 12 to 24 hours. Crystalline strophanthin is also being given, using very small doses, on account of the unexpected irregularity in results encountered some time ago. These studies have been begun too recently to give a report of results.

Experiments are being conducted with the purpose of studying hypertrophy of the heart and its influence on the form of the action current of the heart. The nature of hypertrophy is being analyzed by studying the weight of the layers of the heart as obtained by dissections made according to the method of MacCallum and Mall. When the layers are separated by this method they are not coextensive with single chambers. The method of study is as follows:- after X-ray plates and electrocardiograms are obtained, hypertrophy is produced in one group of dogs, which are made to work by running on a tread mill, and also in other groups in which different val-

ular lesions have been artificially produced. X-ray plates and electrocardiograms are made repeatedly during the period of observation. On the conclusion of each experiment, the heart is dissected in the way described and the layers weighed and the weights compared with controls.

Chemical Laboratory: Dr Van Slyke, with the assistance of Mr Cullen and Dr McLean has continued the work on the fate of protein digestion products in the body, in connection with Dr Meyer. The work with Dr Meyer had shown that amino acids from digested proteins enter the circulation unchanged, and from it are absorbed by the tissues, each of which possesses its own store of free amino acids. It is known that the greater part of the protein nitrogen absorbed is turned into urea and excreted within a few hours. It appeared possible, however, that urea formation might not begin until the tissues in general have taken up such an amount of the absorbed amino acids as they require, the urea-forming mechanism serving to rid the body of the excess. Consequently dogs after a forty-eight hour fast were fed with meat and the blood urea was determined several times per hour. In some experiments X-ray photographs were made in order to correlate the progress of the food through the alimentary canal with the production of urea. It was found that urea formation does not wait until an excess of amino acids above the requirements of the organism have been absorbed, but begins the moment absorption starts. Increase in blood urea occurred within much less than an hour after feeding, as soon as the X-ray showed the first passage of food into the duodenum, and as soon as any increase in the amino acid nitrogen of the blood could be detected. The urea-forming mechanism is, therefore, immediately stimulated into action by the absorption of amino acids, and does not wait until they have accumulated in excess.

One other point in protein metabolism attacked has been the question as to whether not only amino acids, but also peptones or other intermediate protein products are absorbed from the intestine into the circulation. The blood proteins were precipitated under conditions which leave intermediate products, not only peptones but

ever albumoses, in solution. The amino nitrogen was then determined in the filtrates before hydrolysis (free amino acids) and after hydrolysis (increase = intermediate products, peptones or albumoses). It was found that, although in the same experiments large increases in free amino acids of the blood occurred during digestion, no increase at all in the intermediate protein products could be measured. Consequently little or no absorption of "peptone" as such occurs. All the protein, so far as determinable by present methods, is hydrolyzed.

Miss Vinograd is engaged in a determination of the amino acids yielded by the albumin and casein from human milk. This problem is undertaken at the suggestion of Dr Holt. The observation of clinical experience is that less protein is required by infants in the form of human milk than as cows' milk. It is known, from work done last year in co-operation with Dr Osborne of New Haven, that the albumin of cows' milk is much richer in hexone bases, especially lysine, than is casein, and lysine has been found by Osborne and Mendel to be one of the amino acids absolutely essential for growth. Human milk contains much more of its protein in the form of albumin than does cows' milk and the richness of the albumin in necessary amino acids, such as lysine, may explain the high nutritive value of human milk proteins, if the albumin of human milk is similar in composition to that of cows' milk.

Dr Van Slyke has studied, with the co-operation of Dr Losee of the Lying-In Hospital the present theories concerning the nature of the toxic agent in toxemia of pregnancy. The two leading theories have been that the toxemia is caused by either (1) amino acids, which the degenerated liver fails to turn into urea, or (2) acidosis, the foetus intoxicating the mother by acids which it forms. Both theories are false. In no case of toxemia have abnormal amounts of amino acids in either urine or blood been found. Nor is acidosis generally present, except in isolated cases, and even in the latter it is not severe. Furthermore the foetal blood obtained from the umbilical cord at delivery shows bicarbonate content no lower than the maternal blood. The real toxic agent is not indicated by any chemical theory which has previously gained prominence.