

REPORT
OF THE
DIRECTOR OF THE HOSPITAL
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88

200

REPORT OF THE WORK IN

THE HOSPITAL

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Changes in the Staff.

The entrance of our country into the war has led to the departure of a number of the members of the Hospital Staff, to undertake duties in connection with the Army. Those who have been called directly to this service are Doctors Chesney, Fitz, Morton, Larson and Morison. Dr. Chesney joined the Hospital Unit of Washington University and is now with this unit in France. Previously he had accepted an appointment as Assistant Professor of Medicine in this University, his service to begin this autumn, and he has therefore permanently severed his connection with this Institute. Doctors Fitz and Morton joined the Harvard Base Hospital Unit No.5, and are also now in active service in France. Dr. Larson joined the Medical Officer's Reserve Corps and was ordered to Fort Benjamin Harrison. Dr. Morison also joined the Medical Officer's Reserve Corps and was detailed by the Surgeon General to join the staff of the Hospital for Cardiac Diseases of the British Medical Service in London.

In addition to these men, who have entered active military service, Dr. Palmer has left to assist Dr. Longcope in the teaching of medical students at the College of Physicians and Surgeons. Dr. Palmer has received an appointment as Assistant Professor of Medicine at Cornell Medical School, but will not take up his work there until after the close of the war.

During the past year, in addition to the regular staff, four voluntary workers have been engaged in the study of problems relating to the diseases under investigation. These men are Dr. Ernest Stillman,

Doctors Blake, Levine and Lundsgaard. Dr. Stillman has received an appointment on the regular staff of the Hospital for next year. Dr. Blake has been appointed Assistant Professor of Medicine at the University of Minnesota, and has already commenced his work there. Dr. Levine has entered the Medical Officers' Reserve Corps and has been detailed to the Hospital for Cardiac Diseases of the British Medical Service in London. Dr. Lundsgaard will shortly return to Denmark to again take up his studies in the University in Copenhagen.

It may be seen from the above that very serious inroads have been made into the working staff of this Hospital. This, however, was to be expected, and it is a source of satisfaction that the Hospital has been able to furnish so many men ready for active service.

Moreover, during the year, and especially during the present summer, a number of the men have been engaged in activities which are not directly related to the scientific investigations of the Hospital, but which are of aid to the Nation or to the State. Dr. Dochez was given leave of absence during the months of January, February and March to accompany Dr. Biggs to France to investigate the conditions in that country regarding tuberculosis. Dr. Chickering has spent several weeks at the Naval Hospital at Portsmouth, Va., assisting in the investigation of the outbreak of epidemic meningitis occurring there. Since the opening of the War Demonstration Hospital, Dr. Cullen has been engaged there on chemical work in connection with the Carrel-Dakin method of treatment. During the summer, Dr. Avery, Dr. Dochez and Dr. Stillman have given much time to the instruction of army medical officers concerning pneumonia, and in teaching them the actual methods to be employed in diagnosis and treatment of this disease. The Surgeon General has also requested Dr. Cohn to instruct a number of officers of the Medical Reserve Corps in the technique of examination of the

cardio-vascular system. In compliance with this request, a number of officers detailed here for this purpose are now being given a course of instruction by Dr. Cohn. Dr. Van Slyke has spent the months of July and August at the Laboratory of the Hooper Foundation at San Francisco. He has gone there at the invitation of the Director to demonstrate to the members of the staff of that institution new chemical methods which have been developed in this hospital under Dr. Van Slyke's direction. Through the kindness of the State Board of Health, Dr. Stillman had the opportunity last winter of investigating several small epidemics of pneumonia occurring throughout the State. This study gave us much information concerning the mode of spread of this disease.

Scientific Report.

Acute Lobar Pneumonia.

During the past winter, 133 cases of lobar pneumonia were treated in this hospital, making a total of 529 cases that have been studied here. Of these, 438 have been shown to be due to Pneumococcus, and the type of infecting organism has been determined. 151 of these cases were due to Pneumococcus Type I, 133 were due to Pneumococcus Type II, 59 were due to Pneumococcus Type III and 95 were due to Pneumococcus Type IV. 108 cases of Type I infection have been treated with serum, with 8 deaths. 34 cases were treated during the past winter and only 2 died; and one of these fatal cases proved to be complicated by extensive and advanced tuberculosis. The results of serum treatment in this type of case, therefore, have continued to be excellent. Similar results have been obtained elsewhere. Major Nichols has lately reported the treatment of 45 cases among the troops on the Texas border with only 5% mortality.

This work relating to pneumonia has been carried on in three directions during the past year. First, attempts have been made to render

the general routine treatment of patients with Type I infection more practical and convenient. Second, further studies have been made concerning the epidemiology of the disease, in the hope of devising measures for lowering its very high incidence. Third, studies concerning the mode of action of the etiologic agent have been continued.

The need for determining the etiologic agent in every case of pneumonia before serum treatment is undertaken prevents to some extent the general employment of this method. Where the laboratory arrangements for making such determinations can be properly organized, however, the difficulties are really not great; the method is neither complex nor difficult. It has been thought however, that an accurate standardization and description of the method would aid in its general employment, and this has been made by Dr. Blake. ("Methods for the Determination of Pneumococcus Types", Jour. Exp. Med., 1917, xxvi, 67).

Dochez and Avery have demonstrated that changes frequently occur in the blood and urine of patients with pneumonia, so that if samples of these be mixed with specific immune serum precipitation occurs. This fact may be made use of in the diagnosis of the type of infection. (Dochez and Avery; "The Elaboration of Specific Soluble Substances by Pneumococcus during Growth", Jour. Exp. Med., October, 1917.) All that is necessary is to mix small amounts of the urine and equal quantities of the various immune sera. A reaction occurring in one of these mixtures indicates that the infection is due to the same type of Pneumococcus as that employed in producing the serum with which the reaction occurs. In certain cases the diagnosis of type may be made by this method without any trouble and almost at once. The applicability of the method for diagnostic purposes, however, is limited by the fact that the reaction occurs in only about one third of the cases, in those more severely infected, and especially late in the disease. Notwithstanding this drawback, however, the method is of considerable practical value.

Efforts have also been made to determine more accurately the best method of administration of serum, the proper dosage and frequency of treatments. Studies on animals and observations made in patients during the past winter have shown that, after infection has lasted for some time, substances are found in the patient's blood which neutralize the immunity principles in the horse serum. (Cole, "The Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera", Jour. Exp. Med., October, 1917). This fact strikingly emphasizes what has previously been insisted upon; namely, that the treatment should be commenced early and large doses of serum should be employed.

Simplification and improvement in the matter of production of the serum and improvement of methods of standardization have been needed, and these problems have been studied during the past winter. The old method of immunizing horses consisted in the weekly injection of cultures of increasing size, first of dead, then of living bacteria. To produce high grades of immunity, it has been thought necessary to use very large doses. Studies made during the past year have shown that the immunization of horses can be much more rapidly accomplished by making injections of small doses every day on alternate weeks. It has been shown that large doses of culture, such as those formerly employed, may inhibit, rather than stimulate the production of immune substances (Cole and Moore, "The Production of Antipneumococcus Serum", Jour. Exp. Med., October, 1917).

Efforts have also been made to improve the methods of standardization, and especially to fix a practical standard to which all sera used for therapeutic purposes should conform. During the past winter the various antipneumococcal sera produced by manufacturers in this country were tested, and most of them were found to have little or no content in antibodies for

Type I pneumococci. We have therefore worked out a method of standardization which we believe is as satisfactory as it can be made with our present knowledge, and we have recommended that the Hygienic Laboratory of the Public Health Service require that all antipneumococcus sera sold for therapeutic purposes meet the requirements that we have laid down. Major McCoy, Director of this Laboratory, has very willingly cooperated with us in this matter, and it is believed that all the serum employed by the Army, at least, will be of satisfactory potency. The production of serum of Type I in fairly large amounts is now under way at the farm in Princeton, and the production of this serum at the Institute has been discontinued.

The studies concerning the epidemiology of pneumonia have proved of great interest and have yielded results which, it is hoped, afford a basis for instituting rational preventive measures. Up to the time these studies were undertaken, it was believed that infection in pneumonia is autogenous; that is, persons having pneumonia are infected with the organisms they habitually carry in their mouths, the reason for such infection being a lowered general or focal resistance on the part of the patient. The observations made here have brought striking evidence against this assumption, at least as far as pneumonia due to Type I and Type II pneumococci is concerned. They strongly suggest that pneumonia, at least of these two types, does not differ in this respect from other infectious diseases, and that infection in this disease also usually occurs from without. The evidence in favor of this point of view has been derived from a study of the types of pneumococci present in the mouths of normal healthy individuals who have not been in contact with cases of pneumonia, and those present in the mouths of persons living in close contact with such patients. The varieties of pneumococci found in the mouths of pneumonia patients during convalescence have also been studied, and also the types of pneumococci found in the dust of rooms occupied by

pneumonia patients, as well as those in the dust of rooms not inhabited by such persons.

Without going into the details of the study, it may be stated that pneumococci of Types I and II are practically never found in the mouths of healthy persons not in contact with pneumonia patients, although these two types of organisms cause over 60% of the cases of pneumonia. On the other hand, a considerable percentage of persons living in close contact with pneumonia patients, especially members of the family or friends who have cared for these patients, are found to carry organisms of these types, the type of organism found in the carrier being always that causing the disease of the patient. Neither the patients nor these healthy carriers, however, carry pneumococci of these types permanently. Usually these types of pneumococci disappear in three to four weeks, and either no pneumococci are then found, or if present, they are of the type commonly found in healthy mouths, Type IV. Finally, pneumococci of Types I and II are not commonly found in dust, but they may be present in the dust of rooms occupied by pneumonia patients, convalescents, or healthy carriers.

All this evidence strongly indicates that infection in pneumonia is not autogenous, but that the organisms are received by the patient either directly, by contact with another case or a convalescent or a healthy carrier, or indirectly through the dust from the environment of such a carrier. It becomes evident, then, that pneumonia, so far as these two types are concerned, does not differ essentially in its mode of spread from other infectious diseases, such as diphtheria or meningitis. The average susceptibility to pneumonia may be less than to these other infectious diseases, and the number of healthy carriers may therefore be greater, but this is not certain.

In any case, in order to reduce the very great prevalence of pneumonia, measures similar to those employed to prevent the spread of other infectious diseases should be instituted. This will be especially important in the case of troops, for pneumonia ordinarily occurs with great intensity among raw recruits, and it is to be feared that, unless preventive measure can be instituted, the history of this disease in our own National Army will be the same as that in other armies and in other wars.

Another possible method for preventing the occurrence of pneumonia is by the employment of prophylactic vaccination. This does not seem practical in civilian populations, but among troops, where the disease is likely to be widespread, this method should be considered. Considerable work has already been done in investigating whether or not this procedure would be likely to be successful and if so, in devising the best methods for carrying it out. A number of problems are still unsettled, but some of these are under investigation by Dr. Chickering at the present time, and it is planned to continue this investigation during the autumn.

Since it is very important that the present knowledge concerning serum treatment and prevention of pneumonia should be readily available, this has been collected in a pamphlet which it is hoped will be ready for distribution before this meeting of the Board. In this pamphlet is given a detailed and practical description of methods employed.

Among the experimental and theoretical studies concerning pneumonia that have been carried on during the past year, aside from those already mentioned, have been those of Dr. Dochez and Dr. Avery concerning the nature of the precipitable substance arising during the growth of pneumococci, both within and outside the body. The possible rôle of this substance in the intoxication of the disease has been investigated. Dr. Blake has also made further studies concerning so-called "antiblastic"

268

immunity, and Dr. Palmer has studied the question of the increased acidity of the urine in pneumonia. These studies are of much theoretical interest, but are not at present applicable to the practical problem relating to this disease.

Heart Disease.

The work during the year has included a continuation of that previously carried on, having in view the improvement of the methods of treating heart disease, especially the methods of using digitalis.

In addition to this work, the following specific problems have been studied:

1. Estimation of blood pressure in patients with fibrillating auricles. In such persons the pulse beats are not only very irregular in time, but are also of very unequal force. In ordinary measurements of blood pressure, the method employed consists in estimation of the force of the pulse beats. Since in fibrillation no two of these beats may be equal, it is evident that the ordinary methods are not applicable. To overcome this difficulty, the attempt has been made to estimate the pressure by determining the number of beats at each of several levels of pressure, and obtaining an average. This is very unsatisfactory and is believed to give an inaccurate idea of the "effective" blood pressure, which does not depend entirely upon the force of the beats. It seems probable that the "effective" blood pressure is a certain small total amount is necessary to produce effects, but that this amount cannot be taken up until the concentration of digitalis in the capillary system into the capillaries, at which point pressure variations are at a minimum. Dr. Cohn and Dr. Lundsgaard have investigated the variations in pulse pressure in the larger arteries and in the dorsalis pedis arteries in dogs, both when the heart is beating normally and when the auricles are made to fibrillate. It was found that the pulse pressure, which is very small in the dorsalis pedis artery, not over 5 mm. of mercury, is not increased when

the auricles are made to fibrillate. To estimate the blood pressure in man at a corresponding level of the arterial tree, use has been made of the Grtner tonometer, which was formerly used in estimating blood pressure, but which has been given up for other methods which are more convenient. Studies on a large number of patients and normal persons have now been made in this hospital, and it has been demonstrated that it is possible to make accurate readings with this instrument, and that by this method consistent and accurate determination of the "effective" blood pressure can be made in patients with auricular fibrillation.

II. Dr. Levine has carried on a series of experimental studies to determine whether the occurrence of digitalis effects on the heart is dependent upon a certain concentration of the drug in the blood passing through the heart, or whether this occurrence depends upon the actual amount of the drug which has been absorbed by the heart muscle, even though the drug is administered very slowly. This point is of considerable importance in connection with the problem of digitalis dosage. In these studies cats have been used, and in the same cat the results following various methods of administration have been observed. It has not been possible to obtain a complete solution of the problem, but the studies indicate that both the total amount of the drug administered and its concentration are of importance in determining the results obtained. It seems that a certain small total amount is necessary to produce effects, but that this amount cannot be taken up until the concentration of digitalis in the blood reaches an optimum level. However, it is too soon to say how

III. Dr. Morison made the very interesting observation that electrocardiograms taken before and after phlebotomy showed certain differences. It was thought that these differences might be dependent upon blood volume, and he has made a series of experimental studies in

86

animals and has made numerous observations in patients to determine the exact effects, if any, which changes in blood volume cause in the electrocardiograph. It has actually been found possible to produce changes in the electrocardiograms of animals, and also of patients, by producing changes in blood volume by the administration of very large amounts of water or by sweating and freezing. Observations on the blood, made at the same time, by Dr. Palmer, showed that actual changes in volume took place. These studies are of value in explaining the form of the electro-cardiograph, concerning which there are several theories.

IV. Early in the year Dr. Lundsgaard undertook certain studies having for their purpose the development of a method for determining the rate of blood flow, or the minute volume of the heart output. Before coming here, Dr. Lundsgaard had conducted important investigations on this problem and had found that, while accurate results could be obtained by the method devised by Krogh and Lindhard, this method was not suited to clinical investigation. It seemed possible that information could be obtained concerning the rate of blood flow by comparing the difference between the oxygen content of the arterial and the venous blood. If the metabolism is constant, the amount of oxygen removed from the blood is inversely proportional to the rate of flow of the blood through the capillaries. Before any practical use of this principle could be made, however, it has been necessary to obtain much new physiological data, for the matter is much more complex than the simple statement above might indicate. So far as this method of estimating rate of blood flow is itself concerned, it is too soon to say how great its clinical value may be. The studies on patients so far made indicate that, as a means of estimating the changes in the rate of blood flow in the same individual (as during compensation and during decompensation),

the method gives very interesting and instructive results. Whether absolute standards can be obtained which hold good for different individuals, is not yet certain. At any rate, however, the method promises to have considerable value for clinical study. Moreover, out of this work has developed another line of investigation with very practical results.

V. In the course of the preceding investigation it was found important to have methods for the ready determination of the functional lung volume in any individual. Dr. Lundsgaard and Dr. Van Slyke have therefore carried on an investigation to determine whether or not in normal persons there is a constant relationship between the lung volume and the chest volume. The lung volume is determined by measurement of pulmonary gas exchange, and the chest volume is determined by simple actual measurements of the chest wall. From the study of a large number of normal persons it has been possible to show that there is such a constant relationship. From the chest volume, therefore, it is possible to calculate what the normal lung volume should be. A series of patients with tuberculosis were then studied through the kindness and with the assistance of Dr. Garvin of the State Sanitarium for Tuberculosis at Raybrook. In these patients the actual lung volume, as determined by physiological methods, was compared with the lung volume as calculated from the chest measurements, and very interesting results were obtained. It seems that by this method the portion of lung tissue failing to functionate can be, at least roughly, determined.

Diabetes.

During the year Dr. Allen has continued and extended his studies concerning the disturbance of the metabolism of fat in diabetes, which were mentioned in the last annual report. These studies confirm the view that in the diabetic organism fats and lipoids are less readily taken

up by the cells from the blood, than they are in the normal individual. In diabetes there is a primary and specific impairment in the metabolism of fat, as there is of carbohydrates. These studies furnish further evidence that diets of low protein and high fat, such as were previously recommended for diabetics, are improper, and it has been shown in animals that similar diets may even induce a fatal outcome.

During the year much study has been given to the anatomical changes in the pancreas occurring in diabetes. The large amount of material obtained from dogs in which diabetes has been experimentally produced, as well as a considerable amount of human pathological material which Dr. Allen has collected from this and other hospitals, has rendered this study possible. Ever since the demonstration of pathological changes in the pancreas, especially in the islands of Langerhans, in certain cases of diabetes, there has been much confusion concerning the relation of these changes to the disease. Certain pathologists have even denied that the pancreatic changes were of any significance. One reason for this confusion and doubt has been that in certain cases little or no alteration has been present, and that in general there has seemed little relationship between the extent of the alteration and the severity of the disease. It has now been shown that in experimental diabetes in animals, specific changes in the cells of the islands of Langerhans do occur. These changes consist of vacuolization and degeneration, and the intensity is parallel to the clinical course of the disease. Studies of the pancreases of human patients dying of diabetes have shown that an unexpectedly high proportion of these show similar changes. These changes are not striking, must be searched for, and were undoubtedly formerly overlooked. One reason for this is that the tissues were usually not fixed sufficiently fresh. By means of these changes it has frequently been possible to decide from the examination of the pancreas alone that the patient had suffered from diabetes. These changes, however,

279 39

are not recognizable in the milder cases. This statement requires a definition of the terms mild and severe. Dr. Allen thinks that whether a case is mild or severe can only be determined by the reaction to proper treatment. Certain cases, especially in the young, of apparently great severity may improve very much under proper treatment and acquire even high carbohydrate tolerance. Such cases are really mild, although with high fat feeding such patients might have died very quickly in coma. In such a case the finding of little or no change in the pancreas would not be an argument against the rôle of the pancreatic changes in this disease. Dr. Allen thinks that, if the pathological changes are interpreted in the light of the new knowledge concerning the clinical course of and functional changes in this disease, a parallelism becomes apparent.

Dr. Fitz has completed a study concerning the urea index in diabetic coma. Cases not in coma, but bordering on it, gave no evidence of kidney change except possibly hyperfunction. The fatal cases, however, were accompanied by signs of marked renal insufficiency.

Chemical Laboratory:

The studies concerning acidosis which have been carried on by Dr. Van Slyke and the men working with him, and which have been referred to in previous reports, have furnished basis for an extensive report, occupying 165 pages of the Journal of Biological Chemistry, under the following titles:

The Bicarbonate Concentration of the Blood Plasma, its Significance, and its Determination as a Measure of Acidosis. Dr. Van Slyke and Dr. Cullen.

A Method for the Determination of Carbon Dioxide and Carbonates in Solution. Dr. Van Slyke.

The Electrometric Titration of Plasma as a Measure of its Alkaline Reserve. Dr. Cullen.

The Relationship Between Alkaline Reserve and Acid Excretion.
Dr. Fitz and Dr. Van Slyke.

Alveolar Carbon Dioxide and Plasma Bicarbonate in Normal Men
During Digestive Rest and Activity.
Dr. Van Slyke, Dr. Edgar Stillman and Dr. Cullen.

The Blood, Urine and Alveolar Air in Diabetic Acidosis.
Dr. Edgar Stillman, Dr. Van Slyke, Dr. Cullen and Dr. Fitz.

These studies bring evidence in favor of the view that acidosis means a depletion of the alkaline reserve of the body. This alkaline reserve consists of the blood bicarbonate, in that it represents the base available for the neutralization of more acids. The method devised by Van Slyke for the estimation of the ability of the plasma to combine with carbon dioxide under definite tension, from which the bicarbonate content can be calculated, therefore offers the best method for estimating the degree of acidosis present. This method is extremely simple and has already come into wide use and will in the future probably prove to be one of the standard clinical laboratory methods.

Dr. Van Slyke has also developed a new, simple and accurate method for the rapid determination of oxygen in the blood, which has been employed by Dr. Lundsgaard in the studies concerning rate of blood flow previously mentioned. In addition, Dr. Van Slyke and Dr. Fitz have devised new methods for the quantitative determination of hydroxybutyric and diacetic acids in the blood and urine, and the method has been employed by Dr. Fitz in a large number of determinations in diabetic patients. Much information has been obtained concerning the formation and neutralization of the acetone bodies under various conditions.

Dr. Palmer has devised a new and improved method for the quantitative estimation of hemoglobin. In this method the hemoglobin is changed to carbon monoxide hemoglobin by passing a stream of illuminating gas through the diluted blood, and this is compared in a calorimeter with a standard carbon monoxide hemoglobin solution which may be kept in a stable

condition. The method has been thoroughly tested by comparison with crystallized pure haemoglobin, and it has been shown that the error of the result is usually not greater than one percent. The method should prove of great value in accurate quantitative work.

Cancer:

The study of cases of cancer receiving X-ray treatment has been continued by Dr. Murphy and Dr. Morton. With the departure of Dr. Morton, however, it becomes necessary to restrict the extent of this work. As stated in our last report, the entire question of the relation of lymphocytes to cancer growth and the effects of X-rays upon such growths is an exceedingly difficult and complex one, and much time will be required for its complete solution. The present difficulties in obtaining proper assistants will necessarily cause a delay in the further progress of this work. The following is a brief report from Dr. Murphy concerning the clinical results so far obtained:

"Since the last report two patients have died of cancer, and another will probably die within the next few days. All three of these had extensive lung metastasis at the time of admission.

The first two were apparently favorably influenced in the beginning by the treatment and showed very good reactions on the part of the lymphocytes. These reactions, however, were of short duration, quickly subsiding to a point below normal. The reactions became less pronounced, however, until after a few treatments no response could be elicited.

The third case is one which we have had under observation for one and a half years. He had a large sarcoma of the hip with extensive metastasis to the lungs. Under treatment his general condition improved remarkably, and there was also an active retrogression of the

tumor. The lung metastasis remained practically stationary for over a year. Since that time the tumor of the hip has increased and there has been extension of growth in the lungs. About one month ago his resistance seemed to give way completely and there has been rapid extension of the growth.

Another case which gave good reaction on the part of the lymphocytes, and one which was well sustained for over a year, has shown a less elastic reaction and a greater tendency to drop below normal line. She has lately developed a recurrence in the neck.

With these exceptions, the other cases taken soon after operation, but with a bad prognosis, have continued in a satisfactory condition. The group of advance cases which we have had under observation have been of interest. One woman with very extensive recurrence in the wound and metastasis to the neck has shown no response on the part of the lymphocytes whatever, and the progress of the disease has been unaffected. Another with a massive recurrence after removal of a prostatic cancer responded remarkably well with a retrogression of the tumor. He, however, died of intercurrent disease. One of the more recent cases came in with a metastasis in the neck the size of a pecan. Under treatment of X-ray on the distal portions of the body, this has retrogressed until now only a small indurated area can be made out.

It is impossible, as yet, to make any definite statement as to the absolute relationship of the lymphocyte to cancer resistance in man. Much more extensive observation will be necessary. We have, however, seen increasing evidence of the indirect action of X-ray. It is now necessary to improve our method, if possible, to a point where we can get a more sustained reaction and one which will carry the patient over the more critical periods. We feel encouraged along this line and think it can be done, but it will be a slow, long drawn out task."