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REPORT ON THE WORK IN

THE HOSPITAL

Rufus Cole.

The extension of the Hospital laboratory space which has now been provided was much needed and the new quarters will much facilitate the work. There have been some delays in completing the arrangements in the new X-ray laboratory, but it is now expected that within a very short time all the X-ray work can be carried on in the new quarters.

The number of patients admitted to the Hospital during the past quarter has been less than that admitted during the corresponding quarter last year. This is largely due to the fact that the number of diabetes patients admitted has been very much reduced, since Dr. Allen has been devoting his entire time to experimental studies, and only patients of extremely severe type, or showing unusual features, have been needed for the studies being made by the other men sharing in the investiation of diabetes. The number of patients suffering from pneumonia admitted to the Hospital however, had been considerably larger than in any previous year, and at the present time the number of patients suffering from pneumonia being cared for in the Hospital is larger than ever before.

There has been an extremely large demand on the part of physicians for the determination of type of pneumococcus present in individual cases of pneumonia in the city and elsewhere. Fortunately, however, both the State and City Health Department are now prepared to make diagnoses of type, and to provide serum in suitable cases.

No extension of the work has been made in the way of undertaking the study of new disease complexes, but researches concerning the diseases already under investigation have been taken up in new directions, as will appear from the detailed report.

Staff. The only addition which has been made to the staff has been the appointment of Dr Henry Maxwell Larson. Owing to the changes in the staff which were made last year, Dr Dochez no longer residing in the hospital, the number of physicians to actually care for the large number of pneumonia patients admitted was reduced and it has been found necessary to request the appointment of an additional man for this purpose. Dr Larson comes from the Presbyterian Hospital, has had a good clinical training, but has carried on little scientific work, and his appointment is only made for six months, for the specific purpose of assisting in the care of patients with pneumonia.

Owing to the state of her health, Mrs Vinograd-Villchur has been compelled to resign her position in the chemical laboratory, which she has occupied almost since the beginning of the hospital. It is regretted that she finds it necessary to leave, and hoped that later she may be able to return to her work.

Dr Christen Lundsgaard of Copenhagen has been granted permission to work in the Hospital as a voluntary assistant. It will be remembered that this permission was granted to Dr Lundsgaard one year ago, but he was unable to come on account of the war. This year, however, he comes with the assistance of a fellowship granted by the Scandanavian-American Society, and has proved to be a very valuable addition to our working force. We now have in the hospital four voluntary assistants, Dr Stillman, Dr Blake, Dr Levine and Dr Lundsgaard, all well trained men, able to carry on research work.

Dr A.R. Dochez has been granted leave of absence to accompany Dr Biggs to France to investigate the situation in regard to the prevalence of tuberculosis. Dr Dochez' departure would have been a great loss to the Hospital, except for the fact that he is going but for six to eight weeks, and in the meantime the interesting studies which he has undertaken can be carried on by Dr Avery and other members of the staff.

The studies being carried on in the Hospital can best be discussed as grouped under the diseases being investigated, though certain results do not relate directly to these diseases and therefore will be described as special studies from the various laboratories.

Acute Lobar Pneumonia. Preparation of Immune Serum.

Dr Moore has taken entire charge of this part of the work. We have now three horses under immunization for the preparation of serum of Type I, three for Type II and one for Type III. Certain difficulties have been encountered, the horses becoming lame or ill, so that the supply of serum produced has not been as large as was hoped for, but we shall have enough Type I serum for our own supply and that of the several hospitals where the serum is being tried out. There are still some matters to be settled before the serum can be economically and satisfactorily produced. An attempt has been made to produce more active serum by the injection of bacteria grown on agar, instead of the washed bouillon cultures previously employed, with the idea that by this method more of the capsular substances, which it was thought might have specific antigenic properties, could be injected. The results, however, have not fulfilled our expectations.

Dr Moore is also continuing the work on concentration of the serum. A most important practical matter in connect

with the use of the serum is to devise a satisfactory method of standardization. Our present method is somewhat crude and now that the serum is being produced in different places it becomes very important that a proper immunity unit be fixed.

Dr Avery has had this matter under investigation, considerable work has already been done, and it is hoped that by correlation of the protection ratio $\frac{\text{Serum}}{\text{Culture}}$ and the agglutination and precipitation titre of a number of sera, employing cultures of different degrees of virulence, a fairly fixed standard may be established.

Studies by Dr Dochez have demonstrated the presence of a soluble material in bacteria-free filtrates of pneumococcus cultures and that this substance is produced at a time when the organisms are growing at a maximum rate. That this substance is of bacterial origin and retains the specificity of the type pneumococcus from which it is derived is shown by its precipitation with specific immune serum. The fact that it appears early, during the period of maximum growth, indicates that this soluble substance may be a product of the life processes of pneumococcus and not merely a derivative of bacterial disintegration. Dr Dochez has further demonstrated its presence in blood of rabbits experimentally infected with pneumococcus. Its existence has been confirmed by the precipitin reaction and by complement fixation in the filtered blood serum of rabbits four hours after intraperitoneal infection. Similarly, he has shown this substance to exist in the serum of patients during lobar pneumonia. These studies of Dr Dochez' led him and Dr Avery to seek its presence in the urine of patients suffering from pneumonia. They have found that it may be demonstrated with considerable frequency in the urine of patients suffering from infection

with any of the three fixed types of pneumococcus. It has been found as early as twelve hours after the initial chill in the urine of a patient with pneumonia due to mucosus infection, and has persisted during delayed resolution of a Type I pneumonia. Routine examinations of the urine are made in all cases to determine its appearance and disappearance with reference to the clinical course of the disease, its relation to prognosis and its significance in facilitating an early diagnosis. It is present in the urine of about two thirds of the cases, especially in those most severly infected, so its detection is already of considerable practical diagnostic and prognostic value.

Chemical studies so far made show that this substance in urine has the following characteristics:-

1. It is thermostable, resisting boiling.
2. It is not removed from urine by extraction with ether
3. It is not precipated by heat and acetic acid.
4. It is acetone-insoluble and is precipitable by alcohol.
5. It is precipitated by colloidal iron.
6. Its immunologic specificity is not changed by digestion with trypsin or urease.

Detailed study is being made of the fate of this soluble substance in normal and immune animals, and its occurence in the blood and urine of experimentally infected rabbits.

Dr Avery has also been making a study of the cutaneous reaction to pneumococcus and its products in normal and immune animals, with the hope that some knowledge might be gained of factors concerned in pneumococcus infection and resistance. By producing a localised chronic pneumococcus infection, running a self limited course and terminating in recovery, it was thought that the phenomenon of cutaneous hypersensitiveness, if present, might offer a method of attack, and secondly, that

the intradermic route might afford a means of studying the primary toxic action of certain products of pneumococcus, such as its hemotoxin and the soluble substance to which reference has been made. The results so far have been suggestive, but the study has not yet progressed sufficiently to warrant further report at this time.

Dr Blake has been making some further studies concerning the nature of the process resulting in methemoglobin formation by pneumococci and other oxidation reactions associated with the growth of pneumococci. It had been found that if pneumococci were mixed with immune serum and then red blood cells were later added, no methemoglobin formation occurred. In this reaction agglutination of pneumococci occurred and it was questionable whether the failure of the reaction to occur was due to the inhibition of oxidation process of the pneumococcus, or whether the inhibition were in some way associated with agglutination. By a simple expedient, shaking the mixture of immune serum, bacteria and red blood cells, so that agglutination is prevented or delayed, it has been found that the inhibition does not occur making it probable that the inhibition is merely mechanical. The further results of the study will be reported later.

Fate of antibodies after intravenous injection of serum. In a previous report, mention was made of the observation of the fact that, although agglutinins may be present in the blood serum of patients suffering from empyema, not only were no agglutinins present in the fluid obtained from the chest, but such a fluid might inhibit agglutination when added to a mixture of serum and bacteria. Experimental studies in animals showed that this inhibiting power may be possessed by other inflammatory exudates produced by the injection of pneumococci. Studies were then made concerning the disappearance of agglutinins from the blood following the intravenous injection of immune serum into infected and normal rabbits. It has been found that in infected rabbits it is difficult to produce as great

a concentration of agglutinins in the blood and, moreover, in such cases the agglutinins disappear from the blood more rapidly than they do from the blood of rabbits which have not been infected. Curves of the agglutination titre of the serum of human patients being treated with serum are now being made, samples of serum being collected every few hours. It is found that in the severely infected patients the agglutinins introduced in the immune serum disappear very rapidly, and it is difficult to produce any considerable persistent concentration of immune bodies in the blood. On the other hand, in the early or moderately infected cases, the agglutinins introduced remain in the circulation. The clinical course shows a a direct relationship to this phenomenon. These observations offer an explanation of why it is so important to treat the patients early, and why in the severe cases so much larger amounts of serum are required.

All these observations suggest that bacteria when growing in the body, produce substances which neutralize the immunity principles. They therefore also show why it is so difficult to influence local processes by general passive immunization. The difficulty of affecting a local process is due not only to the difficulty of causing the immune bodies to penetrate the walled off process, but also to the fact that in the fluids of the local process there are accumulated substances which neutralise the immunity factors. These facts are possibily of quite wide application. They agree in some measure with the observations of Bail on which the aggressive theory is based, though the interpretation is somewhat different. Whether the neutralizing substances are identical with the precipitable substances now being studied by Dochez and Avery is not certain, though it is possible that they may be identical.

Dr Stillman is continuing his studies concerning epidemiology. Sputum is now being collected from all the persons living in the houses from which pneumonia patients come, and a study is

also being made of the dust of the rooms occupied by pneumonia patients before their admission to the Hospital. Dust has been obtained from the home rooms of 18 of our pneumonia patients. From the dust of 11 of these rooms, pneumococci were obtained. In 4 instances these pneumococci were of Type I, the same as the type infecting the patients; in 2 instances, Type II, also the same as the infecting organism, and in the other cases they belonged to the undifferentiated Group IV. Dust from 5 similar houses in which no pneumonia was present contained in 3 instances pneumococci, all of Type IV.

A description of the study made in one case shows the plan of this work. This patient was admitted to the Hospital with pneumonia due to pneumococci of Type I. Sputum was obtained from the three other members of the household and one daughter, 5 years old, was found to be a carrier of pneumococci, Type I. The other two members of the household were negative. Dust, however, obtained from the room previously occupied by the patient in this house showed the presence of pneumococci Type I. On December 10th this child was sent to board in another household. She remained there but three days. Six days after she left, a child in this house came down with pneumonia, also due to pneumococci of Type I. The cultures from the sputum of the other members of this household were negative, but from the dust of the floor of this house pneumococci of Type I were isolated. When the daughter of the original patient left this household in which she was boarding, on the third day, she was sent to another house in the Bronx to board. No cases of pneumonia developed in this household, however, and cultures from the sputum of the members of the family and also from the dust obtained from the house did not show the presence of pneumococci Type I. Later the child was sent to Brooklyn and while cultures from the sputum of all the members of this house were negative, dust collected from the room occupied by the child showed the presence of

the specific Type I pneumococcus. Later studies of the child have shown that the specific type pneumococcus has disappeared from her mouth.

Several instances which seem to be contact infection or infection from the same source have been studied. One woman admitted to the Hospital had previously been nursing her child at home, sick with pneumonia. Both the child and the mother were found to have a Type I pneumococcus infection. A few days ago an actor from the Irving Place theatre was admitted to the Hospital with Type II pneumococcus infection. The day after he became sick a fellow actor, who occupied the same dressing room with him at the theatre, also became ill with pneumonia, and also had an infection due to Pneumococcus Type II.

This kind of study entails a great deal of work, but it is hoped that by obtaining a large mass of evidence we can determine whether or not we are justified in considering pneumonia due to these specific types as contact infections.

Dr Palmer has been carrying on further studies concerning acidosis in pneumonia. This study has consisted in an estimation with Van Slyke's apparatus of the carbon dioxide combining power of the blood plasma, and a study of the urinary excretion as follows: estimation of the hydrogen in concentration, titratable acidity between the $\frac{+}{H}$ of 5.0 and 7.4, determination of ammonia and phosphates. From the data thus obtained it is possible to calculate the amount of free organic acid in the urine at a $\frac{+}{H}$ of 5.0 Blood analyses reveal the fact that one seldom finds severe acidosis in pneumonia. The lowest combining value was found in a moribund patient, 36 volume per cent; usually it seldom goes lower than 45. volume per cent.

While still at the Massachusetts General Hospital Dr Palmer observed by titration and phosphoric acid determinations that the urine of pneumonia patients oftens contains a weakly acid substance other

than phosphoric acid and not B-oxybutyric acid. By ether extraction and subsequent purification a crystalline substance of elementary composition and molecular weight corresponding to the formula $C_3H_6O_2$ has been obtained. Dr Palmer is engaged in further purification and the attempt to determine its structural composition, which is unusual, as the substance has the properties of neither the low molecular fatty acids nor of an alcohol.

Other studies in the bacteriological laboratory.

Dr Chickering in addition to his duties as Resident Physician has collaborated with Dr Bull in the production of a potent antityphoid horse serum. A horse has been immunized intensively by the intravenous injection of live typhoid bacilli, and up to the present time four bleedings have been made, with a yield of about 12 liters of serum. This serum has an agglutin titre of 1-102400 for certain strains; the one used for the purpose of immunization and the "Rawlins" (U.S.Army)strain. For other strains the agglutinin titre is 1-12800 to 1-51200. Through the courtesy of Dr Gay it has been possible to acquire about 60 different strains from human cases of typhoid fever of the Pacific coast. It has been found that with certain of these strains, about 15 in number, which are culturally B. Typhosus, our serum agglutinates only in dilutions of 1-50 to 1-800 or less. Recently some of these strains have been used in the further immunization of the horse, and this has been accompanied by a moderate increase in the agglutinin titre of the serum. Further work on this point in is progress. By concentrating the antityphoid serum by using the Banzhoef-Gibson ammonium sulphate method, which is the method used for the concentration of diphtheria antitoxin, we have found that almost the whole agglutinin content of the serum is contained in that fraction between 32% and 54% saturation with ammonium sulphate or roughly in the pseudoglobulin fraction. This would seem to be a practical and convenient method

for concentrating antityphoid serum. From the work of other investigators and more especially from certain experimental studies of Dr Bull on the nature of the mechanism of immunity to the typhoid bacillus in animals, potent concentrated antityphoid horse serum would seem to offer a very useful instrument for the study of immunity to the typhoid bacillus in human individuals. It is hoped that an oppotunity to make such a clinical study may be made possible next summer.

Diabetes

Dr Allen is continuing his studies concerning experimental diabetes in animals. Certain diabetic dogs have been kept under observation ever since Dr Allen came to the Hospital, so that observations have now been made on some of them over very long periods of time.

During the past summer much attention has been given to the effects of fat feeding in normal and diabetic animals. The observed effects of fat feeding are classifiable in four divisions.

1. Effect on Acidosis. It is wellknown that the ordinary laboratory animals show no ketonuria on fasting. There is no distinction between carnivora and herbivora in this respect. The experiments confirm the statement of Neumann and others, that young puppies show fasting ketonuria. Their weakness is the main difficulty for experimental uses. Adult dogs become subject to acidosis by partial pancreatectomy under three conditions.

A. Acidosis on feeding. Suitable fat diet gives rise to acidosis in severely diabetic dogs possessing sufficient power of fat digestion. Breakdown of digestion is the principal difficulty to be avoided. With successful management, the acidosis proceeds to typical diabetic coma. The fat ration employed has generally been 100 to 250 grams of suet daily. As in human diabetes, protein and carbohydrate failed to stop this

acidosis, so that dogs go into coma on full mixed diet. The carbondioxide capacity of the blood plasma fails only in the most severe later stage, but in coma approximates that of human patients. Doses of alkali easily maintain the blood alkalinity, but do not perceptibly lengthen life. The excretion of acetone bodies is generally much less than in human patients, but the concentration in the blood is fully comparable.

B. Acidosis on fasting. When a dog with potentially severe diabetes is kept free from glycosuria and gradually fattened by means of a low protein, high fat diet, glycosuria ultimately develops and a condition can be attained in which the animal develops fatal acidosis on fasting, reproducing the condition and the symptoms occurring in certain human patients.

C. Acidosis without glycosuria. Partial pancreatectomy creates susceptibility to acidosis even when glycosuria is entirely prevented by suitable diet. Such animals on suitable fat diets develop ketonuria far more readily than normal dogs.

2. Effect on Glycosuria. Fat feeding alone never gives rise to glycosuria, but in suitably predisposed animals free from glycosuria on a given diet, the addition of fat results in glycosuria. The production of glycosuria by feeding fat to diabetic patients free from glycosuria has already been demonstrated.

3. Production of Intoxication in Normal Animals. Young puppies are easily killed by excessive fat diet, especially by feeding pure fat after fasting for a few days has produced ketonuria. Adult dogs can be made to develop both acetonuria and intoxication if the fat feeding is pushed long enough. There is no parallelism between the production of acetone bodies and intoxication in these animals. The symptoms are loss of hair, eczema, loss of weight, and very pronounced terminal ataxia and generally convulsions.

4. Effect on Lipemia. Partial pancreatectomy occasions only a slight lipemic tendency in the absence of glycosuria, and glycosuria produced by phloridzin is known to be accompanied by only a slight lipemia, but when the partially depancreatized animals are allowed to develop severe glycosuria, they become susceptible to true diabetic lipemia on fat feeding. As high as ten per cent fat has been found in their plasma.

The experiments indicate that acidosis is not due solely to lack of carbohydrate, but that the pancreatic function is somehow concerned, possibly indirectly through the liver or otherwise. The studies further furnish evidence that diets of low protein and high fat, such as were previously recommended for diabetics, are improper and in animals may even induce a fatal outcome.

Dr Fitz, with Dr Van Slyke's assistance, has been working on the application to blood specimens of Van Slyke's method for the determination of acetone and B-oxybutyric acid. Blood or plasma is freed from protein with colloidal iron and the filtrate treated as described elsewhere. Blood from normal individuals shows only 1-2 mg. of acetone bodies per 100 cc. blood, while that from diabetics may show 150 mg. or more.

Dr Stillman and Dr Fitz are preparing to study the relationship between the total metabolism of diabetics (i.e. the amounts and proportions of fat, protein, and carbohydrate burnt) and the formation of diacetic and oxybutyric acids. For determining the CO_2 excretion and oxygen consumption, from which the fat and carbohydrate combustion are calculated, a Tissot spirometer capable of holding 100 liters

has been calibrated. For oxybutyric and diacetic acid determinations we have the new and accurate methods devised by Van Slyke. It is hoped to ascertain by comparison with normal individuals whether, as at present believed but not known, the formation of "acetone bodies" in diabetes is due entirely to the low amount of carbohydrate burnt, in proportion to fat and protein, or whether the diabetic has a specific tendency to form these substances, and generates them when metabolizing amounts of carbohydrate, fat and protein such as would not give rise to acetone bodies in normal individuals.

As by-products of this investigation it is hoped to obtain accurate data on the relationship between the concentration of acetone bodies in the blood and their excretion.

Acidosis. Work by Dr Palmer is under way which promises to clarify the significance of the "alkali tolerance" or "alkali retention" test for acidosis devised independently by Palmer himself, working with Henderson, and by Sellards at Johns Hopkins. The bicarbonate dosage per kilo body weight required to turn the urine alkaline is being compared with the bicarbonate concentration of the plasma at the time the dosage is started. The preliminary results indicate the following: The urine turns alkaline when the plasma bicarbonate concentration exceeds 0.036 molecular, which is about the maximum normal limit. If the body fluids be calculated at 7/10 the body weight, which is approximately correct, and assumed to have the same bicarbonate content as the plasma, enough bicarbonate has to be taken to raise them all to about 0.036 molecular bicarbonate before the urine turns alkaline to litmus. The alkali retention test therefore appears to constitute a titration of the bicarbonate content of the entire body as indicated by analysis of the plasma. If this statement stands the tests to which it will be submitted, it will enable one to calculate exactly from

the plasma CO_2 the amount of bicarbonate required to correct any observed degree of acidosis. The dose needed will be 1.40 g. of $NaHO_3$ per kilo body weight for each per cent by which the plasma CO_2 falls below the normal value of 60 per cent. Thus, a person of 70 kilos, with a plasma CO_2 of 25 percent(severe acidosis) would require $\frac{70 \times 35}{40}$ = 61 g of bicarbonate. In a few tests on diabetics this mode of calculation has seemed to be quite accurate.

Heart Disease, Dr Cohn. Work is being continued on the action of digitalis. In accordance with our plan we are studying patients who fall naturally into groups in which the prominent features are oedema, alteration in rhythm, and elevation of blood pressure. At first the work was confined to observing the action of the drug in cases in which the rhythm was normal, the blood pressure not elevated, and no oedema present Here we found that, except in hearts spontaneously subject to change in rate, no fall in rate took place; that there was no influence on output or urine and no change in pressure. We are not yet ready to make generalizations on the latter part of the study.

The study of the action of digitalis in pneumonia has been concluded. We were able to show with the criteria we used in non-febrile cases - namely the alteration in the auriculo-ventricular interval and in the T wave, that the same effects were noticed during pneumonia. In the cases to which digitalis was given, both conduction time and the T wave changed in 77%, the T wave alone in 16%, the auriculo-ventricular interval in 2%; 97.2% in all. In those cases where no digitalis was given, no change occurred in 88%.

The time required for this effect to take place is, relatively speaking long. We are accordingly making observations by injecting strophanthin intravenously with the view, first of ascertaining whether the criteria we have employed in studying digitalis action are available, and

secondly, in how short a period an effect can be obtained. We believe it necessary to observe the following rules in selecting patients for making these observations; first, that digitalis in no form was administered before the injection, second, that a standard crystalline strophanthin is used, third, that the proper dosage is found. Future requirements mean that the collection of sufficient data will require rather a long time.

We have recently observed in taking human electrocardiograms that after bleeding a patient and also after the ingestion of a large amount of water, the T wave of the curve is not only altered in form, but also changed in direction. In view of the fact that, except for a few definite causes, the electrocardiogram is considered not to alter, this finding is considered of importance. Dr Morison is making experiments with the view of explaining these phenomena.

We have now begun to include the peripheral circulation in our study of the action of digitalis. For this purpose Dr Morison is employing optical registration. The behaviour of the radial artery is recorded by a modification by Wiggers of the Mackenzie receiver and the volume changes of the arm with the plethysmograph. So far he has been concerned with the technique necessary to making curves comparable when obtained at intervals, the form of the apparatus, its adjustment, the temperatures, etc being the factors requiring preliminary study.

Dr Halsey's work is complete and about to be published. His problem consisted initially in finding whether amyl nitrite when inhaled was able to relieve partial heart block. To do this it was necessary to provide a means for producing this condition. For this he used crystalline -g- strophanthin, injecting in about an hour 30 - 40% of the estimated lethal dose. Dogs recover from this. He failed in being able to bring on block uniformly, but accomplished it sufficiently often to show that amyl nitrite had the action he supposed. He compared this action with that

of atropine and found them similar. He was also able to show that atropine had in the early stage after its administration a very decided stimulating action on vagus inhibition as shown by the length of the auriculo-ventricular conduction (P -R) time, and that this action might take place independently of its action on heart rate. This is an observation which confirms one previously made by Cohn and Fraser in patients. Another point of much interest which he established was the following:- It was thought that the failure to produce a continuous block may have been due to the use of the glucoside strophanthin. Accordingly an attempt to obtain a more continuous block was made by using the whole drug in the form both of fluid digipuratum and also a fluid extract of digitalis. These preparations failed as did strophanthin, and in exactly the same way. Contrary to what we experience clinically, digitalis when given intravenously acted as quickly and the effect lasted as short a time as when strophanthin was given. There is in this experiment a possible reason for altering our ideas relating to the difference in action, and consequently in use, between the two drugs.

Dr Levine is carrying on experiments on cats to see whether digitalis acts by virtue of the concentration in which it is present, or by means of the absolute amount of the drug which has been absorbed by the heart muscle. Previous experiments have not decided the point. The work done here was shown that one can expect a certain per cent(between 20 and 40) of the minimal lethal dose to bring about an irregularity of the heart. The irregularity usually consists of extrasystole of ventricular origin. The time required for these to appear is usually about an hour. If the experiment is stopped here the cats recover. If the optimum concentration has been used, an increase in concentration ought not to shorten the time required to cause the effect looked for. If it is the absolute amount which is required, the effect looked for should appear earlier. The fact that dogs

survive injection should facilitate the work. The attempt was made at first to record the observations with myocardiographs attached to the exposed heart the animals being anesthetized. This method has been unsuccessful, for the animals did not survive long enough. The electrocardiographic method of registration which is now used will permit extended observations, lasting several days, if required.

Dr Lundsgaard is co-operating with Dr Cohn in studying, by chemical methods, the minute volume of the heart output in patients with heart disease. Two methods are being tried out. (a) Determination of the difference in oxygen content between venous and arterial blood. From the difference the oxygen taken by the tissues from a liter of blood may be calculated, and from the latter, and the oxygen consumption per minute, the number of liters of blood passing the lungs per minute can be estimated. The arterial oxygen is determined indirectly by saturating venous blood with air. (b) A similar method of Haldane's based on the difference between venous and arterial carbon dioxide contents, and the carbon dioxide excretion per minute. The sources of error in each method are at present being studied.

An outgrowth of the above problem is a study of the relationship between lung volume and the external chest measurements, which has yielded information that apparently enables it to estimate the percentage of total lung volume which is functioning in a given individual. The chest measurements taken are the height of sternum, dorsi-ventral depth measured from sternum to spine at the height of the third rib, lateral measurement at the fourth rib. These three figures multiplied together give the volume of a rectangular prism as high as the sternum, and as wide and deep as the chest, measured at the points chosen. The aerating volume of the lungs is measured by having the subject breathe into a bag containing two liters of oxygen until the gases are completely mixed, for which purpose three expirations usually suffice, though more are taken. The volume of air in the

lungs is then calculated from the nitrogen content of the mixed gases. It has been found that during respiration at rest the normal man or woman has an aerating volume measured midway between expiration and inspiration from 31 to 37 per cent as large as such a prism, the variation being only ± 3 per-cent from 34. Three tuberculosis patients in each of whom one lung was completely collapsed by artificial pneumothorax showed exactly half the normal aerating volume, viz. 16 to 17 per cent in the above units. One patient before pneumothorax showed 29 per cent (only a little below normal), after pneumothorax 16 per cent. The method will be tried on pneumonia patients to estimate the lung involvement.

A second problem has been the development of a rapid method for oxygen determination in the blood. It appears essential to get the results before the blood has stood as long as required by the Barcroft method. It appears that the principle of vacuum extraction utilized in the determination of plasma carbon dioxide can also be applied to oxygen determination, the hemoglobin being treated with ferrocyanide and the oxygen set free extracted by shaking for a few seconds in a Torricellian vacuum, after which the gas obtained is measured. The details are not yet complete.

Nephritis Work on this subject has been temporarily diminished owing to the departure of Dr McLean for China. He has been at the Hospital for a short time this fall to complete work previously reported, and to get it ready for publication. This is now completed.

A study of certain problems relating to nephritis is now being undertaken by Dr Palmer, especially the question of salt and water regulation and the nature of oedema. It is planned to approach the problem by the study of the physical and chemical properties of the serum, namely the molecular concentration(freezing point) and total electrolytes (conductivity), the sodium chloride content, CO_2 combining power, phosphates,

urea(including rate of excretion) and variations in blood volume. Dr Palmer's training fits him especially to undertake this problem and with the assistance of Dr Van Slyke and Mr Cullen it is hoped that important information may be obtained.

Other Studies in the Chemical Laboratories under Dr Van Slyke's Direction. The chemical studies of Dr. Fitz, Dr Palmer and Dr Edgar Stillman and Dr Lundsgaard previously mentioned are being carried on in the chemical laboratory under the direction of and with the assistance of Dr Van Slyke. In addition to these studies, a number of other investigations are in progress by Dr Van Slyke and his assistants.

Work is being concluded on certain details of the beta-hydroxybutyric acid determination. The different factors capable of influencing results have been studied, such as temperature at which the oxybutyric acid is oxidized to acetone and the concentration of the different reagents, viz. sulphuric acid, mercury and dichromates. The work is practically concluded now, and the method in its present form enables one to determine oxybutyric acid not only more accurately, but much more simply than heretofore. It is necessary merely to mix the reagents and the urine in an Erlenmayer flask, boil under a reflux condenser for 60 to 90 minutes, and weigh the precipitate of mercuric-sulfate-acetone compound that forms. The precipitate can be redissolved in 5 per cent H Cl. and doubtless be determined by titration of the mercury. Methods for this will be tested, although the precipitate is so well adapted to convenient weighing that titration can not offer much advantage when a balance and drying oven are available. The "preformed acetone" (acetoneand diacetic acid) is determined the same way, except that no dichromate is added to oxidize the oxybutyric acid.

Mr Cullen has arranged electrical apparatus for an accurate study of the hydrogen ion concentration of the blood, and we hope to find what degree of acidosis(acid retention) usually occurs in diabetics before

the neutrality-regulating mechanism breaks down, and actual change in the reaction of the blood occurs.

With Mr Cullen the work on the fate of protein digestion products also will be continued. The present point under attack is the old question as to whether intermediate products or only amino acids are absorbed into the blood from the alimentary tract. Preliminary experiments have given data which indicate that during the early stages of digestion intermediate products are absorbed, but during the later stages only amino acids.

Mr Cullen is also engaged in a determination from a new standpoint of the acid constant of carbonic acid. This constant is of importance in studies of the neutrality-regulating mechanism of the body, and there is at present disagreement concerning its exact magnitude.

Dr Avery is completing his biological study, by the precipitin and complement deviation tests, of the identity of the caseins and albumins of human and cows' milk respectively. The proteins have been prepared in unusual purity by Mrs Vinograd-Villchur, who actually obtained the albumins in crystals. The results show that the albumins from the two milks are entirely different, the biological test agreeing with the results of the chemical investigations undertaken at Dr Holt's suggestion and reported last June. The biological test, however, goes further, and shows that even though the albumins should each be a mixture of proteins, the albumin from the milk of one species contains none of the proteins of the albumin from the other species. The work on the caseins is not yet complete.

Cancer The study of the treatment of cancer by the use of X-rays has not proceeded sufficiently to permit any conclusions to be drawn. The problems which are presented for solution by this study are:-

1. Is the effect of X-rays on human tumors direct and local, or is

is it a general effect, as the animal experiments would indicate?

2. If it is a general effect, is this due to, or at any rate associated with, a lymphocytic reaction?

3. If this lymphocytic reaction is important, is it possible, by paying special attention to this factor, to make X-ray treatment more effective?

It is readily seen that the whole problem is quite complex and so far as the studies on human patients are concerned the solution is beset with considerable difficulty, for great care must be taken to do no harm to the patient. Since at the time the work was commenced little or nothing was known in regard to stimulation of the lymphocytic reaction in human patients by X-ray treatment, before the clinical studies proper could be started with any prospect of success it was necessary to try various degrees of dosage, kinds of rays, etc. in the hope of producing the desired reaction. This is the kind of work that has been done. Delays in the rearrangement of the X-ray plant have somewhat interfered with the work, but in spite of this progress has been made. The studies on lymphocytic reaction must, of course be made on patients suffering from cancer, and in carrying out this work very careful and repeated blood examinations must be made, the clinical course must be carefully followed ,the X-ray treatments must be accurately given, and given according to a well thought-out plan, subject, of course, to modification depending upon changes in the patients' condition.

This work is being directed by Dr Murphy, who is assisted by Dr Morton in the clinical studies, and Dr Wetherbee who administers the treatment.

The progress of this study must for the reasons I have mentioned be of necessity slow, and the fact that already important observations have been made is gratifying. 26 patients have so far been treated. It has been found necessary to keep these patients in the hospital only for short periods of time, as they can return as frequently as needed for treatment and examination.

It is too soon to speak of clinical results. Four of the patients treated have died. With perhaps two exceptions, the other cases have either remained stationary or have shown small but distinct improvements in the local conditions. The clinical results then, while not striking, are distinctly encouraging. In many cases it has been possible to cause a distinct lymphocytic reaction, in others this has been impossible. The experience so far has not been insufficient to say whether or not there is a definite relationship between the lymphocytic reaction and clinical course, though the observations so far made support this hypothesis.