REPORT

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DIRECTOR OF THE HOSPITAL

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REPORT ON THE WORK IN

THE HOSPITAL

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As usual the midwinter quarter has been the most active of the year. Much of the work under way, however, has not yet been completed and final reports of results can only be given in the report for the succeeding quarter. No changes have occurred in the staff. As usual, so far as possible, the work will be grouped under the headings of the diseases which are being studied.

PNEUMONIA. - During the present winter the number of persons suffering from this disease who have applied for admission has been greater than ever before and it is evident that this year we shall treat in the hospital at least 150 cases of this disease.. The relative number of cases due to the different types of infection corresponds well with that of the cases treated during previous years. About one third of the cases have been due to infection with Type I pneumococci. Up to the present we have had 33 such cases and of these 29 were treated with serum. The remaining 4 cases were not treated because they were admitted late in the disease when recovery was apparently in progress. Of the treated 29 cases all recovered but one. This patient was admitted late in the disease on the seventh day, suffering from an extremely severe infection, cultures from the blood showing 1600 colonies per cc. This patient was very intensively treated, though perhaps not so actively on the first days as we should now consider advisable. Although a marked effect was obtained on the septicaemia, and no extension occurred in the lesion, the patient finally died on the 12th day. Before this time fibrillation of the auricles occurred and it seems probable that in this

case the intoxication and injury were so great at the time treatment was commenced that recovery could not occur, even though progress of the disease were stopped. Adding the cases this year with those previously treated makes a total of 101 cases with only eight deaths. The Brigham and Presbyterian Hospitals which we have supplied with serum have also continued to have very good results. The accumulating experience seems to leave little doubt as to the efficacy of the serum treatment in this type of cases. Determination of type by Board of Health and other laboratories also seems to be practical, though at first there have been difficulties owing to lack of experience of the men making the tests. Interest in this matter has become quite wide spread and considerable time has been spent in demonstrating the technique of determination of type and serum treatment in persons coming here for the purpose. During the past year or two several commercial houses have been extensively advertising and selling so-called antipneumococcus serum. We have made tests of all these sera and are also controlling from time to time the sera prepared by Boards of Health. The sera prepared by commercial houses, up to the past few months, have been worthless. Now one of these houses is preparing a satisfactory serum, and to all of them we are supplying proper cultures and samples of serum for making comparative tests, so that we hope that very soon all of them may be manufacturing satisfactory products. Of great importance, we think, is that fact that most of them are agreeing to manufacture Type I sera and so label it. The determination of a standard of potency has now become important. Steps have been taken to have the Hygienic Laboratory of the United States Public Health and Marine Hospital Service establish such a standard. It has been arranged for us to furnish them with a serum which may be considered of standard strength and against this other sera can be titrated. There

are many problems to be worked out in connection with the standardization of serum and also in connection with the manufacture and preservation of serum. It seems however that this work more properly belongs to the Hygienic Laboratory than to us, provided they will undertake the work.

Studies of the curves of agglutination titre of the blood of all patients following the administration of immune serum have been made and important knowledge concerning proper dosage and proper spacing of doses has been obtained.

During a considerable part of the quarter Dr Dochez has been absent in France, but Dr Avery has continued the study of the soluble bacterial substance which is present in the blood and urine of pneumonia patients, concerning which mention was made in our last report. Further studies seem to show that this substance is a product of the life processes of the pneumococcus, and not due to its disintegration. This is rendered probable from the fact that it is present in considerable amounts in culture filtrates during the early stages of development of the culture when the organisms are growing at their maximum rate and undergoing little or no cell destruction as indicated by growth curves.

If rabbits are infected intraperitoneally with pneumococcus this substance which is specifically precipitable with antipneumococcus serum can be demonstrated in their blood serum freed from bacteria by filtration, from within two to six hours following the time of infection.

Studies of the urine by precipitin reactions in 76 cases of lobar pneumonia due to Type I, II or III show a specifically precipitable substance to be present in about 85 per cent of the cases during some stage of the disease. A positive reaction has been found as early

as 12 hours after the initial chill, and has been demonstrated in one instance as late as six weeks in convalescence. The reaction in different urines may vary from a faint cloud to a heavy precipitate. In certain instances the reaction may be negative when whole urine is used, but be positive in the specimen of urine which has been concentrated by certain chemical methods. A rapid and accurate method of concentration has been devised which is clinically applicable in testing the urine of pneumonia patients for the presence or absence of this substance. Such a method may be of value in facilitating the diagnosis of type in infected cases.

A study of the chemical nature, toxicity, antigenic properties and fate of the soluble substance in normal and infected animals is still in progress. The precipitinogen has been found to pass the kidney of a normal animal and to appear in the urine in demonstrable quantities. The determination of total nitrogen and nitrogen partitions made on the active substance obtained by repeated precipitation with acetone and alcohol show that this substance is of protein nature or is associated with protein.

A large portion of Dr Chesney's time during the past winter has been consumed in the routine clinical work associated with the care of the patients. The clinical work has been greater this year, owing to the increased number of admissions and to the fact that there were fewer internes available for the service. However, he has carried on, with Dr Moore, an extension of the study, begun last year, of the use of ethylhydrocuprein in lobar pneumonia.

Further work has shown that the amount of the drug which can be given safely, and which suffices to produce a bactericidal action of the patient's blood is not sufficient to prevent the death of some of the patients so treated, indicating that the dosage at present employed

is inadequate and that some way should be found to detoxify the drug.

Several opportunities have presented themselves for showing that while the patient was under treatment with optochin the infecting strain of pneumococcus became fast to the action of the drug. We believe this is the first instance where it has been conclusively shown that a parasite in the human body became fast to the action of a destructive agent.

At present studies of the growth of pneumococci in bouillon containing optochin are being pursued, in an attempt to verify some ideas gleaned from the clinical work, and designed to throw light on the reasons why the drug is not more effective. Already it has been shown that the behaviour of pneumococci in the presence of optochin in bouillon varies, depending upon the size of the inoculum of bacteria. These studies, while chiefly of theoretical interest, should have practical siginificance also, if they elucidate the shortcomings of optochin and emphasize the essential requirements of an ideal chemo-therapeutic agent in lobar pneumonia. Apparently there are at least two reasons why optochin is not effective. One possible reason, as above noted, is that the bacteria present in the circulation absorb the drug, removing more than is required for their destruction. Another and possibly more potent reason is associated with the long time required for the optochin to be in contact with the bacteria in order to obtain bactericidal action. In test-tube experiments 12 or 15 hours are required in order that the bacteria be killed. If this is also true in the body, it is evident that the constant invasion of the blood by bacteria from the local lesions makes it possible that the blood may contain even large numbers of organisms, even though such blood may have bactericidal power.

During the last three months Dr Stillman has continued his study of the epidemiology of pneumonia. Sputum and specimens of dust

are collected from all persons living in the houses from which Type I and Type II pneumonia patients come. 96 individual from 28 homes in which a case of Type I pneumonia had occurred were studied. From the saliva of 16(16 per cent) of these individuals a Type I pneumococcus was isolated. A Type II pneumococcus was isolated from only one individual. In 10 of the 28 homes one or more positive contacts were found. 46 other types of pneumococci, Type III and atypical organisms, were isolated from the individuals studied, while from 57 persons no pneumococci could be isolated. Specimens of dust were taken from all 28 homes. In all, 69 specimens of dust were studied, and from 25 pneumococci were isolated. In 16 instances these pneumococci were of Type I (23 per cent) in one instance Type II X and in 8 instances Type IV. From the dust of one or more rooms of 11 of these homes pneumococci of Type I were isolated.

Seventy-five individuals from 24 homes in which a case of pneumonia due to Type II pneumococcus had occurred were also studied. Pneumococci were cultivated from 42 of these individuals, from 33 no pneumococcus could be isolated. Six carriers of Type II pneumococci, one in each of the six of the 24 houses, were found. No one was found carrying pneumococci of Type I. The other pneumococci isolated belonged to Type III and the atypical groups. Fifty-one specimens of dust from 22 houses were studied. In 18 specimens from 12 of the houses pneumococci of Type II were found. In only one instance were pneumococci of Type I present. In 9 of the other specimens of dust pneumococci of Type III or atypical groups were present.

The possibility of direct transfer of infection is suggested by the following two cases. (1) M.K. who had just recovered from a Type I pneumonia left the hospital on March 9th. The next day he went to see his brother who had developed a Type II pneumonia on March 8th. On March 12th

M.K. developed a Type II pneumonia. (2) Miss H. ill with pneumonia (type not yet ascertained) was taken to a private hospital by Mrs. A, who developed a Type II pneumonia in a few days. A friend, Mr A., sat at night nursing Mrs A. but in a few days himself developed a Type II pneumonia.

Through the courtesy of the State Department of Health and the local health officer of Rochester, we have had opportunity to study two epidemics of pneumonia in institutions. The first occurred in an orphan asylum at Rochester, New York. In this asylum were about 200 boys, but the six cases of pneumonia were limited to the boys occupying two of the four dormitories. Three boys in each dormitory developed pneumonia. From the sputum of three of these six boys a Type I pneumococcus was recovered, from two atypical pneumococci, while from one no pneumococcus was recovered. The absence of Type I pneumococci from three cases may be due to the fact that this study was not made until the cases were convalescent. The sputum of the other 56 boys who slept in these two dormitories was studied. From the saliva of six(10 per cent) a Type I pneumococcus was isolated. In 27 instances other pneumococci of Type III and atypical organisms were isolated. A Type I organism was also recovered from specimens of dust taken from each dormitory. The dust from the vacant room which had been used as a ward failed to show a Type I pneumococcus but a pneumococcus of Type II and of Type II B were recovered. In this epidemic 50 per cent of the cases of pneumonia were found to be due to Type I pneumococci, 10 per cent of healthy contacts were found to harbor this type and the same type of pneumococcus was recovered from the dust.

The second epidemic occurred in the Rochester State Hospital

for the Insane. Here six cases of pneumonia occurred among the inmates of one ward of about 200 inmates. A Type I pneumococcus was recovered from four of these patients but the other two patients died before the type of infecting pneumococcus was determined. Each of the patients who died had shared a double bed room with one of the patients who showed a Type I pneumococcus. A Type I pneumococcus was recovered from the dust of one of these two bed rooms. From the saliva of one hundred and forty-eight of the over 200 inmates of this ward where the pneumonia cases occurred, a Type I pneumococcus was recovered in three instances, a Type II in one instance, and in 45 instances pneumococci of Types II X, III and IV. In this latter epidemic six cases of pneumonia occurred in the ward of an institution. A Type I pneumococcus was recovered from 4 of the 6 patients, from 2 per cent of the healthy contacts and from the dust.

		Type I	Pneumococci recovered						
No. of Families	No. of Persons	I	II	IIA	IIB	IIX	III	IV	No P.
28	98	16	1	-	4	11	8	23	57
	Dust Specimens								
28	69	16	-	-	-	1	-	8	44

In 8 houses both dust and individuals positive.

11 " dust ---------- " (23 per cent)

10 " ------- contacts " (16 per cent)

16 " dust --------- negative

17 " ------- contacts "

Type II

No. of Families	No. of Persons		Pneumococci Recovered I	II	IIA	IIB	IIX	III	IV	No.P
24	75		-	6	-	6	9	6	24	33
22		Dust 51	1	18	-	1	-	2	6	24

In 3 houses both dust and individuals positive.

" 12 " dust ------ " (35 per cent)

" 6 " ---- individuals " (8 per cent)

" 10 " dust ------ negative

" 18 " ----- individuals "

Control Dusts

Number 40	Type I	II	IIA	IIB	IIX	III	IV	No P.
	1*	0	0	3	1	1	8	26

36 per cent pneumococci

* A known Type I carrier was visiting in this house.

Dr Blake has given much assistance in the care of patients with pneumonia. He has finished his studies concerning methemoglobin formation, concerning which mention was made in the last report. In addition he has carried on studies to improve the methods of identification of pneumococci for clinical purposes. This was made necessary by the difficulties arising in certain laboratories, where strains of pneumococci which agglutinate in

both Type I and II sera have been encountered. It was shown by means of the precipitin reaction that there is a definite zone of non-specific immunity reaction for all types of pneumococci. The limits of this non-specific zone for the agglutination reaction have been determined and the optimum dilutions of type sera have been worked out that will surely identify all type organisms and fail to agglutinate "atypical" strains which are properly classified in Group IV.

An improved method for the identification of pneumococcus types directly from the mouse peritoneum has also been developed. It has been shown that the clear supernatant peritoneal washings contain a sufficient amount of soluble precipitinogen to give an immediate specific precipitin reaction with the homologous antipneumococcus serum. This method is of particular value in cases where the presence of other organisms in the peritoneal washings causes a delay of 18 to 24 hours in the determination of the pneumococcus type.

HEART DISEASE. - Dr Cohn. We have been interested with Dr Lundsgaard in the problem of the blood pressure in patients when the auricles fibrillate. The ordinary methods are wholly unsatisfactory, for the pressure value of succeeding beats is continuously varying. James and Hart have attempted very ingeniously to supply a means of overcoming the difficulty by multiplying the pressure value(in millemeters of mercury) of the beats by their number, adding these products and dividing by the total number of beats. This of course gives an average figure but it is necessarily inaccurate.

We have proceeded from a different point of view. The difficulty in estimation of the brachial pressure is due to the constantly varying pressure. If there were a point at which the pulse pressure showed less

fluctuation, that would be a more satisfactory point at which to measure the blood pressure. As the smaller arteries and capillaries are reached the pulse pressure diminishes and the flow tends to be constant and continuous; large fluctuations in pressure do not occur. We have accordingly made experiments in dogs under anaesthesia to examine the pressure relations in one large and in one very small artery. One canula was inserted into the right femoral, and one in the left dorsalis pedis artery. These were connected with either a Hürthle or with a mercury manometer, writing on long strips of smoked paper. Artificial respiration was given the chest opened by incising one intercostal space, and electrodes (pincettes) fastened to the right auricular appendix. These were connected to the secondary coil of an inductorium. An interrupted current to the auricle could then be provided and the auricles set into fibrillation. We could therefore get records of pressure variations in the two arteries mentioned, both when the beats were regular and when the auricles were fibrillating. We found of course that the pulse pressure in the small artery was very small amounting to less than 5 mm., that this variation was not exceeded when the auricles were made to fibrillate, and that in fresh dogs in which the level of the blood pressure was normal there was no fall in the blood pressure, barring a slight initial one, when the auricles were made to fibrillate.

We have been able to put the results of these experiments into practice in patients. We have applied a cuff precisely like the brachial one of v. Recklinghausen to a finger and then slowly releasing the pressure in the cuff, have determined that pressure at which blood passed through the digital artery, this point being fixed as the point at which color returns to the finger previously blanched by pressing out the blood with a rubber ring rolled on the finger. This is the method of the tonometer, devised by Gärtner in 1899. That the method is fairly accurate is shown

by the results of readings made by each of us on the same patients. Averages of ten readings on the same patient by each one of us usually do not differ by more than 2 - 5mm. The range in ten reading is usually not more than 4 mm. though occasionally differences of as much as 8 mm. occur. These estimations have been made on both fibrillators and non-fibrillators. The usual difference between brachial and digital pressure is about 20 mm.Hg. We think that we have therefore found a clinical technique for applying the results of our experiments to persons suffering from auricular fibrillation, the digital artery corresponding to the dog's dorsalis pedis. Technically the Gärtner method is extremely simple, the experience very easy to acquire; it requires no calculation and the reading represents a fact.

The experiments on hypertrophy, the studies on human anatomy, the mode of action of digitalis, the action of strophanthine in pneumonia, all referred to in previous reports, are still in progress.

Dr Levine has continued his studies to determine by experiment whether the effect of digitalis depends upon the concentration of the drug in the blood which bathes the heart or upon the quantity bound and held by heart muscle. Both positions are held by numerous investigators. The problem is not without practical interest, for on its solution depend certain therapeutic procedures, especially in infectious diseases, such as pneumonia. It was our plan to employ a less artificial experimental technique than has been used heretofore in the study of this problem and one more nearly analogous to clinical conditions, Cats have been employed because they are known to be susceptible to digitalis in certain known amounts. Crystalline gratus-strophanthine was selected for injection on account of its uniform minimal lethal dose. The reaction looked for was the occurrence of extra systoles, these being detected by the electrocardiographic method. This reaction occurs almost regularly when about

per cent of the minimal lethal dose has been injected. The animals uniformly survive when no more than this amount is employed. The same cat can consequently be injected repeatedly at intervals of from 3 to 4 days. It was thought that if this reaction always occurred following the injection of 60 per cent of the minimal lethal dose, no matter whether the injection occupied 1/4. 1.2 or even 4 hours, the conclusion would be justified that the drug acts by virtue of the amount bound by the heart muscle. For this conclusion to be valid we must assume that unless it were so bound, excretion of a part at least must have occurred before the expiration of the 4 hour experiment. The experiments have shown that extrasystoles do not occur when about 60 per cent of the minimal lethal dose is injected, whether the injections are made during a period of 1/4,1,2, or 4 hours.

The criticism has been made, however, that even during the longest period a considerable amount of the drug may have been destroyed or excreted and that consequently the experiments do not yet show that 60 per cent of the minimal lethal dose was bound. It is still possible that a sufficient concentration to produce the effect was only obtained when the amount in the blood reached 60 per cent of the minimal lethal dose.

To answer the criticism two modifications of the experiment are suggested; first, the period during which the injections are made may be lengthened and second, cross transfusion experiments may be performed. Experiments of both types are in progress and the results will be reported later. The cross transfusion experiments are performed as follows. A cat is taken, the tolerance of which is already known; it is given either an effective dose (60 per cent of the minimal lethal dose to cause extrasystoles) or one just short of effective. Half of its blood is then taken from the carotid or femoral artery and injected into another cat(the tolerance of which is also known); if the strophanthin is in the blood(if the action of strophanthin depends upon concentration) as much more

will be required to cause effects in the second cat as the difference between the total amount required by the second cat and the amount calculated to be present in the first cat's blood, If more than this is required, approaching 60 per cent of the minimal lethal dose, the conclusion may be drawn that some of the strophanthin injected into the first cat must have been bound by heart muscle. At the present time it appears that the problem may be solved in this way.

In comparing electrocardiograms of a patient who had been bled, Dr. Morison found that the electrocardiogram taken after bleeding differed very distinctly from those taken before bleeding. The differences were present in the terminal portion of the electrocardiogram, i.e. in the T wave. He has since been accumulating instances in which similar modifications occur under corresponding conditions. We have thought that the reason for the change lies in an alteration in blood volume which brings about a change in intraventricular pressure and this produces an alteration in the tension of the ventricular muscle. The first step in the investigation of this phenomenon has consisted in attempts to alter blood volume and to correlate the electrocardiographic alterations with this alteration. The estimation of the blood volume has been undertaken by Dr Palmer. He has relied on haemoglobin estimation, estimation of cellular volume, using the hematocrit for the purpose, and conductivity and refraction estimations. The sodium chloride and urea in blood and urine, acidity and amount of the urine and the rate of its excretion, variation in body weight and amount of water evaporation have been ascertained. Electrocardiograms in the 3 leads have been taken at very frequent intervals and blood examinations have been made five or six times during the experiments..

The measures by means of which it was attempted to alter the volume of the blood were: the drinking of large quantities of water in a short space of time (2 liters in 30 minutes), the drinking of sodium chloride solution, the

taking of magnesium sulphate(27 gms. in 600 cc of water,) sweat baths, and cold packs.

So far it appears that the volume of the blood can be altered when these measures are employed and that when such changes in volume occur modifications in the electrocardiogram take place. It appears, furthermore, that the electrocardiongarm is very sensitive to these changes. At the present time two theories to explain the especial form assumed by the electrocardiogram exist, the first held by Einthoven and Lewis that it depends on the distribution of the muscle of the heart by weight; and second, that recently advocated by Fahr, that it depends in part at least on the relative lengths of the conduction paths in the two ventricles or on the relative rate of conduction in the two ventricles. The observations and experiments performed here suggest still another possibility, namely that the tension at which the muscle is held is a factor involved in the curve. A number of experiments designed to test these hypothese occur naturally. These we hope to undertake and to report upon later.

Dr Morison has also undertaken to study the reaction to digitalis of peripheral blood vessels, using for this purpose a plethysmo-graph. The difficulty consists in reproducing from time to time the same conditions in the receiver. He has expended much time and ingenuity on this work, but until now the observations are not in a state to render a report possible.

DIABETES. - Dr Allen. The former report dealt chiefly with questions of fat metabolism. Miss Wishart is continuing this work, using Bloor's method of analysis for total fats, lecithin and cholesterol in the blood. Comparisons are made between normal, phloridzinized and mildly and severely diabetic animals to ascertain something of the nature of diabetic lipemia. In addition to the feeding experiments, a few intravenous injections are being made. The experiments seem to confirm the idea that in the diabetic organism fats and lipoids

are less readily taken up by the cells from the blood. There is a primary and specific impairment in the metabolism of fat as well as of carbohydrate.

Dr Perlzweig's principal work consists of analyses of amino-acids in blood and urine, with the usual comparisons between normal, phloridzinized and diabetic animals. He had previously been concerned chiefly with the acidosis experiments and the amino-acids problem is too new for a definite report, beyond the fact that an increase of amino-acids in the blood and urine of phloridzinized and diabetic animals as compared with the normal is confirmed.

In the work concerning the influence of various organs on diabetic symptoms, it is possible to mention some results obtained with the thyroid. Severe diabetes with continuous hyperglycaemia and ketonuria and glycosuria on feeding a very small quantity of meat, can be promptly and surprisingly transformed by total thyroidectomy. It is apparently impossible to produce a return of any appreciable acidosis. The blood sugar falls and the tolerance as judged by either glycosuria or hyper glycaemia is multiplied. The tendency also is changed so that after excessive feeding the glycosuria and hyperglycaemia tend to clear up promptly instead of to continue. This is a cure of diabetes according to current conceptions, but the result is in keeping with the hypothesis that diabetes consists not in these symptoms but in a specific inability to use food normally for either combustion or synthesis of tissue. The dogs in question eat and digest a diet ample to nourish normal dogs, but they slowly emaciate and finally die in cachexia. There are some possibilities of considerable interest in the respiratory metabolism and Dr Lusk has promised to take these and some other interesting animals of our series for calorimeter observations.

During the past three months things seem to have come to a focus in the anatomical study, so that I believe we can affirm a definite and consistent pathology of diabetes. Some confusion has heretofore resulted from attempted

risons of series of "diabetic" and "non-diabetic" autopsy findings, without rm differences. But the majority of diabetics are old persons, who, we now , are generally capable of acquiring a rather high tolerance, and the possible tence of any degree of lowered tolerance in the "non-diabetic" cases has prac- ly never been tested. Accordingly it is nothing surprising if more or less rosclerosis or other senile changes should be found rather indiscriminately ch series, with no positive diagnostic distinctions. This is merely analogous e state of affairs with the kidney, for which an unquestioned though incom- e pathology exists, and yet it cannot always be told from the microscopic re whether there was albumin in the urine or how much. In addition, the new tment has cleared up some clinical misconceptions. Death in coma does not ssarily mean sever diabetes. It has frequently been merely fat intoxication ases essentially mild. Also, when a young patient suddenly developed intense etes and died in a few weeks or months and the pathologist found numerous nds of Langerhans present it seemed that such evidence was opposed to the - of deficiency of these islands as the cause of diabetes. But, for example, case of Geylin and Du Bois was one of rare intensity, more voilent and rapid n the average in even the young patients. Yet under treatment this patient y quickly acquired a tolerance of some 200 grams of carbohydrate, therefore is obvious that considerable island tissue was present; any other finding ld contradict not support the island theory. We know that these cases of ort rapid course ordinarily acquire tolerance quickly under efficient treat- nt. The following basis for pathology is indicated by our short series of es and by the specimens sent me by a few physicians. We should start with cases demonstrated as severe by the present treatment, namely the ones that ve unable to acquire any satisfactory tolerance and perhaps finally die in ite of the best treatment. I believe it is possible to diagnose diabetes

diabetes with the microscope positively in every such case, by the extreme deficiency in islands. Then, there are the cases of great intensity dying perhaps in coma without adequate treatment. I am inclined now to think that all such cases will show the specific exhaustion in all or some island cells, as in experimental animals. The trouble is that most pathologists do not know how to recognise these significant changes and the ordinary autopsy material is too old for them to be made out positively even by an experienced observer. On the other hand, when the symptoms of even the severest case are held in check and the patient even allowed to starve to death rather than develop glycosuria, as in our case of the Sankey boy, the cells of the few remaining islands are free from exhaustion, just as in animals under similar conditions. There is a further possibility that some of the supposed normal islands in some of the reported human cases heretofore have consisted of A-cells, remaining after disappearance of the B-cells, but this suggestion is based only on analogy with animals and has not been investigated in patients.

In keeping with the above is the outcome of a new group of animal experiments. In seeking a means of producing diabetes without removing so much pancreatic tissues, I last year succeeded in leaving large remnants and pinching them between the fingers so as to set up severe inflammation, then over-feeding with carbohydrate to injure the islands. The result was that the acinar tissue regenerated but the islands were destroyed, so that there was severe diabetes with very large pancreas remnants, which at autopsy appeared fully normal except for the absence of islands. The method is uncertain and failures are more numerous than successes. Therefore recently I tried asphyxia, and found that by clamping the vessels for about 20 minutes diabetes can be produced with a third or more of the pancreas in position. I am seeking to produce it with the whole pancreas present; this attempt will quite likely fail, but there is no inherent reason against it except that dogs are more resistant to diabetes than human beings. Specimens obtained to date indicate that there

is first an inflammation with degenerative and regenerative processes in both islands and acini; the pancreas is hard but not fibrous. The acini are either injured less or regenerate better than the islands. The end result seems to be a normal-appearing pancreas, grossly and microscopically, except for the scarcity of islands. The work is incomplete as yet. The most significant feature seems to be the proof that a temporary acute inflammation, not greatly incapacitating the individual or interfering much with digestion, can destroy the islands so as to bring on diabetes yet leave no signs at subsequent autopsy except this scarcity of islands as found in the human cases. The relation to possible mild pancreatitis set up by accidental infections, injury of the pancreas by bile or other agencies, etc. is still hypothetical, and the hereditary element in diabetes is still important in at least some groups of cases.

CHEMICAL LABORATORIES. - Dr Van Slyke. The method for rapid determination of oxygen in the blood, which was mentioned as an object of work in the last report, has been perfected, so that oxygen can be determined with the same apparatus used for CO_2, and with practically the same simple technique. The blood, 1 to 3 cc. is introduced into the apparatus, laked with dilute ammonia and saponin, and the oxygen set free by addition of potassium ferricyanide. The oxygen is extracted by shaking the evacuated apparatus for about 30 seconds, and the volume of gas obtained is read off. Duplicates usually give volumes of gas so nearly equal that it is difficult to detect a difference in the readings. The results give an average oxygen capacity of about 20 volume per cent for normal blood, which is higher than the 18.5 per cent taken as an average by Haldane. The method has been in constant use in two problems by Dr Palmer and Dr Lundsgaard described below.

The determination of hydroxybutyric and diacetic acids by oxidation of the former to acetone in the presence of mercuric sulfate and weighing or titrating the mercury-acetone precipitate formed, has been tested in some hundreds of

determinations, chiefly by Dr Fitz, in connection with the diabetic work. The results, both with blood and urine, have been so uniformly satisfactory that the method may be considered ready for publication.

Dr Fitz and Dr Stillman are well into the study of diabetic metabolism which has as its object the ascertainment of the relation between the amounts of fat, carbohydrate, and protein burned in the body and the formation of oxybutyric and diacetic acids. The CO_2 formation and oxygen consumption are being followed daily by Dr Stillman with the Tissot spirometer. For the extremely accurate gas analyses required a new apparatus has been devised with which we have obtained unusually consistent results. From the gas exchange thus determined and the nitrogen excretion, the amounts of fat, carbohydrate and protein burnt in the body are calculated. Dr Fitz has been determining the diacetic and oxybutyric acids in blood and urine by the new methods mentioned above, as well as the total nitrogen, urea, ammonia, free acid, sugar and chlorides. The problem is in its infancy, but interesting leads are being uncovered. It appears, for example, that when carbohydrate is withdrawn suddenly from the diet of a moderately severe diabetic, the body requires about two days to get its defensive mechanism against acidosis in order. The first day there is little ammonia formation, the respiratory quotient falls to about 0.72, indicating no utilization of stored glycogen, and acidosis begins to develop, as shown by a sudden drop of 10 to 20 volume per cent in the plasma CO_2. The second day the "acetone acids" are neutralized with ammonia, the plasma CO_2 rises towards normal, and the respiratory quotient also may go up to 0.78 or 0.79, indicating utilization of glycogen. After a few days the glycogen is exhausted and the respiratory quotient falls, moderate amounts of acetone bodies are excreted daily, but the organism has adjusted itself to their elimination, and the alkaline reserve of the blood stays normal.

Dr Lundsgaard is bringing two problems into a very satisfactory condition. The chemical measurement of lung volume, by breathing several times

into a bag containing a measured volume of pure oxygen and analyzing the gas mixture obtained, has been thoroughly tested by comparison with the mechanical measurements obtained with an ordinary spirometer. On all subjects the two methods gave approximately the same values for the vital capacity. The accuracy of the chemical method seems therefore assured. Its advantage over the spirometer lies in the fact that it enables one to determine not only the air that can be expired(vital capacity), but also the residual air that remains in the lungs and cannot be forced out. Consequently while the vital capacity obtained with the spirometer depends upon chest mobility, the chemical method enables one to determine the total lung volume, independent of variations in mobility. We also, by obtaining skeletal measurements on the chest in three dimensions of space (anterior-posterior, lateral at 6th rib, and length of sternum) are able to calculate within 10 per cent what the lung volume is if conditions inside the chest are normal. Consequently we appear to have in our hands a fairly sensitive means of detecting and measuring the extent of decreased aerating volume such as may be caused by tuberculosis, tumor in the thorax, or unresolved pneumonia. A few preliminary results have proven sufficiently interesting to justify an extension of the work to pathological subjects, and Dr Lundsgaard is at the time of present writing taking advantage of the hospitality of the Ray Brook sanatorium to study tubercular patients.

Dr Lundsgaard is obtaining, in collaboration with Dr Cohn, results of importance in studying on heart patients and normal subjects the difference between the oxygen contents of arterial and venous bloods. The venous blood is drawn from the arm vein of the resting subject. The arterial oxygen is estimated by either saturating a portion of the venous blood with air and determining its oxygen content, or by determining the hemoglobin with Dr Palmer's new technique. The oxygen consumption of resting muscle being fairly constant, the amount of oxygen taken from 100 cc. of blood should be proportional to the time required

by the blood to pass through the tissue from artery to vein, i.e. the slower the flow the greater the proportion of oxygen absorbed and the greater the difference between arterial and venous oxygen content One would consequently expect in heart decompensation a venous oxygen content lower than the arterial by an abnormally wide margin. This is found to be the case, and the results are rather striking. A normal individual, or one with a compensated cardiac condition, never shows a venous oxygen content more than about six volumes per cent lower than the oxygen content of arterialized blood, the average figures being arterialized blood, 20 volume per cent, venous 16 per cent. In decompensation, arterialized blood being the same, venous oxygen usually falls to 4 to 7 per cent. Thus far all decompensated cases have shown this extreme change; no intermediary cases have been encountered, although it seems that they must be met when more cases are examined.

Mr Cullen has been collaborating with Dr Avery in an attempt to isolate and determine the chemical nature of the antigen found in pneumonia urine. By alcohol and acetone precipitation, dialysis,etc. a highly active specific product was obtained containing 14 per cent of nitrogen. When completely hydrolyzed 42 per cent of the nitrogen was converted into free amino groups. The same figures were obtained from a product prepared from a broth culture. The total nitrogen content is that of a protein, but the low amino nitrogen obtained on hydrolysis (all proteins thus far studied show 60 per cent or more of their nitrogen in amino form when hydrolyzed)indicates that either a non-protein nitrogenous substance accompanies the protein, or that the protein itself is of peculiar structure. Further experiments are under way to settle the point.

Dr Palmer's comprehensive study of the different factors in edema, mentioned in the last report as being prepared for, is now under way, the difficulties of technique and routine necessary for the various physical and chemical determinations having been successfully disposed of. The work, because of the current

ck of knowledge concerning the causes of edema, must pass through an exploratory ige during which profitable avenues of attack are sought. It is at present in is stage, and, although results of some interest have already been obtained, they be reported more clearly when the work has progressed further.

One outgrowth of the problem has been an improved method for the lorimetric determination of hemoglobin, which Dr Palmer was led to devise from e necessity of an accurate and rapid means of estimation in the edema work. 0.2cc blood are diluted with water, saturated with carbon monoxide by passing illumi-ting gas through the mixture for a minute or less, and compared in a colorimeter th a standard solution of carbon monoxide hemoglobin. The standard is kept in bottle, the gas space of which is filled with illuminating gas and appears to st for months. The color can be read with great accuracy, and results obtained th those calculated from the oxygen capacity(determined as described in first ragraph of this report) with an error usually not exceeding 1 per cent of the mount determined. The standard hemoglobin solutions thus far used have been made rom blood, the hemoglobin of which was estimated from a careful determination of the oxygen capacity. In order to base the entire work on as firm a standard as possible, however, pure hemoglobin is being recrystallized, and further standard solutions of pure hemoglobin will be prepared and standardized not only by the oxygen capacity but also by means of the spectrophotometer.

The alkali retention test for acidosis of Palmer, Henderson and Sellards is being further studied by Dr Palmer, the amount of bicarbonate required to turn the urine alkaline being compared with the plasma CO_2 capacity. Data on normal, diabetic and nephritic individuals confirm the preliminary observations in showing that the alkali requirement is proportional to the fall of plasma CO_2 capacity below the value of 70 to 75 volume per cent. For a subject of 40 kilos weight, approximately 1 gram of bicarbonate is required to raise the plasma CO_2 by 1 volume per cent, and the amount required varies in proportion to body weight. The effect

is what would be calculated by assuming that the body is 70 per cent fluid and the bicarbonate distributed evenly not only to the blood plasma but to all the remaining fluids. The results clarify the explanation of the retention test, as titration of the body fluids, and also make it possible, on the one hand, to estimate from the retention test the approximate level of the blood bicarbonate, and on the other to calculate from the plasma CO_2 capacity the amount of alkali that must be absorbed to raise the blood bicarbonate to the normal level.

Dr Palmer has shown that the hydroxybutyric acid in a diabetic urine can be approximately estimated by bringing the hydrogen ion concentration to 10^{-5} and titrating with N/10 alkali till the point $10^{-7.4}$ is reached, the titration being controlled at each end by a solution of standard hydorgen ion concentration colored with alizarin. The titration gives 83 per cent of the phosphoric acid, 50 per cent of the hydroxybutyric, and only traces of other acids. Consequently when the phosphoric acid is titrated separately with uranium nitrate and subtracted from the first titration, the result indicates approximately the hydroxybutyric. It does not indicate the diacetic acid. Comparison of the results with those obtained by the accurate gravimetric method on a number of urines showed approximate agreement between the two methods. The results calculated from the titrations are of course not so accurate as those of the direct determination; but the agreement is such that the extremely simple titration method may well prove useful.

CANCER. Drs. Murphy and Morton. The problems as outlined in the last report have progressed somewhat. The progress has been for the most part in determining the proper X-ray dosage which would stimulate the lymphocytes. We have certain indications from the laboratory side that changes brought about in the lymphoid tissue are secondary to changes in the blood. The basis for this is the fact that we have observed a depression in the blood lymphocytes following exposure of the ear of a rabbit to X-ray, and this followed by a stimulation phase.

In other words much the same effect is obtained by this method as when a small generalized dose is given to the animal. Studies of the lymphoid tissue, as the spleen and glands, show the same changes when the ear alone is exposed as when the whole animal is treated. With this as a basis, we are giving our treatments over the large vessels. This has given a very sharp and more uniform stimulation than was obtained by the previous methods.

The first study was made with three normal individuals treated as parallels to three cancerous individuals. The chief trouble with the results obtained is that the reaction is not durable enough. If the treatment is continued, a marked decrease in the lymphocytes finally results. The method is being modified now by decreasing the penetration of the rays and increasing the time and area of exposure. Results so far from this dosage indicate a distinct advance in the method.

Few new cases have been admitted, as with the present staff it is not possible to carry more than twenty-five patients at a time. Since the last report, three of the cases with advanced cancer have died, two of these directly from extension of the disease, and the third from the effects of an operation, an attempt to remove a lymphedematous arm. It is of interest to note that as these cases advanced, the fluctuations in the lymphocytes had a more and more downward tendency, until towards the end the counts reached a very low level. Autopsies obtained on two of these cases showed particularly interesting changes in the spleens. The Malpighian bodies were greatly reduced in number and contained only a fraction of their normal quota of so-called mother cells. Likewise there was a great reduction in the number of small round cells, which are usually so abundant in the area around the follicles. The same condition was observed in another case autopsied a number of months ago.

A case of advanced sarcoma of the hip with a large lung metastasis which had been held in a stationary condition for somewhat more than a year has also shown some advance. With these exceptions, the cases which are being followed are practically in a stationary or slightly improved condition.

There are several incidental points of interest which have developed in the course of the study of these cases. In about thirty individuals with cancer of the breast, we have had six with both breasts involved; three of these have had in addition benign tumors elsewhere, two of the uterus and one a lipoma of the shoulder. One patient has given an interesting family history. There is a larger cancer incidence in this family than any yet reported in the literature. There have been nineteen individuals in three generations who have died of this disease, both branches of the family being involved. Records are available for further study of this group. In the light of Slye's work, it seems of importance that such cases should be recorded.

A final opinion of the effect of the indirect X-ray treatment must be reserved for the present. Certain cases have certainly responded well, even with our as yet imperfect method of X-ray dosage.