

REPORT OF THE DIRECTOR

OF THE HOSPITAL.

January 1915.

During the last quarter year patients suffering from one of the following diseases have been admitted to the Hospital for treatment and study; acute lobar pneumonia, diabetes, and heart disease. A few of the patients formerly under treatment for syphilis of the central nervous system have been readmitted for short periods to receive additional treatment.

Acute Lobar Pneumonia: The work on acute lobar pneumonia has been mainly a continuation of that carried on during the past years, especially along the lines discussed in our last report. The number of patients admitted during the present quarter is about twice as large as the number admitted last year during the same period of time, so it seems probable that quite a large number of patients will be available for study during the present year. Unfortunately, so far as testing the value of the method of treatment by means of immune serum is concerned, very few cases of Type I. have been admitted. On the other hand, an unusually large proportion of the patients so far admitted have been infected with pneumococci of Type II. Further experience with the serum treatment of cases of Type II indicates that the value of this method of treatment in these cases is not nearly so great as it is in the cases of Type I. This was to be expected from the experimental studies. Further efforts are being made to determine whether or not some modification in the method can be made which will improve the results in this type of cases. The results of serum treatment in cases due to Type I, however, continue to be very encouraging, and there seems every reason for believing that serum treatment in cases due to this type of organism is of very great value. When one remembers that the number of deaths in New York, due to pneumonia caused by pneumococci of Type I is greater than the deaths due to diphtheria, and much greater than the total number of deaths due to scarlet fever, cerebro-spinal fever, and typhoid fever combined, it is quite evident that we are

justified in considering this type of pneumonia as an entity, and in feeling much encouraged if the method employed is able to materially reduce the mortality in cases of this one type. It is planned during the coming winter to supply a limited amount of serum to several other hospitals, so that it is believed that by spring we shall obtain sufficient statistics to permit of a definite judgement as to the therapeutic value of this serum.

During the present quarter the studies of Dr Dochez and Dr Avery concerning epidemiology have been extended, and the observations previously reported have been confirmed. The report of this study is now in press. Dr Avery's study of the distribution of the immune substances in the various fractions of the protein of the serum have also been extended and completed, and the report will appear in the February number of the Journal of ~~the~~ Experimental Medicine. The studies have shown that practically all the immune substances are contained in the fraction of protein precipitated by 38 to 40% ammonium sulphate. Since this precipitate contains only one sixth of the protein, it is evident that a method has been found for removing a considerable amount of the protein of the serum used in treatment. This is now being carried out on a larger scale, so that treatment may be made with such concentrated serum. This work also has considerable purely scientific interest in relation to the distribution of immune bodies in the serum protein fractions.

Owing to the fact that Dr Dochez, as resident, has been compelled to give a considerable amount of his time to the care of patients, he has had less opportunity than previously to carry on experimental studies. However, he has continued his study of the nature of the immunity in Pneumococcus mucosus infections, and it is to this problem that his experimental work will be largely devoted during the coming winter.

The laboratory studies of the Director of the Hospital have been mainly devoted to a study of methods of quickly producing active immunity and to a determination of the best method by which such rapid active immunity may be obtained. It

has been found that if even the slightest grade of active immunity is produced, the efficacy of immune serum, in such animal, is enormously increased. With the methods so far tested, however, it has been impossible to produce even this slight grade of active immunity inside of a period of six days. It is hoped that a method may be devised for decreasing this period, in order that we may have experimental justification for combining vaccination with passive immunization in our patients. Further knowledge concerning the nature of active immunity in pneumococcus infection is especially of importance in order that the specific treatment of patients suffering from infection due to pneumococci of Type II. may be rendered more efficacious.

Dr Chickering, in addition to the care of patients, has been working with Dr Gay, and the following is the report by Dr Gay of the results obtained in their work.

Report by Dr. Gay.

Through the courtesy of the Board and of Dr Cole, the facilities of the laboratories of the Hospital have been extended to Dr Gay for the past two months, for which he wishes to make grateful acknowledgement. His work has been carried on with the assistance of Dr Chickering, who will share in the publication to be made. The study first undertaken dealt with the possibility of treatment by means of a combination of serum and pneumococcus vaccine, or by means of a sensitized vaccine. The experimental conditions of pneumococcus infection in the animals that have been tested have apparently not lent themselves particularly well to a demonstration of possible therapeutic uses of either plain or sensitized vaccines. Certain suggestions have been obtained which might eventually lead to something of more practical significance.

During the last month, however, experiments along this line have been largely abandoned, owing to the greater interest awakened by another observation. It was thought worth while to try the possible curative effect of a specific precipitate produced in antipneumococcus serum on the addition of an extract of pneumococci. It was found that such a precipitate, which could be produced rapidly and in large volume by adding a water-clear extract of washed, alcohol-precipitated and ground pneumococci, is apparently

as protective against pneumococcus infection in mice and rabbits as an aliquot amount of the original serum. This precipitate may further be washed in saline and still retain its curative properties, and in some instances, when freshly produced and dissolved by a small amount of alkali (NaOH) will still retain as much curative value as the original serum from which it is derived. The addition of too great amount of alkali, even if it be subsequently neutralized with HCl, may destroy the curative value. The same effect, however, is also produced by the addition of large amounts of alkali to the original diluted serum. This curative precipitate contains a very small amount of proteins as determined from the total nitrogen. Whereas the original serum contains 6 to 8% of protein, various specimens of the specific precipitate, restored to its original volume of serum, have been found to contain from .18 to .34%. From the observations hitherto made, it would seem that the strength of the protection afforded by this precipitate is not proportionate to the percentage of protein present.

The concentration of the precipitate in smaller volume apparently renders it possible to protect mice against somewhat larger doses of the pneumococcus than can be protected against by the whole serum. The serum from which the precipitate has been removed contains much less protective value than the original serum, although it usually contains a perceptible amount. The method for producing the maximum amount of precipitate, the possibility of putting this precipitate into solution without destroying its protective value, and many other problems remain to be worked out in more detail. We do not know, for instance, whether the precipitate itself is the protecting substance or some other combination of antibody adherent to it. It seems evident that the precipitate does not protect in some mechanical way, owing to the fact that it may protect equally well when dissolved, and also owing to the fact that the undissolved precipitate does not protect against a type of pneumococcus other than the one against which the serum employed is active.

It would seem that these observations open a field of considerable interest for investigating the nature of immune bodies of various sorts, and indicate a means of concentrating immune bodies in a solution of low protein content which may be advantageously in treatment, not only of pneumonia but possibly also of other infections.

Dec. 14th.

Curative Experiment

With varying doses of serum and dissolved precipitate
and a fixed dose of culture.

Volume = 0.5 c.c.

1.	Diluted serum	0.1	+ Culture Pneumococcus I 98 ⁱ	0.05cc	Survived
2.	"	"	0.05		"
3.	"	"	0.025		"
4.	"	"	0.0125		"
5.	"	"	0.00625		+ 14 days
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6.	Dissolved precipitate	0.1	+ "	" " " "	Survived
7.	"	"	0.05		"
8.	"	"	0.025		"
9.	"	"	0.0125		"
10.	"	"	0.00625		"
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11.	Exhausted Serum	0.1			"
12.	"	"	0.05		+ 36°
13.	"	"	0.025		+ 36°
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14.	Control		+ 0.05		+ 20°
15.	"		+ 0.0001		+ 18°
16.	"		+ 0.00001		+ 40°
17.	"		+ 0.000001		+ 48°

Diabetes: During the past quarter the efforts of Dr Allen and Dr Stillman have been mainly directed to the treatment of patients suffering from diabetes, along the lines discussed by Dr Allen in his report to the Board, last April. It will be recalled that the studies on animals suffering from experimental diabetes led Dr Allen to believe that for the successful treatment of diabetes it would be important to keep the patient on as low as caloric diet as possible, in the hope that the demand then made upon the assimilative functions of the body would be reduced as far as possible, the theory being that any increased demand made on these functions, over that absolutely necessary for the supply of sufficient energy to carry on the activities actually necessary for life, would cause a strain on the organs functioning in assimilation, including the pancreas, and so reduce the functional power of such organs. It will be recalled that Dr Allen showed that if two dogs be each rendered diabetic to the same grade, and that if one be fed on a high caloric diet, and the other on a low caloric diet, the one receiving the high diet would, in spite of this, lose weight, and would also become feeble, and finally die. The other one would also lose weight, but remain apparently active and in a comparatively normal state.

Twenty seven patients have now been admitted to the Hospital, suffering from diabetes. Sixteen are still in the Hospital. The study of these patients has shown that, by the withdrawal of all food except alcohol, all patients suffering from diabetes can rapidly and completely be relieved of glycosuria. It is also of very great importance that, at the same time, the excretion of the abnormal fatty acids is also reduced to a minimum, so that, instead of the withdrawal of food causing an intensification of acidosis, it is the best means of relieving the patients from threatened acid intoxication. In order to obtain this freedom from glycosuria and acidosis, it is sometimes necessary to withhold food from the patients for a considerable length of time, in certain cases as long as eight days. After the patient is free of glycosuria and acidosis it is then necessary to get him back to a living diet, containing a sufficient amount of the various kinds of food. No effort is made to have the patient increase in weight

however. If he is emaciated, however, it is thought important that the weight should remain stationary. By carrying out these simple measures, it has been possible in a large number of the cases, to keep them free from glycosuria and acidosis and on a caloric diet of sufficient size to maintain life.

It will be remembered that in his previous report Dr Allen stated that he thought that by this method, the total metabolism might be reduced. To test this hypothesis a series of calorimeter experiments have been carried on with Dr Lusk and Dr De Bois, the patients being temporarily removed to the Bellevue Hospital for this purpose. This study is still in process, but in one case, at least, a reduction of 20% in the basal metabolism has been observed, following treatment as outlined. Most of the patients have shown increased tolerance to carbohydrates and protein following the procedures described, though it is still impossible to say whether it is essentially greater than that observed when patients with diabetes are made free of glycosuria and acidosis by the slower methods previously employed. It must be remembered, however, that with the methods previously used it has been impossible in many cases to render them free of glycosuria and acidosis. Only further extended studies can show how great prolongation of life may be expected by the method employed, as compared with that obtained by other methods. It is generally assumed, however, by clinicians that in the treatment of diabetes it is of great importance to render patients free of glycosuria and acidosis, and that thereby tolerance may be increased and life prolonged. It seems that the method proposed offers an improved way of doing this. That the total caloric value of the diet is of importance, and not merely the actual amount of glucose-producing sugars and proteins, is shown by the fact, now well established by these studies, that where a patient is free of glycosuria and acidosis on a given diet, containing proteins and fats, with or without carbohydrates, the addition of a given amount of pure fat, without any change whatever in the amount of protein and carbohydrate, may cause such a patient to again become glycosuric. This fact together with the fact that lipaemia so often occurs in diabetes, has suggested the importance of further study of the fat metabolism in diabetes, especially a study of the fat content of the blood. Consequently it is

planned that during the coming quarter Dr McLean and Dr Stillman will carry out further studies dealing with glycaemia and lipaemia. Dr Allen is also engaged in the study of the pathological material obtained from experimental animals and cases of human diabetes to study further, by means of more delicate stain reactions, the finer changes in the pancreas occurring in diabetes.

Heart Disease:- Studies concerning the mode of action of digitalis have been continued by Dr Cohn with the assistant of Dr Jamieson. The studies made last year of the action of digitalis in patients with normal cardiac rhythm without oedema, and with blood pressure within normal limits, are now in press. During the present year studies are being made of the action of digitalis in patients with abnormal cardiac rhythm, and in patients in which oedema, and abnormally high blood pressure are present. Special studies are being made of the mode of action of digitalis in patients with fever, especially in cases of pneumonia.

In previous studies, in order to determine that digitalis was actually active in an individual, it has been necessary to push the administration to the point of altering the heart's rhythm (heart block) or of inducing gastro-intestinal symptoms. These were the most certain tests. In reviewing the electrocardiograms made during these studies it has been found frequently almost uniformly - that before these signs became manifest the shape of the so-called T wave in the electrocardiogram became altered. With greater attention to the details of calibrating the curves, it has been found that the beginning of this change can be detected easily - in two to three days - after giving the drug. This change, together with a change in conduction between auricles and ventricles, which also often occurs early, offers two new, sure criteria for deciding early that digitalis is acting on the heart. By observing these signs, patients may be saved from the disagreeable effects of this form of treatment. In a single instance abnormal primary negative T waves have been seen to become less negative, and later positive. These changes persist varying lengths of time, and the curves return to their initial form after about ten to fourteen days after stopping the digitalis.

Tests of these signs in patients with fever (pneumonia patients) have been made.

The failure of digitalis in these circumstances to lower heart rate is familiar, and its use by many persons has been discontinued. In many of these patients the electrocardiographic changes already mentioned also occur after the administration of digitalis probably after the same length of time, and with the same dosage, as in cases of cardiac disease. If further experience bears out these observations, we shall have valuable new methods of judging the value of certain stimulants in these conditions.

It has previously been supposed that for digitalis preparation to be effective in cases with fever more than the usual dose was required. Dr Jamieson has therefore compared the lethal dose of crystalline strophanthin in normal cats and in cats with experimental pneumonia, induced by insufflation. He has found that in both series of animals death occurs after the same amount of the drug has been injected; that there is no difference in the action of strophanthin in the infected and in the non-infected animals. This result parallels the observations made in patients. However, while the infected cats showed well-marked consolidation of the lungs, they failed to develop fever. It is possible that the absence of fever indicates that a true intoxication, interfering with the action of digitalis, was absent, and that, had fever been present, the result would have been different. It is planned, therefore, to repeat these experiments in dogs.

Human hearts in which electrocardiograms have supplied evidence that the smaller branches of the auriculo-ventricular conduction system had undergone pathological changes (bundle-branch lesions) have been studied in serial sections. Structural alterations were found, but it was impossible to say definitely whether these are to be correlated with the alterations in the electrocardiograms. The hearts were supplied by Dr Thomas Lewis in a state of dissection designed for weighing the cavities separately, and were not quite fitted for the purpose of the histological study because the continuity of the endocardium had been sacrificed. The failure to find an adequate lesion to account for the change may lie in this circumstance.

Further experiments on the distribution of the vagus nerves and more especially of the accelerator nerves are in progress. It has been found that the sinus node does

not form a relay in the path of the vagus nerves. The new experiments are based on the idea that during left vagus stimulation, the accelerator nerves especially are responsible for continued auricular activity.

Chemical Laboratory:- The following is a report of the work carried on by Dr Van Slyke and the physicians working under his immediate direction.

The study of the fate of the products of protein digestion, begun two years ago with Dr Meyer, and interrupted last year in order to develop reliable methods for urea determination in blood and tissue extracts, has been taken up again.

Mr Cullen and Dr McLean have investigated the question of urea formation in the liver in etherized dogs. Perfusion of excised livers by the Folin school failed to reveal an ability on the part of this organ to transform amino acids into urea, and has thrown doubt on the former view that the liver is the chief seat of urea formation. Working with live animals at varying periods after meat feeding, however, it has been found that the hepatic blood in every case contains urea in greater concentration than the portal, the increase in the urea resulting from passage of the blood through the liver varying in different experiments from 3 to 15%. Passage of the blood through the muscles causes relatively slight increase, usually none.

Mr Eebeling of Dr Carrel's department, is experimenting with portal vein fistulas in dogs. When the experiments are successful, as promises soon to be the case, it will be possible to follow the time curve of the rise of amino acids in the portal blood after the ingestion of protein; by determining at the same time the curve of the blood urea, the two curves may be related to the progress of the food proteins along the alimentary canal, as shown by X-rays. It will be of interest to ascertain how soon after the ingestion of proteins it is possible to detect the presence of their products in the blood and how soon after this the formation of urea begins. It is also of theoretical interest to ascertain whether the body begins to break absorbed amino acids into urea as soon as their absorption is under way, or whether it waits until the tissues in general have become charged with amino acids in excess.

With Mr Eebeling it is also planned to experiment with dogs having thoracic duct

fistulas, in order to determine how important a channel the lymph is for protein absorption.

Mr Cullen has assisted Dr Avery in studying the effect of immunizing horses against ~~stixx~~ pneumococci on the relative proportions of the different proteins in the blood. It is of interest to determine whether the protein fraction containing the immune bodies increases during immunization, and whether such increase in any way parallels the protective power of the serum.

Dr McLean is making a study of kidney function in diabetes, and, in conjunction with Dr Cohn's department, in heart insufficiency. The ratios of the concentrations of urea and chlorides in the blood to the rates at which these substances are eliminated by the kidney has been mathematically expressed in equations by Ambard, and Dr McLean's studies indicate that these ratios are very delicate indicators of the excretory power of the kidney. The effect on these ratios of the administration of digitalis to edematous heart patients is striking, and it is hoped that a comparison of the results of this study with electrocardiograms may decide the question as to whether the primary effect of digitalis in such cases is on the heart or the kidney.

Some of the diabetics show a peculiar, abnormally increased permeability of the kidneys to chlorides, the significance of which is still uncertain. This condition is also being studied.

In order that sufficiently numerous data on the blood chlorides might be obtained in the above work it was found necessary to devise a method which would permit accurate determinations with much less material than the 20c.c. required for the usual Volhard titration. Dr Van Slyke and Dr McLean have devised an idometric method which permits the determination of the chlorides in one or two c.c. of serum with an error of less than 1 part per hundred.

The study of the chemical constitution (amino acid content) of certain food proteins, begun by Miss Vinograd last spring in conjunction with Dr Osborne of New Haven is being continued.

Miss Vinograd with the collaboration of Dr Losee of the Lying In Hospital is engaged in a thorough study of the Abderalden serum reaction, using the Van Slyke amino nitrogen method in order to obtain a quantitative measure of the extent of proteolysis occurring. The technique has been so developed that an active serum usually gives an increase of 100% or more in amino nitrogen; so that there is no longer doubt as to either the occurrence, or the degree, of proteolysis occurring under the conditions of the reaction. It does not appear that the reaction is very specific; but a final decision as to its value has not yet been reached.

Recently several European writers have announced that in the most dangerous types of diabetes the organism loses not only its ability to burn sugar, but also its ability to metabolize the alimentary amino acids. In consequence an abnormally large proportion of the urinary nitrogen is in the form of amino acids. The determination of amino acids in diabetic urine is subject to peculiar pitfalls, and it appears uncertain that any of the clinicians reporting the above results have been aware of them. It is planned therefore to take advantage of the diabetic material in the Hospital to obtain data on this important point.

R.I. Cole