

June, 1915.

To the Board of Scientific Directors of the Rockefeller Institute for Medical Research.

Gentlemen:

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

During the months which have passed since the preceding report, the work has consisted mainly in a continuation of the work previously reported as in progress, with completion of a number of the studies which are now ready for publication.

Acute Lobar Pneumonia. The type of pneumococcus concerned has now been determined in 237 cases of pneumonia admitted to this Hospital. In addition, Dr Richardson has determined the type of pneumococcus concerned in 195 cases of pneumonia admitted to the Pennsylvania Hospital. We have thus quite satisfactory observations in 432 cases. The results are shown in the following tables:

Cases in the Hospital of the Rockefeller Institute.

Etiological Agent	No. of Cases	Percentage Incidence	Mortality in Cases not treated with Serum.
Pneumococcus type I	78	33%	25%
" " II	75	32%	29%
" " III	22	9%	45%
" " IV	48	20%	12.5%
Other Bacteria			
Influenza Bacillus	5		
Streptococcus	3		
Streptococcus mucosus	1		
Staphylococcus	2		
Bacillus Friedlander	2		
Streptococcus, Staphylococcus and Influenza Bacillus	1		
	<hr/> 14	6%	
	<hr/> 237		

Cases in the Pennsylvania Hospital.

Etiological Agent	No. of Cases	Percentage Incidence	Mortality in Cases not treated with Serum.
Pneumococcus type I	60	31%	30%
" " II	39	20%	25%
" " III	13	6%	50%
" " IV	<u>83</u>	43%	12%
	195		

The figures indicating percentage of incidence in the two series are not exactly comparable since Dr. Richardson has not included in his list the cases due to organisms other than pneumococcus. The results indicate, however, the correctness of the conclusions previously drawn from a small number of cases.

At the last meeting of the Board Dr. Janeway, drew attention to certain races of pneumococci isolated at Baltimore, which, while agglutinating in undiluted serum of type II, nevertheless did not agglutinate when then diluted serum was added to them, and when protection tests were made with them the results were not clear cut and unequivocal. Dr. Bloomfield kindly sent us these five races and these have been thoroughly studied by Dr. Avery. They were all found to be of low virulence and, as has before been noted of the type strains of low virulence, the protection afforded by the sera of different types was irregular and inconstant, in certain instances even normal horse serum was able to protect against them. All these strains were rendered highly virulent by frequent passage through mice. Now, on testing protection against these virulent strains, it was found that type II serum protected against all of them in a typical manner, while type I serum and Normal Horse Serum had no protective power whatever. The agglutinability of these strains, however, has in this manner not been increased, It seems evident therefore that these are true type II strains, but which have relatively slight agglutinability. This is quite analogous with what is known of *B. typhosus*, certain strains of which are slightly agglutinable. It is not thought that these experiments offer any evidence that the atypical strains are changed into fixed types.

The occurrence of such strains, moreover, need not necessarily cause any confusion in the method of diagnosis of type employed by us.

Serum Treatment of Cases due to Pneumococci of type I. Forty-eight cases due to pneumococci of type I have now been treated with immune serum. Of these, four died, contrasting with the mortality of 25 - 30 per cent. in the untreated cases of this type. Of the four fatal cases, however, one died suddenly during convalescence from pulmonary embolism; two of the cases were only treated when they were almost "in extremis", a few hours before death. This leaves only one case that can be considered to have been treated with any hope of success, and this was treated only on the fifth and sixth days, the patient dying on the sixth day.

Epidemiology. Dr. Dochez and Dr. Avery have completed their study of carriers. The types of pneumococci occurring in the mouths of 113 normal individuals have been studied. Pneumococci of the fixed types were found 11 times, and these were always present in the mouths of persons in close contact with pneumonia patients, the type found in each case being that present in the case of pneumonia with which the person studied was in contact. In 55 other persons pneumococci were also present, but these were all of the atypical group, Group IV. The persistence of fixed types in the mouths of pneumonia patients and of carriers has also been studied, the final results agreeing roughly with those previously reported.

Anablastic immunity. Dr. Dochez and Dr. Avery have completed the study of anablastic immunity, and the results are ready for publication.

Extraction of Immune Bodies from Serum Precipitates. Dr. Chickering has continued the study commenced by Dr. Gay and Dr. Chickering and has so developed the method as to obtain constant results. The best method of extraction has been found to consist in dilute sodium carbonate at 42° C. One patient suffering from an infection with a type II pneumococcus has been treated with such an extract given subcutaneously in frequently repeated doses. In this case the clinical results were excellent, and the tests of the patient's blood seemed to indicate that this

treatment caused a greater increase in immune bodies than had previously been observed. The work of Dr. Bull also suggests that this may possibly be the method of choice as by this method the immune bodies may reach the blood more slowly. This method will be tried further in cases of type II infection. In the study of these extracts a number of observations of theoretical interest have been made. The paper by Dr. Chickering dealing with these points is ready for publication. Dr. Chickering has been granted leave of absence for six months. He goes to work with Dr. Gay and will cooperate with him in treating a series of patients with typhoid fever by an analogous method. He will return in November to continue his work here on pneumonia.

Effect of Combined Injection of Optochin and Immune Serum. Dr. Moore has worked in the Hospital during the past six weeks and has extended his studies of optochin, commenced with Dr. Flexner, in an endeavor to learn whether the effectiveness of immune serum may be increased by the addition of this drug. The results have been quite clear cut and show that the maximum dose against which immune serum will protect is definitely increased when the animals are treated at the same time with .5 gm. of optochin given simultaneously, or better, when 0.5 gm. is given the first day, 0.45 gm. the second day, and 0.4 gm. the third day. These doses, however, are relatively very much greater than the doses that can be safely administered to man. Experiments are now in progress with larger animals of other species to see whether it is possible that a relatively smaller dose may be effective in larger animals.

Methods of producing Active and Passive Immunity. Studies carried out in large series of animals show that the development of immune bodies in the serum of immunized animals is inhibited if very large doses of dead culture or antigen prepared in various ways are employed. Eighteen rabbits so treated failed to show any immune bodies in the blood whatever. They all showed some active immunity, however, in certain instances of considerable grade. These experiments bring further proof that there are certain features in active immunity besides the

presence of immune substances in the body fluids. We have called the former type of immunity somatic immunity in contrast with humoral immunity.

All the studies indicate, however, that pure humoral immunity may be effective if the infection be not extreme, and if the concentration of the immune bodies in the blood be of sufficient degree. The attempts to increase the effectiveness of the humoral factors by other methods of immunization have shown that this may be done by frequently repeated small doses of dead cultures or probably better by giving frequently repeated small doses of live culture, combined with immune serum. From the studies on rabbits and goats it seems that a very definite advance has been made in the practical method of immunization;

Heart Disease

Dr. Cohn and Dr. Jamieson

The records from cases of pneumonia have been collected and are being studied; first, to see, in properly standardized curves, such as these, what changes occur in the electrocardiogram as the result of the disease; second, to see whether digitalis causes changes in the curves from these patients similar to those seen in the curves from patients suffering from heart disease. The studies indicate that certain changes do occur as the result of pneumonia, and these changes serve as a basis for determining the degree and nature of cardiac involvement due to pneumonia. In regard to the second point, it has been found that digitalis does induce in pneumonia patients changes similar to those seen in patients with non-febrile heart disease, as indicated by electrocardiographic curves.

The problem of the reliability of the electrocardiogram as an indicator of cardiac hypertrophy is being studied. Comparisons are being made with the X-ray shadows, and also with the weight of heart muscle. Dr. Jamieson is trying to produce hypertrophy in dogs by work (on a treadmill). Dr. Cohn is making a similar effort in dogs in which artificial valve lesions have been produced.

The study of patients with chronic heart disease is being continued along the lines previously indicated.

Studies concerning phenomena of contraction and conduction are planned. To

render these studies possible it has been necessary to install a second galvanometer, so that simultaneous records from two points on the surface of the heart or on other contracting organ may be made. This second galvanometer was ordered last autumn but, owing to delays incident to the war, has just been installed. The installation of this galvanometer is of importance in the work, not only because these special studies are rendered possible, but also because the new instrument is of much greater accuracy than the old one, and so much more exact studies are rendered possible. The new instrument was mainly constructed in this country according to design furnished by Dr. W. B. Williams, and the tests have shown that the instrument entirely fulfills the expectations.

Diabetes. Dr. Allen is continuing experiments showing the effect of raising and lowering metabolism (food, temperature, exertion, thyroid, etc.) upon experimental diabetes, observations thus far supporting the idea that increased metabolism increases, and diminished metabolism diminishes the strain upon the internal pancreatic function. The coming of Dr. Palmer has made possible a series of experiments to test the hypothesis of combined sugar. This series of experiments deals with feeding and injection of sugar in normal and diabetic animals, with tests of the blood for sugar, estimation of hemoglobin content, and estimation of various physical properties, (viscosity, surface tension, freezing point, conductivity) and parallel observations concerning the urine, lymph and tissues.

Dr. Stillman is carrying on the treatment of patients on the lines previously laid down. The number of patients at any one time averages from ten to fifteen. He is studying particularly the question of acidosis and blood-sugar. In regard to acidosis, the analyses made are for the three acetone bodies and ammonia in the urine, and $C O_2$ tension in the alveolar air, in parallel with the blood studies of Drs. Van Slyke and Cullen. The $C O_2$ determinations in the alveolar air, and blood seem to offer the most satisfactory index of acidosis. Patients with slight acidosis or none may, during the initial fast, show the same slight acidosis as a fasting normal person. Cases with severe acidosis, however, invariably show

a decrease in acidosis during the fasting. All tests confirm the clearing up of acidosis under the treatment. Sugar is determined in the whole blood and in the plasma, with some idea of observing the permeability of the corpuscles, but chiefly to learn whether the treatment reduces the sugar content to normal. This has proved to be so in some very severe cases, but in some older patients it may perhaps not be necessary to attempt this, and the question whether it is possible in every case cannot be answered at present.

Studies carried on in the Chemical Laboratory.

Much of the work reported in April is still being continued, but some of the problems have been brought to a sufficiently definite conclusion to prepare for publication:

Studies of the Abderhalden Reaction by Dr. Van Slyke and Miss Vinograd

Sufficient data have been collected with our quantitative method on the protease content of normal and pregnant sera to justify considering the problem as closed, and the Abderhalden reaction for pregnancy as worthless.

Miss Vinograd, with material furnished by Dr. Isaac Levin, has had similar results in attempting to apply the Abderhalden reaction to cancer diagnosis. As only one preparation of cancer tissue was used in the tests made, however, the uselessness of the reaction for cancer diagnosis cannot be affirmed with the same degree of finality that appears justified in reporting the results of the pregnancy test.

Diabetic Acidosis. Dr. Van Slyke, with Drs. Cullen and Stillman, is making an extended study and has obtained sufficient data for publication on the first points of attack. Data have been obtained covering, in some cases, months, with almost daily analyses of the urine and determinations of the alveolar carbon dioxide, with, for comparison, determinations of the actual reserve alkalinity of the plasma by our new methods, viz. the determination of its carbon dioxide capacity, and of its ability to maintain a neutral hydrogen ion concentration after addition of acid. These tests show the actual condition of the blood, and are

so delicate that they readily show even the slightest physiological variations in reserve alkalinity. The alveolar carbon dioxide determinations run fairly parallel with the blood results, and we have not yet observed a pathological change that was not shown simultaneously by both. After the direct blood tests, it appears that the alveolar carbon dioxide tension is the most sensitive indication of a state of acidosis. Urine analyses of any kind are much less reliable, although a gross change in the direction of acidosis is usually accompanied by an increase in the ammonia output. The acetone bodies, on the other hand, may give no warning, even on the verge of comma.

One point in which the blood and alveolar air tests promise to be of aid in the Allen Treatment of diabetes is in controlling the condition of fasting patients. Some develop no acidosis, or very little; but in other cases acidosis does develop rapidly, becoming marked after a single day's fast. A control by quick and sensitive methods for detecting the presence and degree of acidosis seems important, for as yet there is no way of telling which cases will develop acidosis on the treatment, and which will not. The sensitiveness of the methods developed has uncovered a physiological problem as an offshoot of the acidosis work. It has been believed by some authors that during digestion acid products were poured into the blood, and that these were responsible for the increased general metabolism and heat production noted after a meal. By others it has been believed that, on the contrary, the alkalinity of the blood increases, because of the secretion of gastric hydrochloric acid. Experiments on men which we have already performed to test this point have already shown that an appreciable increase in blood alkalinity usually follows a meal. The work will be continued on both animals and men, the effect of digestion of carbohydrates, fats, and proteins being studied, and also the effect of stimulation of gastric secretion in the absence of digestible foods, so that the relative effects of H Cl. excretion and of absorbed digestive products of various nature of the blood alkalinity can be determined.

The work of Miss Vinograd with Dr. Osborne of New Haven on the amino

acid composition of food proteins is now being prepared for publication. The basic constituents of rice protein, wheat gliadin, and milk albumin have been determined by entirely different methods in the two laboratories, so that errors by each could be eliminated. Consequently these determinations are probably the most thoroughly controlled that have ever been made in amino acid determinations of proteins. The results have a direct bearing on the interpretation of the important work of Mendel and Osborne in their "Growth Studies", in which lactalbumin and gliadin have been used as representative proteins.

Nephritis. Dr. Mc Lean's studies with the sensitive functional tests of urea and salt excretion, are being continued, with a gradually accumulating mass of data which promises to be of definite value in the diagnosis and prognosis of different types of nephritis.

One case of post-pneumonia nephritis was particularly interesting as the nephritis was accompanied by an exceptional type of acidosis. Plasma tests showed a degree of acidosis which, at its height, was nearly equal to that seen in diabetics threatened with coma, but the ammonia excretion, instead of being increased, was abnormally low, being less than one per cent of the total nitrogen. During convalescence the return of blood alkalinity to normal has accompanied the restoration of kidney function, and the ammonia excretion has risen gradually to normal. Henderson and Palmer, of Harvard, have reported nephritics in whom a low ammonia excretion accompanied an acid urine, but could not demonstrate existence of actual acidosis, as has been done by the plasma tests in this case.