

REPORT
OF THE
DIRECTOR OF THE HOSPITAL
TO THE
BOARD OF SCIENTIFIC DIRECTORS OF
THE ROCKFELLER INSTITUTE FOR MEDICAL RESEARCH
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I N D E X

| | <u>Pages</u> |
|--------------------------------|--------------|
| Hospital | 1 - 17 |
| Department of Animal Pathology | 18 - 27 |
| Babies' Hospital | 28 - 31 |

REPORT OF THE WORK IN THE HOSPITAL.

Dr. Cole.

During a large part of the past quarter the director and several members of the staff have been away from the hospital, engaged in army activities. While their work during this period was not carried on within the walls of the hospital, it nevertheless was directed toward the solution of problems on which the hospital staff has been engaged, and therefore should be considered a part of the actual work of the hospital.

In my last report I drew attention to the fact that pneumonia due to streptococci was probably becoming prevalent in the army. This view was based on the following observations. Among 76 cases of pneumonia in soldiers treated in this hospital up to the middle of January, 4 were due to streptococci. In December Dr. Dochez was sent by the Surgeon General to Camp Bowie, and his observations there indicated that a considerable number of the cases of pneumonia occurring there were not cases of typical lobar pneumonia, but were cases of broncho-pneumonia associated with the presence of haemolytic streptococci. Two autopsies which had been performed here on the streptococcus cases and the observations of Dochez and Jobling at Camp Bowie indicated that the pathological anatomy of the streptococcus cases differed essentially from that of true lobar pneumonia. It seemed of great importance to learn more concerning the nature of this acute pulmonary infection. This was especially important for us in view of the fact that considerable difficulty was being encountered in certain of the camps in determining the type of pneumococcus responsible for a considerable number of the cases, and also that, owing to this difficulty, a satisfactory selection of cases

suitable for serum treatment was not being made.

Consequently the matter was presented to Col. Russell and Col. Longcope of the Surgeon General's office and it was decided that a group of men should be sent by the Surgeon General to one of the army camps for the purpose of studying this problem. In order to carry on this work satisfactorily the civilians in the group chosen were given temporary commissions as contract surgeons. This commission included Dr. Cole, Dr. Avery and Captain Dochez from this hospital. In addition there were Dr. MacCallum and Lieut. von Glahn from the Johns Hopkins Hospital, who were especially detailed to study the pathological anatomy, Lieut. Blake formerly of this hospital, Captain Kinsella and Lieuts. Rivers, John and Stevens.

It was decided to carry on the study at the Base Hospital, Fort Sam Houston, San Antonio, Texas. In the prosecution of this work the director was absent from his regular hospital duties from January the 28th to March the 25th.

The preliminary survey of the cases in the base hospital made it evident that all the cases were not of the same variety and that our present knowledge did not permit a ready differentiation of the cases of the different kinds. An extensive statistical study was therefore out of the question and therefore a very careful clinical, bacteriological and pathological study of a limited number of cases was undertaken. The following is a copy of the conclusions from my report to the Surgeon General.

DISCUSSION AND CONCLUSIONS

"The studies indicate that the cases of pneumonia at the Base Hospital, Fort Sam Houston, are chiefly of two varieties: first, acute lobar pneumonia, which does not differ essentially from that which occurs elsewhere; and second, broncho-pneumonia, which in most cases, at present

3

at least, follows measles.

The pulmonary lesions in most cases of this type of broncho-pneumonia are characteristic and specific and have been studied and described by Dr. MacCallum. The etiologic agent in all the cases studied by us has been *Streptococcus haemolyticus*. There is no evidence presented by this work that indicates that pneumococcus causes the lesions and symptoms of this condition. Pneumonia following measles may be due to pneumococci, but the pulmonary lesion is then of the lobar variety. This complication of measles, however, is comparatively rare. Cases may occur in which both types of infection and both types of lesions are present. The sequence of events in such cases is difficult to determine and is probably not always the same.

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Streptococcus infections following lobar pneumonia occur with considerable frequency in this hospital. Broncho-pneumonia similar to that following measles may also probably occur as a sequel of acute lobar pneumonia, though the evidence for this is not conclusive. Whether in the cases of streptococcus empyema, complicating lobar pneumonia, pulmonary lesions due to the streptococci are always present or not, has not been determined.

The mortality in the cases of broncho-pneumonia is very high; that of uncomplicated lobar pneumonia is low. Practically all the fatal cases of broncho-pneumonia are complicated by empyema. The incidence of empyema among the uncomplicated cases of lobar pneumonia does not seem to be extremely high.

The number of measles cases infected with haemolytic streptococci on admission to the hospital is not large. The majority of the patients with measles acquire this organism during their stay in the hospital. The chance of developing post-measles streptococcus infections is therefore

increased by residence in this hospital.

A very large number of the patients in this hospital suffering from acute lobar pneumonia have haemolytic streptococci in their throats. We have no direct evidence that they acquire these bacteria in the hospital, but the presumptive evidence indicates that many of them do so.

The work indicates that the high incidence of pneumonia in this hospital, and the resulting high mortality, has been due, to some extent at least, to infection occurring within the hospital itself. The conditions are not unlike those surrounding puerperal fever and surgical wound infections. While in measles, raw surfaces do not exist on which infection can occur, this disease renders the respiratory mucous membrane especially vulnerable to infection with streptococci. Possibly in other diseases, as scarlet fever and even lobar pneumonia, similar conditions exist. When infection is once started in a ward in which the patients are closely associated, the streptococci become widely distributed; they probably gain in virulence with repeated transfer through the human subject, and serious and wide-spread infection results.

Probably the conditions in this hospital are not unique. It is possible that the wide-spread incidence of fatal pneumonia in the other army hospitals may have a similar explanation."

Upon our return from Texas we learned that a considerable number of soldiers suffering from acute pulmonary streptococcus infection were also being admitted to the Hospital of the Rockefeller Institute. Most of these cases give no history of previous measles infection. A considerable number of them suffer from empyema. It has been impossible to learn as yet whether or not these cases are identical with those seen at San Antonio. In any case empyema is a most serious complication

and the further study of this condition is most important.

About 150 cultures of haemolytic streptococci, the source of each one of which is known, were brought back with us from San Antonio. Dr. Dochez and Dr. Avery are now engaged in a complete study of the cultural and especially of the immunological properties of these strains. It is obviously of very great importance to learn whether all the organisms obtained from these cases of pneumonia and empyema are identical and especially whether they are identical with the haemolytic streptococci which we have isolated from normal throats.

During my absence the hospital facilities have been largely devoted to the care of patients suffering from pneumonia, soldiers, sailors and civilians, and to the instruction of army medical officers in the care and treatment of patients suffering from this disease. Since November first 25 army medical officers have received or are now receiving training here. The large amount of clinical material has made it possible for these men to receive an extensive experience. Since October first of this year 235 patients suffering from pneumonia have been treated; 100 of them were soldiers, 28 sailors, and 107 civilians. Our records show that of these cases 185 were frank lobar pneumonia, and of these 66 were due to Type I pneumococci, 32 Type II, 25 atypical Type II, 13 Type III, and 49 Type IV. Of the remainder of the cases 41 have been considered to be due to streptococci. This figure, however, may not be absolutely correct owing to difficulties in diagnosis. Thirty-five of the patients have suffered from empyema. In 10 instances cultures from the empyema fluid showed the presence of pneumococci. In 25 cases streptococci were present. Of these 25 cases 12 have already died. Thirty-two of the cases of empyema were operated upon; of these

10 have died and 22 are still living. The high mortality in the empyema cases even under conditions so satisfactory as those in our own War Demonstration Hospital afford further evidence of the great need for further study of this condition at the present time.

Antipneumococcic Vaccination.

In my last report I stated that preliminary work on this subject was being undertaken and that Captain Austin had been detailed to the hospital to work on this problem. The work has been continued during my absence and its practical application in a considerable number of soldiers has been made at Camp Upton. All the vaccine has been prepared here and the work has been carried on jointly by Captain Austin working here and Major Cecil at Camp Upton. The following report has been prepared by Captain Austin.

"The following report covers the preparation and administration of antipneumococcic vaccine and the study of the effects of the vaccination on the sera of a few of the vaccinated cases and the statistical data upon the incidence of pneumonia among the vaccinated and unvaccinated troops up to March 24.

PREPARATION: The media adopted was 0.5 per cent glucose broth, one liter of which incubated 12 to 14 hours gives the same yield as 10 liters of plain broth or as 100 Blake bottles of glucose agar. Organisms grown in glucose broth give as good agglutinin production in rabbits as those grown in plain broth and better than those grown on agar. Centrifuging was done at first on the two large bucket centrifuges, taking 2 and 5 liter charges respectively. Run continuously from 9:30 a.m. to 5 p.m., these would centrifuge about 18 liters. A Sharples centrifugal centrifuge^{was}

later installed in the laboratory, which centrifuged 15 liters in 90 minutes and could be prepared for a repetition of this yield in a half hour. This made the handling of 25 liters of broth daily, the capacity of the media room, easily possible. The vaccine has been suspended in salt solution and has received a double heating at 55 degrees for a half hour, once before centrifuging and again afterwards. Standardization has been done by dilution and comparison of the opacity with sealed tubes of known suspensions, controlling this method with frequent Wright counts. Tricresol was added and the vaccine was bottled in 20 cc. bottles. One dose was contained in each 0.5 cc..

ADMINISTRATION: Preliminary experiments on nine members of the Hospital staff were made, each receiving a first dose subcutaneously of 8 billions each of types I, II and III. Severe general reactions followed in three cases and moderate to severe local reactions in seven cases. The dosage for use in the Camp was accordingly reduced, 1 Billion of each Type I, II and III being given at the first inoculation and 2 billions of each type at each of three subsequent inoculations at weekly intervals. The total dosage was therefore 7 billions of each of the three types. All injections were made subcutaneously. The vaccine was distributed by Major Cecil to the Regimental Infirmaries and the injections and records were made by the regimental surgeons under his direction.

RESULTS: The sera of 13 cases were studied before inoculation. None showed any agglutinins. Only one showed any protection (against Type I). The sera of 30 cases were studied 8 days after the last inoculation. 16 showed agglutinins against Type I and 14 against Type II. In 7 cases the agglutination occurred in a dilution of 1:10; in the other cases at lower dilutions. Protection tests were made on 28 of the 30 sera.

Mice were protected against 0.001 cc. of culture (1000 lethal doses) of Type I in 15 cases and against 1/10 this dose in 21 cases. Mice were protected against 0.001 cc. of culture Type II in 15 cases and against 1/10 this dose in 24 cases. No agglutinins against Type III were observed. Mice were protected against 0.0001 cc. of culture of Type III in 6 cases. Eight of these 30 cases received about $1\frac{1}{2}$ times the standard dose; two received $\frac{1}{2}$ the standard dose. The increased dose increased the amount of agglutinins definitely but had very little effect on the protective power. Nine cases received the total standard dose in a single injection; four received the total standard dose divided into 7 daily injections. No clear difference between the response in these groups could be detected.

STATISTICAL RESULTS:

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| Average strength of Division Feb. 4 to Mar. 24, the period of the inoculation, | 30,000. |
| Number of troops vaccinated against pneumonia, | 12,570. |
| Number of severe local reactions, many with sterile abscesses, | 194. |
| Number of severe general reactions (quarters or hospital) | 25. |
| Number of cases of pneumonia occurring among unvaccinated troops, Feb. 4 to Mar. 24, | 83. |
| Etiology determined, | 63. |
| of Type I, II or III, | 14. |
| Number of cases of pneumonia occurring among vaccinated troops, Feb. 4 to Mar. 24, | 17. |
| Etiology of all determined, of Type I, II or III, | 1. |
| (A Type I case occurring within 36 hours of the first inoculation). | |

Records of vaccinated troops have been made and complete records of cases of pneumonia occurring in the Division are being made. Arrangements have been made with the Division Surgeon for the continued typing and recording of all cases of pneumonia occurring in the Division during its foreign service and the necessary diagnostic sera have been provided for this purpose. The severe local reactions, occurring in about one case in 65, amounting in some cases to sterile abscess formation, occur apparently in certain susceptible individuals and these individuals react severely to each injection. They may develop a severe local reaction to the first injection, an abscess after the second (or vice versa) or they may develop an abscess after each injection. The abscesses develop slowly, beginning to fluctuate about the seventh day after inoculation. They have not incapacitated the men nor kept them from duty. Cultures from the abscesses have always been sterile. We have found that these same men develop a marked reaction to the intradermal injection of a dilute pneumotoxin prepared by dissolving pneumococci in bile. This reaction may serve as a means of picking out such individuals before vaccination.

It will be of importance to study the serum of such individuals before inoculation and to determine whether they are immune. It is also possible that this test may permit the institution of some modified method of inoculation, by which the abscess formation may be avoided.

Studies are in progress concerning the relative merits of antigens prepared from broth and from solid media, heated and killed without heating, and injected in salt solution or in oil. "

Dr Cohn

The latter part of January Dr Cohn entered the army and has been engaged in the organization of the cardio-vascular work. Early in March he left for duty in France.

I. A clinical study of the action on syphilitics of the drug

"A-189", synthesized by Dr. Jacobs, was begun on January 3 by Dr. Stillman. Recently Dr. Stadie has entered the hospital from the Presbyterian Hospital and taken part in the work. The initial dosage and mode of administration were based on the animal experiments of Drs. Brown and Pearce, and planned in consultation with them.

The effect of the drug on the heart during and between injections was controlled by Dr. Cohn with the electrocardiogram, the results being consistently negative. The effect on the kidneys was controlled by urea, chloride, and phenolsulphonphthalein excretion tests, as well as by albumin and microscopic tests, likewise with negative results. No evidence of organic injury could be obtained at any stage of the treatment.

At first the attempt was made to inject intravenously the drug dissolved in 3 times the amount of sodium hydrate required to neutralize its phenolic hydroxyl groups and dissolve it. The reason for so doing was that the results of Brown and Pearce had shown excess of alkali to decrease the toxicity of the drug in rabbits and increase its therapeutic effect, without injury to the veins. In patients, however, the alkali caused thrombosis so frequently that the excess was reduced until at present only 1 molecule instead of 3 is used to dissolve the drug. Under these conditions there is no vein injury, and the therapeutic effect seems to be maintained. The substance dissolved in 1 molecule of alkali can be injected in a concentration of 1 to 350 without vein injury or other apparent harm.

Unfavorable reaction on the part of the patients during or after injection appears to be much less than in the case of Salvarsan. In two out of thirteen cases the first injection was followed by a temperature of 101° to

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102° and slight discomfort. Subsequent injections did not elicit this reaction even in these patients. In the others there was no discomfort either during the injections or the 24 hours following them. When, however, doses were crowded very closely, two or three of 0.5 gram each within a week, severe abdominal cramps resulted in most patients. The cramps began 1 to 3 days after the last injection and lasted at intervals for 2 or 3 days. There was no evidence of injury to heart or kidney function, or of other organic injury either during or after the attacks, and they left the patients without any detectible residual damage. With doses distributed at weekly intervals there has been no recurrence of the attacks.

As the result of the first three months' experience we believe that we have overcome the difficulties in the way of a fairly satisfactory administration of the drug. The substance is dissolved in 1 molecule of N/2 sodium hydroxide, and diluted with 350 parts of 0.9 per cent sodium chloride. The solution thus obtained is injected intravenously by gravity. The first dose is 5 mg. per kilo. body weight. Three days later, and thereafter at weekly intervals, doses of 10 mg. per kilo. are given. No other drug has been given until negative Wassermann reactions have been consistently obtained. Thereafter mercuric inunctions and iodide therapy are instituted preparatory to discharging the patient.

Results. Thirteen cases have been admitted to the hospital since January 3 - 11 soldiers and 2 civilians. Twelve of these cases are still under observation. One of the civilians refused further treatment after 4 injections and was discharged from the hospital at his own request.

(a) Clinical manifestations have been cleared up in a most satisfactory manner. (Chancres, cutaneous rashes, mucous patches and condylomata.)

(b) Lesions containing treponemata have been sterilized after 2 to 3 injections.

(c) Wassermann reactions. Of the 9 patients who have been under treatment for more than two months, 7 have changed from + + + + to negative Wassermans. One, a civilian, refused further treatment after four doses. The remaining patient has changed from + + + + to +.

Arsenic excretion. The arsenic of the drug is excreted partly in the urine, partly in the feces. The drug is retained in the body for a considerable time, as excretion continues for three weeks or more after dosage is stopped. During this period the retained drug appears to continue to exert its therapeutic action, for at least two Wassermann reactions were observed to clear up two or three weeks after injections had been temporarily suspended because of the cramps reported above.

Experiments on rabbits indicate that the final elimination of the arsenic from the body is complete. Rabbits were heavily injected, and kept some weeks until arsenic no longer was excreted in the urine. They were then killed and the different organs analyzed for arsenic. No more was found than the traces observed in normal controls. Apparently disappearance of arsenic from the urine indicates that the drug has entirely left the body.

2. With Dr. Palmer work was reported last year on a method for the estimation of total organic acids in urine. The process at that time involved a combination of gravimetric and volumetric methods, and was rather laborious. We now find that it can be greatly simplified. By shaking with an excess of calcium hydrate carbonates and phosphates are precipitated. The filtrate is neutralized to phenolphthalein, and is then titrated with acid using methyl orange as indicator until a maximum color change is attained, which occurs

when the hydrogen ion concentration reaches that of a thousandth-normal HCl solution. At this point organic acids are practically all set free, but mineral acids, aside from carbonic and phosphoric, to only a slight extent. Consequently the titration following treatment with calcium hydrate gives an approximate and extremely simple estimation of the organic acids. In diabetic urines tested the organic acid excretion in ketonuria exceeded the normal excretion by amounts corresponding closely to the sum of the hydroxybutyric and diacetic acids present.

3. Dr. Goto, a voluntary assistant, is engaged in a study of the location of the reserves of mineral alkali which are drawn upon in acidosis. Rabbits were given doses of N/5 HCl by stomach tube daily in such amounts that death occurred after 2 to 4 weeks. The soft tissues and skeletons are being analyzed separately for phosphates, sodium potassium, and calcium. It is hoped that the results will indicate the relative extent to which the skeleton and soft tissues contribute their mineral constituents to neutralize unusual amounts of acid introduced into the organism. The urines are also being subjected to mineral analyses.

4. Dr. Goto has also, with Dr. Allen's advice, made an interesting study of renal diabetes on himself. He regularly excretes small amounts of sugar after taking meals with ordinary amounts of carbohydrate. The excretion is not accompanied by hyperglycemia, however, and there appears to be no loss of sugar-burning power.

5. Dr. Goto's work required a method for estimating carbonates present as calcium carbonate in bones, and a method was consequently devised which is apparently superior in speed and simplicity to the conventional methods now used for determining carbonates in mineral analyses. The process depends,

like the blood bicarbonate method previously reported, on the rapidity with which carbon dioxide is removed from water solution in a vacuum. In this case, the solid carbonate is weighed into a test tube, and the latter is suspended in a suction flask which contains an excess of N/10 barium hydroxide solution. The flask is evacuated, and dilute hydrochloric acid is run onto the carbonate in the test tube. The CO₂ escapes immediately, and is completely absorbed in about 3 minutes by the barium hydroxide. After filtering off the precipitate of barium carbonate, the excess of hydroxide is titrated with N/10 acid.

6. Dr. Dernby, a voluntary assistant has studied with Dr. Avery the effect of the reaction of culture media on the growth of pneumococci. The latter were found to be sensitive to relatively slight changes in hydrogen ion concentration. The growth zone for all types lies between neutrality (pH = 7) and an alkalinity (pH = 8) about equal to that of blood serum from which CO₂ has been allowed to escape by exposure to air. Outside of this narrow zone no growth occurs. Within it growth is most rapid at pH = 7.8.

7. Dr. Dernby has also studied the autolytic enzymes of the tissues. He finds that each of the tissues studied (liver, spleen, pancreas, stomach mucosa) contains both trypsin and pepsin, although in the pancreas trypsin is so abundant that special methods are required to detect the pepsin, while conditions are reversed in the stomach mucosa. The optimum conditions for self-digestion of tissues appear to be those under which both enzymes can act, the pepsin accomplishing the first steps of digestion, the trypsin completing the hydrolysis to the stage of amino acids. These conditions are met by a hydrogen ion concentration of $10^{-6.6}$, which permits both enzymes to act, although it is not the optimum for either. The conditions are also met by first suspending the tissues in acid solution, in which the pepsin acts, then transferring them to alkaline solution, where the trypsin becomes active.

The clinical monograph is now complete as far as the writing is concerned. While I think it suffers from the defects which I predicted, it will be found to contain groups of clinical experiments which I have been able to carry out, concerning the influence of metabolic variations represented by exercise and more especially by changes in the fat and total calories of the diet. The basic principle of limiting the total diet and metabolism in the treatment of diabetes is believed to be adequately established by these experiments. The permanency of the results effected by this method has also received a test, so far as the principle of treatment has been followed. I am convinced that certain cases of diabetes will progress downward in spite of any dietetic treatment. These apparently are not more than a small minority, as far as present evidence indicates. We have a series of patients in various stages of diabetes, who have been under observation for from one to four years now, without alteration in tolerance except as can be accounted for by diet. At one extreme are youthful patients taken in the early and more hopeful stage of their diabetes, such as Natalie Colby, who has shown no decline in tolerance, and Stuart Bradley, who apparently is progressing toward recovery. These patients appear normal and lead normal lives, with care only in diet, though they are of the type who formerly died regularly within a few months. At the other extreme are the examples of diabetes of maximal severity, such as Stephen O'Brien and Miss Martin, who are hopeless invalids, unable to live outside this hospital. The important feature of such cases is that even these patients apparently continue to live through months and years, unable to gain tolerance, but yet not in any way perceptibly progressing downward. The observations would indicate that in the majority of cases the etiologic basis of

16

diabetes is not an inherently progressive process. The great majority of our high proportion of deaths have been due either to disobedience of patients or a mistaken plan of treatment.

It has been impossible to pursue the clinical study intelligently without an accompanying pathological study. This has included both animals and patients, and a preliminary sketch of the results is included as one chapter of the monograph. There is reason to believe that the basis of diabetes is invariably pancreatitis, probably very often of acute character. This holds out the hope of preventing downward progress if injury from diet is avoided. The nature of the injury from diet is conclusively established by both animal experiments and observations of human specimens. The functional overload results in a characteristic form of degeneration of the islands of Langerhans, which does not occur when the diet is kept within the true tolerance. In addition to the extensive animal work, I have already examined several hundred human specimens, and there is a little more work in this direction to be done before complete publication.

It is hard to make a detailed report of the chemical studies now approaching completion, except by reference to previous outlines. The conception of diabetes as a disorder of total metabolism rather than of carbohydrate combustion alone, which is the underlying basis of this treatment, presents a broader problem and requires more extensive experimental support than has apparently been appreciated in this institute, and the work involved is not likely to become clear to others than the participants until the finished material can be turned in for publication. The following lines, which I sketched in Staff Meeting a year ago, are included in this work:

First: The defect of carbohydrate metabolism is distinguished from

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the simple loss of sugar occurring with such conditions as phloridzin poisoning.

Second: The defect of protein metabolism necessarily appears in the form of the carbohydrate and fatty end-products, but a few suggestive observations concerning amino acids have been made.

Third: Since carbohydrate and protein were already restricted in diabetic diets, the chief investigation has been demanded by the fat metabolism. This has been in two branches, the first indicating that diabetic acidosis is a specific fault of fat metabolism and not due merely to loss of sugar, the second showing the specific nature of diabetic lipemia. These studies will give the treatment a scientific instead of an empirical basis. They can easily be finished by this summer, but I am not sure that the long series of papers giving the results will then be complete. This publication may encroach by a few months upon the coming year.

As the research, so far as I have guided it, has been a unit, its completion marks a good stopping point; and in view of the military situation, I shall acquiesce in bringing the entire investigation to a close.