REPORT OF THE

DIRECTOR OF THE HOSPITAL

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To the Corporation of
The Rockefeller Institute for Medical Research

Gentlemen:-

One year ago the Hospital was practically a military hospital. The chief activities concerned the care of sick soldiers, the instruction of army medical officers and assistance to the government in the solution of immediate practical problems. Practically all the members of the staff of the Hospital had entered the army, many of them were in France, and research, " the diligent inquiry and laborious, persistent search of truth", was at the lowest level since the Hospital was opened.

Today the Hospital is again an institution for investigation. Some of the men have returned to their old activities. Some have gone elsewhere, but their places have been filled by capable, well-trained men. Enthusiasm for obtaining new knowledge about disease is in the air; many of the men have already entered diligently upon the solution of new problems.

A year ago it seemed doubtful whether at the end of the war any spirit of investigation would remain, or students to do the investigating. Today it seems certain that this spirit is alive, and that men, a few years older it is true, are still ready to quietly undertake the study of disease.

It is hoped and believed that the reorganization of the Hospital is in progress and that the coming year will be the best we have ever had.

Hospital Staff.

During a large part of the past year the staff has consisted of a few regular members of the staff who did not enter the army or were assigned to duty here, in addition to the medical officers who were ordered here for special training. Following the signing of the armistice and the release of men from military service, some of the old members of the staff returned, but it was impossible to satisfactorily reorganize the staff before the beginning of the summer vacation.

During the past months numerous additions and changes in the staff have been made. The most important loss has been that of Dr. Dochez, who goes to Johns Hopkins University, where he and Dr. Palmer, also a former member of the staff, become Associate Professors of Medicine. Dr. Dochez has been associated with the Hospital since its opening and he should share very largely in any credit for the results of the Hospital activities. His departure is a distinct loss to the Institute, entirely apart from the personal loss to all the workers.

Among the new appointments on the staff of the Hospital are the following; most of these men are only now undertaking their new duties:

Dr. Robert Levy has been appointed Resident Physician. Dr. Levy has had a large clinical experience as Assistant Resident Physician at Johns Hopkins Hospital.

Dr. Homer Swift has been appointed an Associate

in Medicine. It will be remembered that Dr. Swift was formerly a member of our staff and made important contributions to the subject of the treatment of tabes and cerebro-spinal syphilis. He left us to become Associate Professor of Medicine at Columbia University and later was appointed Professor of Medicine at Cornell University, but before taking up his duties there, entered the army and was sent overseas. Here he did important and distinguished medical work, taking an important share in the investigations which resulted in showing that trench fever is transmitted by body lice. Dr. Swift will undertake the investigation of acute articular rheumatism.

Dr. Francis Blake has been appointed Associate in Medicine. Dr. Blake was also formerly a member of the staff. A graduate of Harvard Medical School and interne at Peter Bent Brigham Hospital, he worked one winter in this Hospital under a Harvard Traveling Fellowship. While here he carried on interesting studies concerning pneumonia. He was later made Associate Professor of Medicine at the University of Minnesota, and after a year entered the army. While here he has done extremely important work on pneumonia. Collaborating with Dr. Cecil, he has succeeded in inciting the production of pneumonia in monkeys by injecting into the trachea very minute amounts of pneumecocci or streptococci or influenza bacilli. The pneumonia developing in each case has greatly resembled the type pneumonia in man which has been considered to be due to the same respective organisms. Dr. Blake is to share in the studies concerning acute respiratory disease and in collaboration with others may undertake the study of measles.

Dr. Binger of the University of Harvard and

Massachusetts General Hospital becomes an Assistant Resident Physician. He has had considerable experience in the laboratories of Dr. Folin at Harvard and of Dr. Able at Baltimore, and has already made a number of scientific publications. Dr. Austin of the University of Pennsylvania becomes an Assistant Resident Physician. He has had an extensive clinical training in the University Hospital and has worked for several years with Dr. Pearce and has made a number of important publications relating to nephritis and blood diseases.

Other assistant resident physicians will be Dr. James Trask, coming to us from Cornell University; Dr. Arthur Lyon, from Harvard Medical School, and Dr. Ralph Boots, from the University of Pittsburgh.

We are therefore starting the new year with a well-trained, enthusiastic and capable staff.

Training Courses Given to Army Medical Officers.

Up to the time of signing the armistice the following training courses were given in whole or in part by the Hospital staff:

I. A course in bacteriological methods given for medical officers in the Institute laboratories. The instruction of the men in the methods of studying the bacteriology of acute infections has been given by Dr. Avery and Dr. Dochez, assisted by Dr. Stillman, and this has required a considerable amount of their time.

II. A course in chemical methods for members of the Sanitary Corps has been given in the chemical laboratory of the Hospital.

III. A course designed to teach women the bacteriological

methods employed in the etiologic diagnosis of acute respiratory diseases was given during the quarter from October 1918 to January 1919 in the Hospital. This course was under Dr. Avery and Dr. Stillman.

IV. Training medical officers in clinical methods. These officers also acted as internes.

Clinical and Laboratory Investigations.

Pneumonia and Influenza.

It will be recalled that in my previous report in the autumn of 1918 I devoted considerable space to a discussion of our observations concerning the acute pneumonia which had prevailed during the preceding fall and winter. This disease took on a true epidemic form in the camps, but also spread to some extent among the civilian population. It was due in part at least to the commission from this Hospital that the demonstration was made that the disease was due to infection with Streptococcus haemolyticus. Considerable information was also obtained concerning the mode of spread of the disease, the pathology, etc. I also mentioned that about the time of writing the report a new type of pneumonia had just appeared. This was the beginning of the epidemic of influenza which during the next months prevailed to such a terrible extent throughout the entire country.

We were therefore compelled to devote much of our efforts during the past winter to this disease. Owing to the large incidence of the disease among the staff, workers and employees of the Institute, it was necessary during the height of the epidemic to employ a considerable part of the energy of the staff in caring for these individuals. The need on the part of the public for proper hospital attention was also so great that it was necessary for the hospital to do its share in caring for patients.

Notwithstanding this fact and also that the staff was greatly depleted, an effort was made to do what was possible in the study of the disease and in investigating the cause of the epidemic.

Clinical Features of Influenza.

Although an enormous literature has developed concerning the symptoms and cause of influenza, there is still much difference of opinion as to the essential features of the disease, - indeed, there is still doubt in the minds of some whether influenza is a single specific infectious disease. During the epidemic of the past winter pneumonia occurred with very great frequency. In exactly how many patients suffering from influenza, changes in the lungs sufficient to justify the diagnosis of pneumonia occurred, will probably never be known. Even in a hospital like this one where facilities for diagnosis are very good, it was impossible under the conditions prevailing last winter to be certain that no cases of pneumonia were overlooked, or that no influenzal broncho-pneumonia cases were included among the lobar pneumonia cases and vice versa. Of the 213 patients suffering from acute infections of the respiratory tract that were treated, 41 were considered to have had typical lobar pneumonia. Of these 12, or 29 per cent, died. There were 168 cases which were considered to be influenza, and of these patients, 32, or 13 per cent, died. Ninety-one, or considerably over half of the influenza cases, were believed to have sufficient inflammatory reaction in the lungs, as indicated by dulness, tubular breathing etc., to justify the diagnosis of broncho-pneumonia, and of these, 32, or 35 per cent, died. Of the 77 cases of influenza without demonstrable pneumonia not one died. Of these 77 cases diagnosed as influenza and which were not thought to have pneumonia,

29 had rales or other signs which indicated some degree of pulmonary involvement. The experience here indicates that influenza is a disease of the respiratory tract, though in some cases the infection of the lung is of a mild grade and in some possibly, the infection never reaches below the larger bronchi. In the recent epidemic the lungs became involved in many cases, and it was among these cases that the mortality was so high.

It is true that after the height of the epidemic had been passed it was preferred to admit to this Hospital only those patients having pulmonary involvement. For this reason it is probable that a larger percentage of our cases had pneumonia than was the case in the general hospital or in civilian practice. Nevertheless our experience indicates that pneumonia was much more common in the epidemic than was generally assumed.

An effort was made to determine the bacteria present in the lungs in our cases. This was done by making a careful bacteriological study of the sputum and by making cultures from material removed from the lung by puncture either during life or immediately after death, and by making cultures from the lungs at autopsy. The results of these cultures indicated that a number of pathogenic organisms were concerned in the process. In the cultures made in the various ways mentioned Pneumococcus, chiefly pneumococcus group IV, Streptococcus haemolyticus, in a small number of cases, and Staphylococcus aureus, in a few cases, were found. Influenza bacilli were present in 85 per cent of the cases, as demonstrated by cultures made from the throat, from the sputum, or by cultures at autopsy. It is an interesting fact that influenza bacilli were cultivated from 20 of the 32 fatal cases of broncho-pneumonia in such numbers and under such conditions that it seemed likely that they played at least a

part in the pathologic process.

The very frequent presence of B. influenzae in cases of the disease made it seem important that our chief attention at the Hospital should be directed to learning more concerning this organism and its relation to the disease and the epidemic. As is well known there are two chief opinions concerning the etiology of the disease and the epidemic: first, that B. influenzae plays an etiologic role, and second, that this organism is a secondary invader, analogous to S. haemolyticus, Staphylococcus, Pneumococcus etc., and that the primary organism is unknown, probably a filterable virus. As the staff of the Hospital was too much disorganized to permit any special investigations starting from the second of these two premises, it seemed better to confine our studies largely to the influenza bacillus.

In order to carry out these studies it was first necessary to find improved methods of cultivating this organism so that we could be reasonably sure that it was not being overlooked when it was actually present. Dr. Avery undertook this problem and succeeded in devising a new method, employing a medium containing sodium oleate. In this medium the growth of certain common bacteria is inhibited, while influenza bacilli grow with very great luxuriance.

Since influenza bacilli were found to be almost constantly present in the throats of persons suffering from influenza or other acute respiratory disease during the epidemic, it seemed important to learn more concerning their distribution in the throats of healthy persons or in persons who had recovered from influenza. Consequently several surveys were made under the direction of Dr. Ernest Stillman of all the persons associated with the Institute. In the first survey made during

the September-December quarter, it was possible to cultivate influenza bacilli from the throats of 42 per cent of all individuals associated with the Institute. In January only 11 per cent of the individuals were found to be carrying influenza bacilli, but this low percentage may probably be accounted for by certain defects in the medium employed. In February influenza bacilli were cultivated from 30 per cent of the personnel, in March from 50 per cent in April from 36 per cent and in May from 41 per cent. The results show that a large number of the individuals in the Institute during the past year have been chronic carriers of this organism. From some individuals all of the cultures made have been positive; from others the cultures have been persistently negative; while still other individuals, who at first were negative, later became carriers, and vice versa. Investigations were made to show whether the cultivation of the organism from the throat might depend upon some incidental factor; for instance, whether cultures might be positive and cultures made a few hours later might be negative. The evidence so far obtained indicates that this is not the case, but indicates that the technique employed may be relied upon to show whether or not a person is a carrier of influenza bacilli.

Investigations were also made to determine from what part of the naso-pharynx the organisms were most readily isolated, or most frequently encountered. In a series of about 90 individuals three cultures were made from the throat - one culture from each tonsil and one from the posterior wall of the pharynx. In five individuals positive cultures were obtained on plates from all three sources. In five individuals the cultures from the pharynx, and from one or the other tonsil, were positive. In 13 individuals only the culture from the pharynx showed a growth of influenza bacilli. In no case were the organisms isolated from the tonsil and not

from the pharynx. In these 90 individuals, therefore, positive cultures were obtained from 23 or 26 per cent, and the results show that the organisms were most likely to be encountered on the posterior wall of the pharynx. Consequently in most of our cultures since these observations were made, and in most of the cultures before, the cultures were made by touching the posterior wall of the pharynx alone.

In tabulating the results, the persons who gave a history of having had influenza during the present epidemic were separated from those persons from whom no such history could be obtained. The percentage of carriers of influenza bacilli did not differ in these two groups of individuals. The results of cultures from the sick and the well, as mentioned above, indicate that during the epidemic of acute respiratory disease of the past winter, influenza bacilli could be cultivated from a much larger proportion of the persons suffering from influenza or acute respiratory disease than from the healthy. Doubt might be thrown on this statement if we depended entirely upon the observations of the physicians in the wards, since in these cases a very great effort was made to isolate influenza bacilli in every case, while cultures from the healthy persons were made in a more or less routine manner. However, Miss Winchell, who made the routine cultures from the normal individuals, also made studies in a series of patients, making the cultures in exactly the same way as they were made from the healthy. Whereas among the well persons influenza bacilli were cultivated only from 30 to 40 per cent of individuals, they were obtained by exactly the same technique from over 85 per cent of the cases in the wards. There can be no doubt, therefore, that during the epidemic of influenza of the past winter influenza bacilli have been frequently present in the mouths of healthy persons living in New York, and almost invariably present in patients suffering from acute respiratory

disease. Further than this we cannot go at the present time.

Whether during the previous winter, or whether during subsequent winters when no epidemic is present, similar conditions existed or will exist, cannot be stated. However, another survey has just been made, September 1919, and it has been possible to cultivate influenza bacilli from only 13 per cent of the Institute personnel. This is of some interest but gives us little real information, for it is possible that exactly the same conditions may have been present in previous years, namely, that when persons return from their vacations during the period when respiratory infections are not prevalent, few persons may be found carrying influenza bacilli, but later when these infections become more common, a larger percentage of persons carry these organisms.

Dr. Stillman and Miss Winchell also during the past winter made observations concerning the prevalence of influenza bacilli in two institutions near New York. At the New York State Training School for Girls at Hudson, N. Y., influenza prevailed to a considerable extent during January and early in February. On February 16th cultures were made from the throats of 52 patients still in the hospital, but convalescent. From these 52 patients influenza bacilli were cultivated from 20, or 38 per cent. One of the cottages at this institution had been under close quarantine since October 1918 on account of trachoma. No case of influenza had developed in this cottage. Cultures were made from 20 inmates of this cottage and of these 5, or 25 per cent, showed B. influenzae.

Cultures were also made from a number of children at Mt. Loretta, a Catholic institution for children on Staten Island. This institution was said to have been under strict quarantine during the influenza epidemic, but investigation showed that the quarantine had been quite lax.

The employees went to town from time to time and the doctor and priest were frequent visitors to the institution, and the population was more or less shifting. No definite history was obtained, however, of the occurrence of influenza. Cultures were made from 190 of the children, and from 74, or 39 per cent, influenza bacilli were cultivated. The results of all these studies indicate that it will be very difficult by this line of investigation to demonstrate any etiologic relation of influenza bacillus to this type of infection, unless it can be shown that influenza bacilli are not all identical, but that different types or varieties exist.

A study to determine if possible by immunologic methods whether all influenza bacilli are or are not of the same type has been undertaken by Dr. Lyon. He has immunized a considerable number of rabbits to B. influenzae and now also has a sheep in process of immunization. By paying attention to certain factors, such as salt concentration of the medium, it has been possible to devise a method by which agglutination reactions of influenza bacilli can be readily distinguished. Sera have been obtained which cause characteristic agglutination, but in our experience all races of influenza bacilli agglutinate equally well. This reaction, however, has not been found to be absolutely specific. This study is still in progress but so far no definite evidence of differentiation of influenza bacilli into types has been obtained.

During the studies of influenza bacilli in normal throats a haemoglobinophilic bacterium has been frequently encountered which differs from B. influenzae in being hemolytic for red blood corpuscles. It is usually slightly larger than B. influenzae but otherwise resembles it very closely. It has been tentatively called B. X. It has not been found

under circumstances in which it seems to have pathological significance.

In summarizing our studies concerning influenza we may say that considerable knowledge has been obtained concerning the clinical features of the disease and the pneumonia associated with it. The bacteria present have been carefully determined in a series of cases. It has been shown that B. influenzae was almost constantly present in cases of the disease, and during the past winter was very frequently present in the mouths of normal persons. Whether this organism bears any etiologic relationship to the disease has not been determined, but this possibility has not been excluded. Some new knowledge concerning the characteristics of this organism has been obtained.

Streptococcus haemolyticus.

In view of the severe epidemic of pneumonia during the winter of 1917-18 which was apparently demonstrated to be due to infection with S. haemolyticus, it seemed most important that the study of this organism should be continued during the past winter, especially as we were in possession of a very large number of strains collected from cases of pneumonia occurring during the previous epidemic.

This work has been carried on by Dr. Doches and Dr. Avery and has involved a very large amount of work, and has necessitated the employment of a large number of smaller animals. The work has resulted in the demonstration of certain principles which apply to the development of pathogenicity in organisms belonging to other groups of bacteria, as well as to the bacteria of this group.

As regards streptococci it has been possible to show that:

I. Immunological differences exist between strains of S. haemolyticus of the human type.

II. Four biological types have been identified by means of the reactions of agglutination and protection.

III. At least two other types have been encountered and the indications are that more exist.

Much of our knowledge concerning the epidemiology of streptococcus pneumonia has been obtained by means of throat cultures. The question arose as to whether wrong conclusions might not be drawn, owing to the cultivation from the throat of haemolytic streptococci of the bovine type derived from milk and cheese which had been previously eaten. Dr. Stillman has thoroughly studied this question and has shown that error is not likely to occur from the cultivation of milk streptococci, owing to the slight degree of haemolysis which these organisms cause when they are grown on the surface of blood agar plates. Cheese streptococci are more likely to cause confusion, but it has been shown that by employing proper methods in any case where doubt exists, the origin of the streptococci may be determined without great difficulty.

Acute Lobar Pneumonia.

Although during the past two years many more cases of acute respiratory disease were treated in the Hospital than ever before, the number of cases of typical lobar pneumonia has been comparatively small. All cases of Type I infection have been treated with immune serum and the results have continued to be as good as those previously reported. This experience has also been repeated in certain army camps where it was possible to carry out the method properly. Unfortunately this was possible in only a few places owing to the prevalence of the epidemics of streptococcus

pneumonia and of influenza.

In the autumn of 1918 Dr. Stillman made a further study of a large number of strains of so-called atypical type II pneumococci. It was found that organisms belonging to certain groups were encountered very frequently in cases of disease and probably are quite pathogenic for man, while other organisms belonging in other groups are frequently present in normal mouths, but are seldom found in patients with pneumonia.

Dr. Avery and Dr. Cullen have carried on extensive studies with pneumococci to determine the final hydrogen ion concentration of pneumococcus cultures and also the optimum hydrogen ion concentration for growth of these organisms. The results obtained have a practical bearing on the best methods for cultivating these bacteria, as well as on the more ready and certain identification of them.

Dr. Barber has studied further the question of so-called antiblastic immunity, employing for this problem the method which he has devised for isolating and cultivating single bacterial cells. He has not been able to demonstrate that anti-pneumococcus serum has any power to inhibit the growth of these organisms, either in artificial culture medium or in the body of the animal. We are compelled therefore to believe that the action of the serum is chiefly dependent upon some activity of the protected animal, probably in part at least upon phagocytosis. Dr. Barber's study, which was carried out with great care and attention to detail, is of much theoretical importance.

Treatment of Syphilis with A 189.

The study of the therapeutic effect of the drug A 189 was commenced in January 1918 and continued until January 1919.

As the toxic dose for man was entirely unknown the work had to proceed at first with great care in order that no harm might be done. Various modes of administration had to be tried out in order to learn the most effective one. Without going into details, it may be said that it was demonstrated that this drug is effective in curing syphilis. It was decided from our studies that probably the most effective method of treatment would consist in the administration of 7 mg. of the drug per kilogram body weight every ten days, combined with treatment with mercury. If the drug were given in larger doses or more frequently, toxic effects might result; if smaller doses were employed, the therapeutic results were not satisfactory. Having obtained this information, it seemed advisable to discontinue the studies here and have the drug tested on a larger scale elsewhere.

Chemical Laboratory.

During the early part of the year research activities in the chemical laboratory were very greatly diminished owing to Dr. Van Slyke's illness and the employment of Dr. Cullen in the War Demonstration Hospital. The laboratory space and equipment were largely employed for the course in clinical laboratory methods given to the men of the Sanitary Corps. Since the signing of the armistice and the return of Dr. Van Slyke and Dr. Cullen, the laboratory has been gradually reorganized and new problems have been undertaken. In spite of all the difficulties and disorganization during the war, a considerable number of studies were made and results of importance obtained.

A brief survey of this work follows:

Dr. Van Slyke, with the assistance of Lt. Donleavy, has devised an improved method for estimation of blood chlorides. He has also devised a method for titration of the organic acids in the urine. With Dr. Stillman and Dr. Cullen he has improved the method for determining plasma bicarbonates.

Miss Hiller has continued her work assisting Dr. Van Slyke in the study of proteins. She has brought about certain improvements in the methods employed in the hydrolysis of proteins and has been studying a new method for the determination of histidine.

Dr. Stadie, in connection with the study of A 189, has investigated the question of the distribution of arsenic in the body after intravenous injection of A 189, and the mode and rate of its excretion.

Dr. Salvesen, of Christiania, who since April has worked in the laboratory as a voluntary assistant, has devised an improved method for measuring the carbon dioxide content of the blood. This work is an extension of the study of methods for estimation of blood gases so successfully undertaken by Dr. Van Slyke. The possession of an accurate and simple method for determining carbon monoxide has permitted a further development of the Haldane method for determining blood volume. In employing this method, the subject is allowed to absorb into his blood a measured amount of carbon monoxide, and the amount present per cc. of blood is then determined. Dr. Salvesen has employed this method both in animals and in man, and with the improvements in technique which he has devised, the method seems both reliable and comparatively simple.

Cyanosis in Pneumonia.

Dr. Stadie has demonstrated that the withdrawal

of small amounts of arterial blood from man is a perfectly safe and harmless procedure, and for the first time determinations of the blood gases in arterial blood in a series of patients have been made. These studies have led to much increase in knowledge concerning cyanosis, about which there had been a great deal of difference of opinion. It has now been demonstrated that cyanosis in pneumonia is due to incomplete oxygenation of arterial blood and that a low oxygen saturation is of bad prognostic importance. This method has already been applied by others to the study of cyanosis in heart disease and it is planned to extend the investigation along this line here during the coming year. Dr. Stadie has also devised a gasometric method for the determination of methaemoglobin. This will permit a more accurate study of the question of methaemoglobin formation in vivo and in vitro by pneumococci.

Circulatory Disturbances.

Dr. Cohn was absent with the American Expeditionary Forces until February. Since his return he has made an extensive study of the size and functional capacity of the heart in 200 returned soldiers. He is also engaged with Dr. Peabody in writing a book concerning the cardiac disability which occurs so often in soldiers, and concerning which he has had exceptional opportunity to gain information.

Dr. Levy has been studying, both in animals and in man, the mode of action and dosage of strophanthin. It is hoped that this information will permit a much more accurate and rational therapy with this drug of the digitalis series.