REPORT OF THE DIRECTOR OF THE HOSPITAL

April 15, 1922

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During the period since the last report was written no fundamental changes have been made in the general plan of work or in the chief problems engaging the attention of the hospital staff. The loss of an unusually large number of the members of the staff to accept academic positions elsewhere delayed progress to some extent during the early part of the winter. Moreover, much of Dr Binger's time was occupied with the trip to South America and Dr Lundsgaard and Dr Linder did not arrive until February. However, the hospital now has a fairly large staff of workers, and the organization of the work is more satisfactory than it has been for some time.

Following the departure of Dr Austin, Dr Morgan acted as resident physician until the arrival of Dr Lundsgaard, and he carried out the duties of resident in a very efficient manner. As he was the only assistant engaged in the care and study of patients with acute respiratory diseases, the number of these patients who could be admitted was necessarily limited. Nevertheless, during the epidemic of influenza it was possible to study a number of patients suffering from this condition, and information regarding the clinical features and evidence relating to etiology were obtained. Considerable attention is being given to the study of the disturbances of respiration in pneumonia, and the oxygen chamber, which was built last year in Ward 6, is proving to be of much use in this study. It is believed that through its employment a number of important questions

relating to the pathology of respiration may be solved.

Much attention is now being given in the hospital to the study of nephritis and it is hoped that in the immediate future, active progress will be made in this investigation. Dr Lundsgaard, Dr Edgar Stillman and Dr Linder are giving their entire time to this work and Dr Van Slyke is also much interested and is giving it his time and attention.

The following reports indicate the character of studies which are being carried on in the laboratories and wards and describe the results which have recently been obtained.

Acute Rheumatic Fever.

Dr Swift, Dr Miller and Dr Boots.

As the physicians of the city are becoming accustomed to apply to the hospital for the admission of their patients suffering from this disease, the study of acute rheumatic fever has been facilitated by a fair supply of clinical material. One difficulty is that the patients are often not referred until several days have elapsed following the onset of the acute disease. In the consideration of acute diseases in general, especially from the viewpoint of etiology, the desirability of seeing the patients at the onset is self-evident. As we are continuing to observe all of the patients who have been under our care for the past two years, and to readmit to the hospital any of them showing evidence of recurrence, we have a better opportunity to see these early stages.

The value of a detailed and prolonged clinical study of a comparatively small group of patients suffering from a disease of

such obscure nature is becoming more and more evident. From our observations we are gaining the impression that in many patients the nature of "the rheumatic infection" is similar to that seen in syphilis: there are alternate periods of activity and latency. In many of the patients it is hard to explain the recurrence of rheumatic manifestations on any other ground. The various so-called specific anti-rheumatic remedies - such as salicylates or atophan and related compounds - seem to act in much the same manner as do insufficient doses of mercury and iodides in syphilis: they control the symptoms and signs of the disease, but do not completely eliminate the etiologic agent. These anti-rheumatic remedies are of value in making the patient more comfortable and in preventing the severe general depression due to prolonged active intoxication; thus the patient is assisted in building up his general resistance. It seems to us that recovery is brought about in a manner similar to that seen in tuberculosis; the patient's own reaction to the infection brings about the cure.

In this connection the weight charts of our patients have been of considerable interest: as long as the patients continue to lose weight or fail to regain the weight lost during the acute/early stages of the disease, there is little tendency towards complete recovery, and relapses frequently occur. Relapses are often heralded by a renewed loss of weight, and are practically always accompanied by similar losses. Attention to the proper nourishment of these patients is, therefore, most important in treatment. It has seemed to us that a detailed study of this phase of therapy might be of value, for the prevalent viewpoint of "focal infection" and the relief

provided by salicylates has directed the attention of physicians away from other general manifestations of infection.

During the past few months a new feature has been brought to our attention: many of the patients have shown an acute rhinitis with many fine punctate hemorrhages in the nasal mucosa. This may have been a feature of the recent epidemic of "influenza"; the nasal mucosa, nevertheless, might easily have been the point of entrance of the virus of rheumatic fever. From these clinical observations we were led to attempt inoculation of monkeys by placing the nasal secretions from rheumatic patients with rhinitis into the noses of monkeys, following the scarification of the surface of the turbinates and nasal septum. The noses of these animals were also packed with cotton soaked with nasal secretions from patients. It was hoped that the resulting rhinitis in the monkeys might allow the supposed virus of rheumatic fever to enter the circulation. At the same time the legs of the monkeys were immersed daily in cold water in order to lower the resistance of the knees and ankles and thus favor the implantation of infection. Thus far these experiments have failed to induce any of the ordinary manifestations of rheumatic fever in the monkeys.

A detailed study is being made of the evolution and recovery of the arthritis in patients treated with large amounts of antipneumococcus serum. No detailed reports of studies of this form of polyarthritis are available; they are of value because a number of observers have claimed that the polyarthritis of rheumatic fever is an anaphylactic manifestation or a phenomenon of hypersensativeness. Wherever possible joint fluid is withdrawn from the serum disease

patients to compare it with similar fluid from patients with rheumatic fever. A detailed study of the cytology of the fluid in both conditions is in progress.

Drs Boots and Cullen have completed a study of the reaction of the joint fluids from patients with various forms of arthritis. These determinations were made: (1) to compare the reaction of the exudates of the various forms of arthritis; (2) to determine if an acidity existed in inflamed joints of rheumatic fever patients sufficient to permit the liberation of free salicylic acid following salicylate therapy.

It had been suggested for a number of years that the specific action of salicylates in this disease might be due to the liberation of free salicylic acid in inflamed tissues. Most of the determinations were made by the colorimetric method recently described by Cullen for determining the hydrogen ion concentration of the blood. Where a sufficient amount of exudate could be obtained from the joint the electrometric method was used.

Hydrogen ion concentrations in 27 joint exudates were determined; 16 of these were from inflamed joints of patients ill with acute rheumatic fever; 7 from patients with arthritis of undetermined origin; 2 from joints definitely infected with pyogenic bacteria; and 1 of the fluids was an effusion into the knee joint of a patient with marked myocardial insufficiency.

Results:- The reaction of the joint exudates from patients with acute rheumatic fever were all slightly alkaline; their hydrogen ion concentration varied in pH from 7.2 to 7.38. Exudates from patients with chronic arthritis varied in pH from 7.27 to 7.4.

The pH of the joint effusion from the patient with myocardial insufficiency was 7.28. An exudate aspirated from the knee infected with Staphylococcus aureus had a pH of 6.68, and that from a knee infected with Streptococcus hemolyticus was also acid, having a pH of 6.13. These results show that all the exudates were slightly alkaline except those from joints infected with pyogenic bacteria.

Since a definitely acid medium is necessary for the liberation of salicylic acid from a salicylate salt, and since all the joint exudates from acute rheumatic fever patients were slightly alkaline, it is highly improbable that free salicylic acid can exist in these joint fluids following the administration of salicylates.

During the past winter the patients with acute rheumatic fever have been treated with tolysin, which is the trade name of the German preparation "neoatophan" and known also in this country as "neocinchophen". Recently many reports have appeared in medical literature calling attention to the marked therapeutic and slight toxic effects of this drug in various forms of arthritis. As we have detailed studies of patients treated with salicylates, it was thought advisable to carry out similar studies with the new drug in order to be able to state definitely whether there is a distinct advantage in using either preparation. Ten patients have been treated. The results are more easily interpreted if the patients are divided into two classes: the arthritic and the cardiac. The first type is characterized by a severe polyarthritis with moderate or no cardiac involvement; the second, by marked cardiac disease and little or no arthritis.

Arthritic type: Five patients, all adults, were treated. The dose during the first twenty-four hours varied from 0.11 to 0.22 of of a gram per kilo body weight; on the following day a similar, larger, or smaller dose was given according to the appearance of toxic symptoms; and for the next two or three weeks the dosage was gradually diminished. All except one of the patients showed marked amelioration of the arthritis on the first day; in the other patient improvement did not occur until after forty-eight hours. Antipyretic action has been marked in all of the patients; in one, the temperature fell from 104° to 96° F. The difference between toxic and therapeutic dose seems to be greater than it is with salicylates; hence the drug has been diminished or discontinued before severe toxic symptoms have appeared. All of the patients showed marked sweating on the first day of administration; two had nausea; none have vomited; tinnitus, deafness, vertigo, have been absent or only slight. The urine of two of the patients showed a slight increase in albumin and casts; no marked or permanent toxic effect on the kidneys has been observed.

Cardiac type: Four patients, all children were treated; the dosage varied between 0.13 and 0.26 of a gram per kilo body weight per day. In each case there was a fall of temperature to subnormal within eighteen hours; this more marked antipyretic action of the drug in children is noteworthy.

In both children and adults it has been possible to maintain a normal temperature with smaller doses of the drug than were administered on the first day; in several cases in which the drug was discontinued or decreased too rapidly there has been a return of

fever or other signs indicating that the infection was still present though dormant. We have also observed the onset of signs of cardiac involvement while the patient was receiving sufficient doses of the drug to keep his temperature normal. In this respect neocinchophen resembles the salicylates.

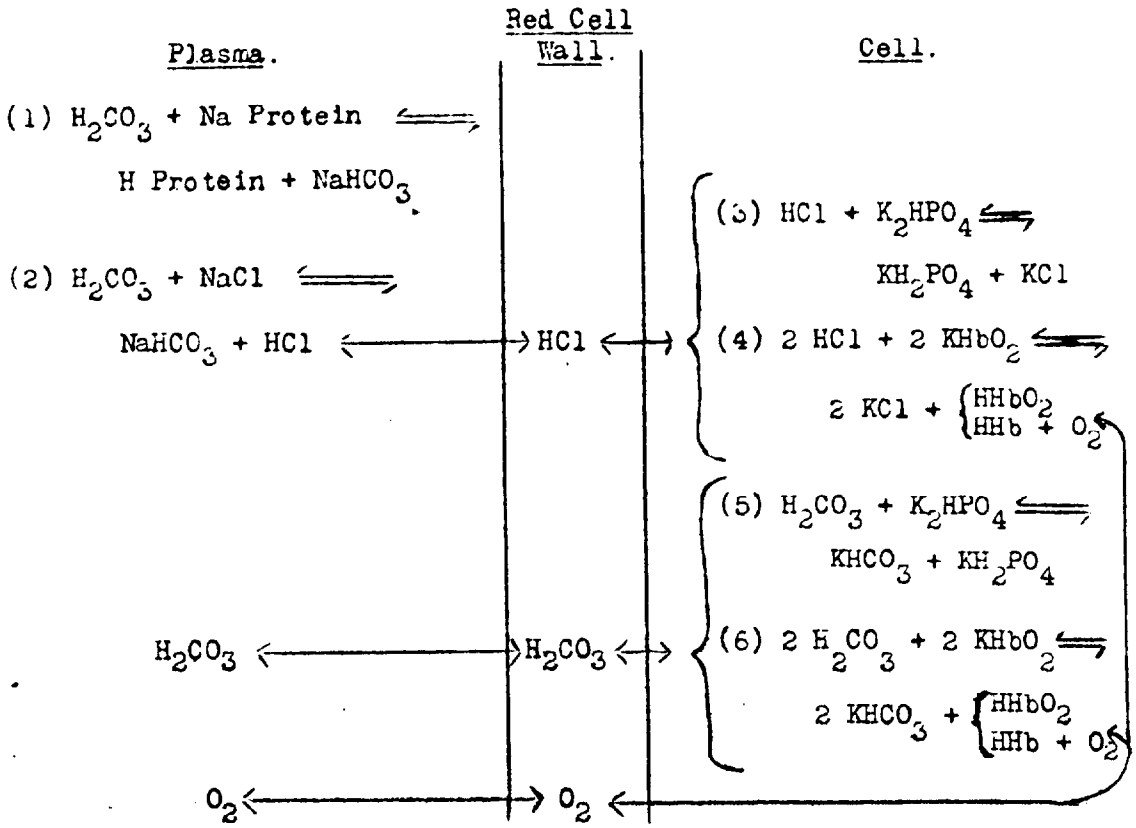
The study of the cutaneous nematode infection of monkeys has been completed; it was not thought advisable to attempt to determine the life history of the parasite. It was found that the subcutaneous nodules were due to the presence of larval forms and possibly adult male parasites. The peripasitic reaction quickly kills the worm and insures that it is removed from the body without being able to continue its activity. The blisters in the horny epithelium of the palms and soles, however, furnish a suitable environment for the female worm to mature and continue her egg laying life. The ease with which the blisters break insures the distribution of the eggs to the external world where they are in position to infect new hosts. We have been unable to find any reference to ary exactly similar example of parasitism. A free adult male worm has not been found. For this reason it has not been possible to classify the parasite exactly. Dr Charles Fardell Stiles has suggested the name Trichosoma cutaneum.

Dr Van Slyke.

The work begun a year ago in collaboration with the laboratory of L. J. Henderson to obtain data on the respiratory changes in blood was continued by Cullen and Austin until they left, and

since then by Hastings, Heidelberger and Neill.

The reactions, the quantitative relations of which form the object of the study, are represented in the accompanying diagram, presented chiefly as used in a publication last year (The CO_2 carriers of the blood. Van Slyke, Physiological Reviews, I.)



All 6 reactions are forced from left to right by increase in H_2CO_3, which results in formation in the plasma of $NaHCO_3$ from 2 sources (Reactions 1 and 2), and in the cells from 2 other sources (Reactions 5 and 6). The acidification of hemoglobin that results from H_2CO_3 increase results in partial loss of O_2, as indicated by the last stages of Reactions 4 and 6. On the other hand, increase

of O_2 (from the lungs) forces Reactions 4 and 6 backwards, and thereby through 6 and 2 sets H_2CO_3 free. By these reactions oxygen pushes CO_2 out of the blood in the lungs, and CO_2 pushes oxygen out in the tissues to the assistance of both CO_2 excretion and of O_2 absorption and utilization. It does not appear that our understanding of the normal respiratory processes will be as complete as is attainable, nor our knowledge of the abnormalities in disease, until the quantitative relationship of the above reactions are worked out, and the technique to do so seems now to be available. A certain amount of data has already been collected, but as the results are still incomplete, we shall report them later when they permit more comprehensive conclusions. The indicated ratio, in the final stage of Reactions 4 and 6, of 1 molecule of oxygen freed for 2 molecules of hemoglobin set free from combination with alkali is approximate, and the quantitative relations of the other reactions have been approximated, but we hope to fix them closer with the technique for control of O_2 and CO_2 tension, for blood gas analyses, and for blood electrolyte determinations, which is now in use.

In connection with this work Dr Heidelberger has devised a new technique for the preparation of crystalline, electrolyte-free hemoglobin. He has found that hemoglobin under proper conditions can be readily made to crystallize from water solution by saturating with a 4 to 1 mixture of CO_2 and oxygen. The crystals, which come out almost instantly, can be purified by redissolving in alkali, and recrystallizing with the gas mixture, and are finally freed from electrolyte by rapid dialysis through collodion tubes. By this means crystalline hemoglobin has been obtained free from electrolytes

and with its full oxygen capacity. It is doubtful that this has been accomplished by previously available methods.

Dr Heidelberger has at the same time made definite advances in the purification of the substance discovered by Avery in the urine of certain pneumonia patients, which forms precipitates with specific antipneumococcus sera. The details will be reported by Dr Avery.

Miss Hiller has finished an investigation of the behavior of the different protein precipitants used in studying blood and protein digests. The precipitants include picric, trichloracetic, metaphosphoric, and tungstic acids, colloidal iron, mercury salts, and alcohol. The amino and peptide nitrogens were determined in the filtrates from blood with and without the addition of known amounts of amino acid and peptone nitrogen. The action of the precipitants on Witte peptone solutions was also studied, in order to ascertain which ones remove most completely the intermediate protein products, and which remove the protein with a minimum of the intermediates. The data obtained will enable future investigators to choose precipitants adapted to their especial objects in a way that has not heretofore been possible. The immediate object of this work was to ascertain conditions for studying the absorption of intermediate products along with the amino acids during protein digestion. We hope to attack this problem, which is an unfinished portion of the study of the fate of protein digestion products.

Miss Hiller has also been preparing a supply of the unknown amino acid discovered in the hexone base fraction of gelatin, for future work on its constitution.

At present she is engaged on a method for determining blood fat in the plasma of nephritics. In the type of nephritis known as nephrosis, the most abnormal factor in the composition of the blood appears to be the high fat content. Since we are directing especial attention towards this class of patients, and present blood fat methods are either unsatisfactory in accuracy (the nephelometric) or require considerable amounts of blood (gravimetric) the possibility of finding a technique that will yield reliable results on small amounts of material seems to justify the attempt.

In connection with our studies of acidosis two theoretical papers have been prepared, one of which, entitled "The normal and abnormal variation of the acid-base balance of the blood" has been published. In it the demonstration has been made on the basis of facts found in this and other laboratories, that associated with each condition of high, normal, or low blood bicarbonate may be a high, normal, or low pH. There are thus 9 possible and actually observed combinations of $BHCO_3$ and pH, of which only 1 is normal, viz. that in which both pH and $BHCO_3$ are normal. Each of the other 8 conditions indicates a specific abnormality either in the metabolic processes by which non-volatile acids are formed and excreted, or in the respiratory processes by which the CO_2 tension in the blood is regulated. For the general diagnosis of an abnormal condition, determinations of both the pH and bicarbonate existing in the circulating blood becomes obviously necessary, although in special conditions abnormality in one factor is so characteristic, such as the low $BHCO_3$ in diabetic acidosis, that the other can be

neglected. In connection with our nephritic service, the determination of the acid-base balance by combined pH and $BHCO_3$ estimation has already proved of clinical value.

For the pH estimation on plasma a method simpler than the electrometric and more accurate than previous colorimetric ones became necessary. It was supplied in the form of an improved colorimetric technique by Cullen. He found that if plasma is diluted with 20 volumes of neutral saline solution, without loss of CO_2, the pH determined colorimetrically at 38° with phenolsulfonephthalein as indicator is identical with the electrometric, and increases by 0.01 for each degree below 38°. Colorimetric determinations performed at room temperature, with the indicated correction, agree with the electrometric estimation performed at 38° with an average difference of only 0.02 pH. The method has already been used in experimental work on dogs, and is being employed clinically with nephritic patients. It is about to be employed by Dr Neill in a study of the, at present, somewhat confused question of the state of the acid-base balance in pneumonia.

The other theoretical paper is on the subject of buffer measurement, and the buffer values of weak acids, bases, and amphoteric substances, of various dissociation constants. Despite the work that has been done with buffers, these relationships have not heretofore been worked out; in fact, there has not even been a unit for expressing buffer effect in qualitative numerical terms. As such a unit we have used the amount of strong alkali or acid required to cause unit change of pH. On this basis, a solution possesses a buffer value of 1 when the pH changes at the rate of 1 unit per gram

equivalent of added strong acid or alkali. Mathematically expressed, the buffer value of a solution is $\frac{d\ B}{d\ pH}$, when dB is the increment of added strong base (NaOH or KOH), d pH the accompanying increment of pH. From the quantitative known relationships, formulated according to the mass law, of hydrion concentration to the ratios $\frac{\text{buffer salt}}{\text{free buffer acid}}$ and $\frac{\text{buffer salt}}{\text{free buffer base}}$ (in the cases of weak acids and weak bases respectively acting as buffers) it was possible to derive by means of the differential calculus a general equation expressing the buffer value of any buffer solution, viz.

$$\text{Buffer value} = \frac{d\ B}{d\ pH} = 2.3\left(\frac{KC\ [H^+]}{(K + [H^+])^2} + [H^+] + [OH]\right)$$

For weak acids as buffers, $K = K_a'$, the acid dissociation constant. For weak bases $K = \frac{10^{-14}}{K_b}$, where K_b is the dissociation constant of the buffer base. For solutions near enough to neutrality so that $[H^+]$ and $[OH]$ are relatively negligible, viz. between pH 3 and pH. 11, a zone covering nearly all biological solutions, the equation simplifies to

$$\text{Buffer value} = \frac{d\ B}{d\ pH} = \frac{2.3\ KC\ [H^+]}{(K^+ + [H^+])2}$$

As is evident, the effectiveness of a given buffer is different for every $[H^+]$. The effectiveness of every buffer at varying pH follows the same curve, which reaches its maximum when $K = [H^+]$ (or $-\log K = pH$), and becomes insignificant when the ratio $\frac{K}{[H^+]}$ falls outside the limits $\frac{100}{1}$ and $\frac{1}{100}$, that is, when $-\log K$ differs from pH by more than 2 units. At its maximum effectiveness, when $K = [H^+]$ any buffer is

half in the form of free buffer acid or base, half in the form of its salt. At this point the value of an N/1 solution (where C = 1) of the buffer is $\frac{2.3\ K^2}{(2K)2} = \frac{2.3}{4} = 0.575$. The molecular concentration, and hence the molecular weight, of a dissolved buffer may be ascertained by dividing 0.575 by the observed maximum $\frac{d\ B}{d\ pH}$ value. The latter is experimentally determined by adding known increments of strong base (d B'), or acid (-d B) to the solution and measuring the pH change, (d pH).

The $[H^+]$ of maximum buffer value also indicates the dissociation constant of the buffer acid or base, since at this point $[H^+] = K$.

For buffers containing more than 1 buffer group (polyvalent weak acids or bases, or amphoteric substances) the buffer value is the sum of the buffer values of the different groups.

$$\frac{d\ B}{d\ pH} = 2.3\ C\ [H^+] \left(\frac{K_1}{\left(K_1 + [H_1^+]\right)^2} + \frac{K_2}{\left(K_2 + [H_2^+]\right)^2} \cdots \right)$$

The above principles are being applied by Dr Hastings to a study of hemoglobin, and have already yielded results.

The question was recently raised by Evans, of England, as to whether electrometric pH estimations on CO_2-containing solutions are valid. Evans claimed that some acid is formed by reduction of CO_2 at the electrodes, and causes the pH to be markedly too low. Cullen and Hastings have checked the matter up carefully on phosphate solutions with and without CO_2, and found theoretical results in both cases. They believe Evans could not have been sufficiently accurat

in regulating the CO_2 tensions in his electrodes.

The study of nephritis is being continued by Dr Edgar Stillman, who has now been joined in this problem by Dr Lundsgaard and Dr Linder. It is our intention to perform on a considerable number of patients physical examinations, blood analyses, and functional tests, according to a routine which will be established chiefly on the basis of the data already available from Stillman's work, to follow the clinical histories of the cases and repeat these examinations at intervals, and to use the data thus gained in obtaining eventually as logical a classification of nephritis as may be possible, and of treatment according to classification. It is intended while these data are being accumulated by relatively short observation periods on a fairly large number of nephritics of all kinds, to attack one at a time certain specific problems that arise in connection with the study. For example, as already stated, the abnormally high blood fat of patients of the so-called "nephrosis" type raises the question of the nature of the metabolic disturbance which causes the lipemia. Absorbed fat is normally either burned or deposited in the body's fat depots so rapidly that it never rises in the blood to the heights found in these patients. The question is presented as to whether such patients fail to burn fat as rapidly as normal individuals, and we have prepared to obtain data on it by means of total metabolism experiments following fat feeding.

Another specific question is whether in so-called hydremias there is really a dilution of the blood, with increased total blood volume, or whether the low protein content of the blood is due to decrease in the total blood protein content of the body, without

increase in blood volume. We hope to obtain information on this point by means of the available blood volume methods.

Heart Disease.

Dr Cohn and Dr Levy.

Quinidine.-

The study of quinidine which we commenced last year has been continued. At that time our experiments on dogs were designed to show the effect of this drug on the behavior of the heart, from the point of view of the circulation as a whole. We showed that small doses (0.01 to 0.04 grams) lowered the blood pressure distinctly for a brief period of time and that a partial recovery only took place. Of greater importance was the fact that at the same time a favorable effect on the contractile power of the ventricular muscle took place. This was measured after opening the chest in the mid line, by means of the Roy and Adami myocardiograph which gives an index of the shortening that takes place between the base and apex of the ventricles. The question arose as to whether this effect, which seems to be important, did not result from the marked fall in blood pressure. In order to elucidate this point we compared this effect with the result, in identical preparations, after bleeding and after the injection of histamine. We found that when the blood pressure was lowered to the same degree by these procedures as with quinidine, a similar increase in the height of the contraction wave did not occur, or if it did occur, that it was a temporary effect, quite unlike the continued change in this respect that we had seen with quinidine. Meanwhile experiments on hemorrhage in dogs, performed by

Meek and Eyster were reported in which small bleedings comparable in size to ours were produced and in which the size and output of the heart were directly measured by X-ray and cardiometers. In these experiments as in ours, no change was noticed in the output of the heart. We have corroboration then that small hemorrhages of about 1 per cent of the body weight are not followed by a change in output; this is the conclusion to which we came by using the myocardiograph, which gave us a linear measure rather than the cubic one of the cardiometer. We think we are the more justified, since having instituted this comparison with the effect of histamine and of hemorrhage, in concluding that there is an effect on the contractile power of heart muscle, quite apart from any effect on blood pressure. In what manner the increase in the contractile power of the ventricle is brought about we have not ascertained.

This year we have addressed ourselves more especially to the effect of quinidine on certain functions of the heart muscle. It will be remembered that in 1908 A. G. Mayer showed that in medusa prepared in special ways a single impulse could be started at a given point of a ring of muscle tissue and that the impulse so started would course around the ring, returning to the point at which it began and would then continue around the ring again performing this circuit indefinitely. Mayer believed that this was a type of contraction wave which, although obviously possible, the structure of the organism as a whole, through its innervation, served to prevent, and that similar circuits were not to be found in nature. In 1913, W. E. Garrey and G. R. Mines both applied this suggestion of Mayer's in experiments of their own in loggerhead turtles and in dog-fish. They were able to repeat his results and developed the thought that this "circus" type

of impulse movement lay at the bottom of the fibrillatory process as it is seen in mammalian cardiac tissue. It was clear in their experiments that a circus in order to continue required a ring or mass of tissue of sufficient size; rings or bits of tissue which were too small failed to support the circus. There are two reasons for this; first, if the paths were too small, the impulse returned to its starting point to find the muscle it had just left in a refractory state, unable to be re-excited by the returning impulse, and this occurred irrespective of the rate at which the impulse was propagated. In larger rings both these factors were important; the rate of conduction and the duration of the refrectory period. In elaborate experiments in dogs, Lewis by recording action currents, found that after he had induced fibrillation in the auricles, he could actually identify and plot the location of the circus. Later he was able by using three suitable simultaneous leads in man to show by the method of Einthoven that, during the progress of a single electric wave representing auricular activity in the fibrillatory state, the direction of the actidn current wheeled in a single plane through 360°. This seems to be satisfactory evidence of the existence of circus movements in man.

At this point we undertook our investigations to establish which functions of the heart muscle quinidine affected in terminating the fibrillatory process in the auricles. Our aim was to study the rate of conduction and of the refractory period; it was obviously unnecessary to determine the mass of tissue involved. We employed dogs, under ether anesthesia, given by the method of Meltzer and Auer. We opened the chest in the median and incised the pericardium

sufficiently to expose the right auricle only. To the base of the auricle, near the head of the sino-auricular node, was sewed the wick of one non-polarizable electrode, the circuit of which through one string galvanometer was completed by an indifferent electrode inserted in the skin. To the apex of the auricle, another wick was sewed, the circuit of which through a second galvanometer was completed as in the first case. The movements of the strings of both galvanometers were photographed simultaneously on the same film. Since we knew the distance between the two cardiac electrodes and could calculate from the records the difference in time of the appearance of the action current at the two points of the cardiac surface, we could calculate the rate of conduction through the muscle.

The refractory period we studied by stimulating the auricles with break shocks. This was done by connecting the secondary coil of an inductorium with the right auricle by means of a pair of fish hook electrodes which stayed permanently in place. The primary circuit was closed by the following device. On the same shaft were mounted three discs, on each of which there projected four knobs equally spaced, the whole driven by a motor belted to a pulley also on the shaft. As the discs revolved, the knobs pressed down keys each closing a circuit. The rate of stimulation was varied by changing the speed of the motor. The first disc controlled the key of the primary circuit; the second one, synchronous with it, that of a signal, the motions of the armature of which were photographed on the record; the third controlled the secondary circuit and was so timed that this circuit was short circuited when the primary circuit was made and opened before the primary circuit was broken. In this

way only break shocks were communicated to the auricles through the fish hook electrodes. To measure them the films were projected on a screen so as to magnify the curves. The time intervals which appear on the films are ordinates 0.04 second apart. When the films were projected the distance between the ordinates was 30 mm., so that each millimeter equalled 0.0013 second. Two errors are possible in this measurement; first, an error in the tuning fork which controls the time wheel, and second, inequality in the rate of motion of the film between two ordinates. These are errors, however, which do not affect the third place of decimals.

In estimating refractory periods the time between a given P-wave or wave of auricular activity and the stimulus, which could be seen as a small sharp deflection of the curve and which could be identified by the signal, was measured. Certain stimuli were followed by auricular responses; others failed to produce this effect. When these measurements were arranged chronologically it was found that they could be separated easily into two groups; one of no responses, the other of responses. The last measurement of the group of no responses, was, of course, the measure of the refractory period.

The results of these experiments with quinidine were as follows; the rate of conduction was usually decreased; it was sometimes scarcely changed, but it was never raised. This result so far as the theory of fibrillation is concerned is an unfavorable result or, at least, one which does not contribute to success in terminating a circus. . . On the refractory period the effect was materially to increase its duration. This did not occur uniformly, but did so in the majority of cases. This effect is favorable. In certain

instances the increase was not great, but in others it amounted to from 50 per cent to 100 per cent. This increase is sufficient, taking into consideration the probable length of the circus, to overcome the unfavorable effect on the rate of conduction. The increase in duration of the refractory period is in point of fact the more striking because the rate of the heart usually increases considerably after giving quinidine and an increase in rate is associated with a fall, not a rise, as occurred here, in this measurement.

Attention should be directed to the lack of uniformity in our results. These, it will be recalled, are parallel with the lack of uniformity which has been encountered on giving quinidine to patients. There success has followed administration in about 50 per cent only of the cases in which this remedy has been administered. During the course of these experiments, similar ones by Lewis have appeared. His differ from ours in that he has striven for uniformity in results, eliminating the influence of two factors which might produce variations, namely, the rate of beat and the influence of the vagus nerves. The rate he maintained uniform by rhythmic stimulation; the vagi he eliminated by injecting atropine. Under these circumstances he obtained uniform results. His experiments are corroborative of ours in principle. The two sets considered together point to the factors which are perhaps concerned in the divergent results seen in the clinical results with this drug.

We are continuing experiments in this subject, with the view to seeing what the effect in the action of quinidine is of vagus stimulation. In view of the well known effect of morphine in stimulating the vagus mechanism, we are trying this means first.

Rheumatism.

We have continued the investigation of the mechanism of the heart in cases of rheumatic fever studied by Dr Swift. The changes which were found last year we continue to find. Almost from day to day alterations in the conduction interval between auricles and ventricles take place, indicating probably continuous change in or damage to the auriculo-ventricular system. Not infrequently changes in the ventricular complexes of the electrocardiogram appear, which indicate the occurrence of a disease process in the ventricles of such a nature as to interfere with the normal propagation of the excitation impulse.

It is, of course, already known that heart block, partial or complete, is occasionally encountered in this disease, but for the continuous variation from day to day in most cases, we were not prepared. It seems to us not improbable that weight may be attached to these findings in our study of cardiac involvement in rheumatism and that evidence of this sort should be considered in making prognoses.

These frequent alterations in the behavior of the heart, have suggested a study of the limits of variation of behavior in normal persons. We are now engaged in collecting such information. We have been at pains to find six individuals whose health is sound and whose electrocardiograms correspond to an ideal of normality. We intend to photograph the three usual leads simultaneously and have arranged three galvanometers for this purpose. In no other way can we be certain of estimations of the direction of the action current and of its progress of the excitation wave through the

heart. In view of the fact that respiration alters the form of the curves, we have arranged to record simultaneously on the electrocardiographic film a curve of the respiratory excursions. These respiratory curves are to be curves of the actual tidal air. The individuals are to breathe into a spirometer. The movements of the spirometer are conveyed to a piston recorder; this recorder is connected with a second piston recorder, the motions of the lever of which are photographed. A change of each 100 cc. of air in the spirometer is signalled and photographed. This is accomplished as follows: as the drum of the spirometer rises and falls its scale pointer passes over a series of contacts properly spaced, so completing the signal circuit. At the same time the curve of respiratory motion is being inscribed. A comparison of this curve, which by means of the signal permits an estimate of the volume of the tidal air, with the electrocardiogram will allow us to draw conclusions of the effect of phases of respiration on the cardiac curve. These curves are to be taken daily for a period of 10 days. We ought then to be in possession of data which will give exact information on the degree of uniformity of behavior of a group of normal individuals. In terms of these findings we should be able to tell how great a deviation from normal the rheumatic patients exhibit.

Clinical Studies of Quinidine.

The introduction of quinidine into clinical medicine may perhaps be regarded as the most important advance in the drug therapy of heart disease since Withering's account of the foxglove in 1785; for it is unique as a pharmacotherapeutic agent in that it serves to restore to normal a disturbed physiologic mechanism. It has also

furnished a valuable means of studying the nature of the disturbance which is at the basis of fibrillation and flutter of the auricles.

In May 1921, a preliminary report was published on "Restoration of the normal cardiac mechanism in auricular fibrillation by Quinidine". In that paper, four cases were described, in two of which it was possible to restore the sinus rhythm by oral administration of this drug. During the past year, twenty-two patients with auricular fibrillation have been treated. In nine (40.9 per cent) the normal rhythm has been restored for varying lengths of time. A detailed study of these cases has been made.

The drug has been administered by mouth in gelatin capsules. After a preliminary dose of 0.2 to 0.4 gm. to test for idiosyncrasy to members of the cinchona group, 0.4 gm. have been given three times at intervals of two hours on the first day; four times at similar intervals on the second day; five times at similar intervals on subsequent days. Regularization of rhythm has occurred for the most part on the first or second day of treatment. It has, in general, been futile to continue beyond five days of quinidine therapy.

Headache, tinnitus, epigastric discomfort, diarrhea and palpitation have been among the unpleasant symptoms attending quinidine administration. These are more frequently observed in patients in whom it is not possible to restore the normal rhythm than in those in whom the desired effect is accomplished.

By means of frequent electrocardiographic records, alterations in the cardiac mechanism have been carefully observed. The first effect has usually been acceleration of ventricular rate. This

has been followed in a number of patients by occasional premature beats of ventricular origin. The transitional mechanisms in the common order of their appearance were: coarser fibrillation, denoting retardation of auricular rate; impure flutter; flutter, and normal rhythm. In one patient the transition from auricular flutter to normal rhythm was, by good fortune, photographed in the second lead. The change was rather abrupt, in that there was a short period of altering auricular activity, slowing of ventricular rate for several beats, a relatively long period of asystole of both auricles and ventricles, and then prompt resumption of sinus rhythm. Alterations in the form and direction of the T-wave of the electrocardiogram have been observed after quinidine which are similar to the changes described after the administration of digitalis. Intra-ventricular block, sino-auricular block and alterations in the form of the ventricular complex have also been seen. Digitalization prior to quinidinization was not essential for success in therapy; for in the same individual a normal mechanism was restored on one occasion with ventricular rate of 180, and at another time, after the administration of digitalis, with the ventricular rate ranging from 90 to 100.

Of great significance for the clinic were certain toxic effects of the drug. Several sudden and unexplained deaths have been reported by competent observers. In one of our patients it was clear that heart failure was induced following a simple tachycardia resulting from quinidine. In several others, ventricular tachycardia was seen after doses ordinarily regarded as within therapeutic range. This mechanism assumes importance if it is borne in mind that in dogs poisoned by digitalis or strophanthin it is not infrequently the

precursor of ventricular fibrillation and death. It is, therefore, wise for the present to carry out the administration of quinidine with the patient in bed in a hospital, and preferably controlled by graphic records.

The reasons for the variable outcome of therapy are not clear. The normal rhythm has been restored in a variety of organic heart conditions, and therapy has failed in cases which, on clinical examination, differed in no way from those in the first group. It has been thought that a long duration of the fibrillatory process is unfavorable and that the recent occurrence of this abnormality tends to favor restoration of the sinus rhythm. This criterion is, however, not valid, for the normal mechanism has been restored in a patient who has been known to fibrillate for as long as seven years.

The duration of the effect after a single course of the drug is extremely variable, ranging from a number of days to as long as five months in our own experience. By properly spaced doses of the drug given over long periods of time it has been possible to maintain the normal rhythm for as long as nine months.

All of the patients in whom the normal mechanism was restored have been subjectively improved. In particular they were no longer aware of the action of the heart, and the sense of substernal pressure which is so often a source of complaint, disappeared. They are relieved, furthermore, of the necessity of continually taking digitalis. A number who have been chronic invalids have been restored to working capacity.

Teleroentgenographic studies of the changes in the size of the heart have in certain individuals, revealed striking differences

during the period of fibrillation and the period of normal rhythm, in the sense that when fibrillation was present there was an increase in the size of the heart. The dilatation occurring while this arrhythmia is observed is, in all probability, an attempt on the part of the heart to maintain efficient ventricular output by increased length of muscle fibre. An analogous diminution in the size of the heart has been observed in patients in whom no alteration of rhythm has taken place but in whom compensation has been restored following the administration of digitalis.

Studies of the vital capacity have shown very slight increase following restoration of the normal rhythm. Great changes were not to be anticipated for in all of these patients a fair degree of cardiac compensation was brought about by rest, regulation of fluid intake, digitalis administration, etc., prior to the administration of quinidine. The effects of atropine injected while the auricles were fibrillating and again given when the normal rhythm prevailed have been studied electrocardiographically. The results have not as yet been critically analyzed.

Teleroentgenographic Studies of the Size of the Heart in Pneumonia.

A preliminary report of these studies was presented last year. A technique for outlining the cardiac silhouette was described at that time. In brief, it was found that in a considerable percentage of cases of lobar pneumonia, and in a somewhat smaller percentage of cases of bronchopneumonia, there was a significant increase in the size of the heart during the active stages of the disease with gradual return to a fairly constant level during convalescence.

An attempt has been made this year to make studies of a similar series of cases to which digitalis was administered. Several hundred plates have been made but the measurements are not yet complete. It would appear from the material so far at hand that in patients who have received adequate digitalis dosage, marked cardiac dilatation does not occur. Whether this is to be regarded as a desirable effect is not altogether clear and depends in a measure upon the interpretation which is put upon the dilatation itself. This may be regarded as a compensatory lengthening of the muscle fibre in an attempt to maintain ventricular output during a period of stress or may be looked upon as an evidence of poisoning of the heart muscle accompanying the pulmonary infection. Certainly there are in the course of the ordinary pneumonia no outspoken manifestations of heart failure. It has been shown in this laboratory that in the normally beating heart digitalis in therapeutic doses serves to increase ventricular volume output. It has furthermore been shown that in pneumonia the T-wave of the electrocardiogram is affected in a manner quite like that seen in the absence of an infection. The marked grade of dilatation observed in certain cases of pneumonia and the very gradual return of the heart to its usual size has led us to believe that the enlargement in the course of this disease is evidence of a deleterious or perhaps compensatory effect. Prevention of such dilatation may be desirable. But in any case, if it can be prevented by the administration of digitalis additional concrete evidence is at hand to show that the drug acts upon the heart muscle in a definite and presumably favorable manner in this disease.

Studies on Respiration.

Dr Binger.

Since October 1921 Dr Binger's time has been spent largely in activities associated with the Anglo-American Physiological Expedition to the Andes. In October these consisted of accumulating equipment for the expedition and arranging details of transportation and finances. He was engaged too in a survey of the literature on the physiology of adaptation to low oxygen pressures. Until the time of his departure on November 16th, he was occupied with preparation for work which he was planning to take up upon his return. This consisted in some modifications necessary in the lung volume method. An elusive source of error which had troubled him for a year was discovered and the error corrected by somewhat changing the apparatus. Furthermore the oxygen chamber had to be over-hauled, made more leak-tight and improved in a variety of other ways to make it practicable and economically feasible.

On November 16th, 1921, he sailed in company with the four other American members of the expedition on the Grace Line S.S. Santa Teresa for Callao Peru, which is the Port of Lima. They spent the first week in Lima setting up their laboratory. Through the courtesy of the Peruvian Corporation which operates the Central Railroad of Peru, they obtained a baggage car, which, with the aid of a little carpentry, was converted into an excellent laboratory. A freight car which the Peruvian Corporation also furnished them served as a store house for supplies. These two cars were placed on a siding at Montsarrati about ten minutes by train from Lima and as soon as possible they started making base line observations on themselves.

The prime object of the expedition was a study of the phenomena of adaptation to low oxygen pressures - particularly an inquiry into the question of oxygen secretion, a subject over which there had been much controversy and which they felt, with the methods now at hand, could be definitely settled. This necessitated a study of the various phases of the problems concerned with hemato-respiratory functions of the body.

First.- A study of the mechanics of ventilation including not only observations on the minute volume of pulmonary ventilation, but also studies in lung volume, oxygen consumption, CO_2 elimination and alveolar oxygen and CO_2 pressures.

Second.- A study of the rate of diffusion of oxygen through the alveolar epithelium.

Third.- A study of the percentage saturation and oxygen pressure of the arterial blood which was to be the critical test of the oxygen secretion theory.

Fourth.- A study of the reaction of the blood and particularly of the oxyhemoglobin dissociation curve and CO_2 absorption curves.

This series of investigations was designed to study the physiology of respiration at all the salients now accessible. The problem of O_2 pressure of the tissues had to be left out because at present there was no method for such an investigation in the human subject.

Besides these observations a number of collateral observations were carried out concerned with pulse rate, circulation time, blood volume, red blood cell count, fluid balance and acid base

excretion. Dr Binger's participation in the work was concerned in the main with the studies in ventilation and lung volume, but chiefly with the construction of the oxyhemoglobin dissociation curves and the CO_2 absorption curves.

After two weeks at Lima the British members of the Expedition arrived, consisting of Mr. Barcroft and Mr. Doggart of Kings College, Cambridge, and Professor Jonathan Meakins of the University of Edinburgh. A day after their arrival some of the party (Dr Redfield and Dr Binger) proceeded by rail to Oroya (12,000 ft.). The others followed in gradual stages. All the members of the expedition were detained at Oroya from two to five days until the acute symptoms of mountain sickness, or "soroche" as it is called, had subsided. At Oroya as well as at Cerro de Pasco where they made their permanent headquarters, they were the guests of the Cerro de Pasco Copper Corporation who extended every courtesy and hospitality to them. They remained at Cerro de Pasco (14,200 ft.) for a little more than three weeks. The material for study they divided into three groups; I, themselves; II, the anglo-saxon residents mostly engaged as mining engineers; III, the indigenous population of Peruvian Indians and Mesistos, or half-breed Spanish Indians. These three classes made an interesting and valuable material for study: themselves, new arrivals; the anglo-saxons, resident intermittently for periods up to five years, and the indigenous population who had lived at altitudes approximating 15,000 ft. often for many generations. It was believed that any process of adaptation which was not initiated or completed in themselves after short exposure would surely manifest itself in the natives.

The more important results of their studies can be briefly stated as follows:-

1. Cyanosis and unsaturation of the arterial blood (15 to 20 per cent) were found in members of all three groups.

2. In no case was the arterial oxygen tension found to be higher than the O_2 tension in the alveolar air - or than could be accounted for by simple diffusion.

3. A shift to the left of the oxyhemoglobin dissociation curve was found in all the members examined of the three groups.

4. A shift downward of the CO_2 absorption curves was found in themselves.

5. It was found that the value of the diffusion constant as determined by the technique of Marie Krogh was the best index available to determine which members of the expedition would suffer from soroche.

A full report of these findings has been given in Mr. Barcroft's Lowell Institute Lectures and will be included in the report of the expedition which will be published by the Royal Society in its proceedings. A number of valuable and interesting anthropometric measurements were made particularly of the size and shape of the thorax and in this the portable X-ray outfit was of great service.

The expedition left Cerro de Pasco on January 12th, climbing Carlos Fransisca to the height of 17,500 ft. on January 13th, and sailed from Lima on the S.S. Ebro of the Pacific Steam Navigation Company, on January 15th. The homeward voyage was spent in figuring data and writing up the work, as well as in making further sea level observations. They arrived in New York on January 31st, being

delayed three days by a severe storm.

Since Dr Binger's return he has been engaged with investigations of ventilation in cases of lobar pneumonia and observations on oxygen therapy. He has had a patient with a positive pneumococcus Type II blood culture living in the oxygen chamber for 16 days. An exposure of this duration required a revision of the ventilation system - particularly of CO_2 removal. Besides it was found desirable to simplify the mechanical arrangements so that now the chamber can be easily managed by the nurses alone, without other assistance.

Dr Binger plans to continue this study until the pneumonia season is over and then to take up again the work with heart patients. The two problems are intimately associated and can profitably be approached with similar technique. The next stage in the solution of the problem relates to the function of pulmonary epithelium to the passage of gases into and from the blood as in the case of mountain sickness. Following this, there is the problem of the constitution of the blood in respect to the transport of gases. And then comes the effect of the constitution of the blood on the central nervous system. Associated with these problems connected with the blood, the mechanism by which peripheral (pulmonary) influences are conveyed to the central nervous system must be studied. The underlying idea is to determine what disturbs the character of breathing, what the disturbed character of breathing does to the organism and how it and its effects can be remedied.

The work on temperature, undertaken with Dr Clark, had to be discontinued owing to Dr Binger's trip to Peru. A method for

accurate temperature determinations to be used in this investigation has been published by Dr Clark.

Acute Respiratory Disease.

Dr Avery, Dr Morgan and Dr E. G. Stillman.

Prior to the recent work of Blake and Cecil on the experimental production of acute respiratory disease in monkeys, there was little definite knowledge concerning the pathogenesis of the various types of pneumonia, in spite of the fact that the pathology of this group of diseases has been known for many years. For example, there has been little accurate information concerning the primary pathways of infection, the initial point of bacterial invasion of the lungs, the character and location of the earliest lesions or the methods by which infection spreads throughout the lungs and consolidation develops. Even more important from the epidemiological standpoint, it has not been definitely known which of the various organisms concerned in the production of pneumonia are capable of initiating an infection without the assistance of the other contributing etiological factors. These questions, which might appear comparatively simple in the case of lobar pneumonia due to pneumococcus alone, become very complex in the case of the secondary pneumonias of measles and influenza.

The work of Blake and Cecil indicates that in pneumococcus lobar pneumonia, infection takes place solely by way of the respiratory tract; that pneumococci are incapable of initiating an infection of the healthy upper respiratory mucous membrane and that these cocci must gain access to the lower respiratory tract through the

intervention of some other factor or factors which break down the normal defensive mechanism before infection can be initiated. These experimental results are in accord with those of clinical investigation. It has been shown that the majority of cases of lobar pneumonia are caused by the highly parasitic pneumococci, Types I and II, and furthermore, that these types are not found in the mouths of normal individuals, but only in the secretions of those sick with the disease and occasionally in the mouths of persons intimately in contact with the sick. The importance of the mere presence of the organisms, therefore, as far as lobar pneumonia associated with these special types of organisms is concerned, becomes very great. It is hardly conceivable, however, that even in these cases the mere arrival of these virulent parasitic pneumococci in the mouths of individuals is the only factor concerned, for if it were, lobar pneumonia would obviously be very readily transmissible and assume the characters of an epidemic disease. Why it does not ordinarily do so finds partial explanation at least in the experimental facts previously referred to,- that a highly parasitic pneumococcus is incapable of inciting lung infection in a very susceptible animal unless it is able to gain access to the lower respiratory tract by factors entirely unrelated to the bacteria themselves. What some of these factors are, are matters of common but experimentally unsupported observation, such as exposure, fatigue, etc., and probably most important, mild upper respiratory tract infections such as common colds, all of which are assumed to operate in breaking down the normal defensive mechanism which guards the lower respiratory tract.

With the hope of determining more accurately the nature

and effect of certain of these factors on the production of pneumococcus infection of the lungs, the work of the bacteriological laboratories of the hospital has taken a twofold direction.

One problem has been the attempt to induce experimentally in animals respiratory infection with pneumococcus under conditions more closely approximating the natural infection in man. Normal animals, and animals previously subjected to procedures designed to lower resistance, have been exposed in suitable chambers to an atmosphere sprayed with virulent pneumococci. At varying intervals after exposure some of the animals have been killed and their lungs and other viscera cultivated for the presence of pneumococci, while other animals have been kept under observation for evidences of subsequent infection. These procedures have already yielded certain facts concerning the mechanism of infection, and the fate of virulent microorganisms implanted on the respiratory mucosa of normal susceptible animals.

The second problem of investigation concerns the kinds and nature of the microbial agents associated with the mild upper respiratory infections, which have already been referred to as probably the most important of the contributing etiological factors in the causation of pneumonia. Because of the advance in our knowledge of the respiratory flora already made by Olitsky and Gates in their experimental studies of the nasopharyngeal secretions from influenza patients, the present work has concerned itself largely with the attempt to isolate from the upper respiratory tract of normal individuals and of persons suffering from acute respiratory infections, microorganisms identical with or closely allied to the anaerobic

group of which B. pneumosintes probably represents the type.

The first of these problems, namely, that having to do with the production in animals of pneumococcus infection by aspiration and the factors influencing air-borne infection is being investigated by Dr E. G. Stillman. Mice and guinea pigs were placed in specially constructed metal chambers and sprayed with cultures of pneumococci, the virulence of which for the test animals had been previously proved by the intraperitoneal inoculation of other animals. Of the 147 mice used in these spraying experiments, 33 were killed and autopsied at intervals of from ½ to 48 hours after spraying. Pneumococci of the same type were recovered from the lungs of all of the 12 mice autopsied within 1 hour of spraying. After this period the incidence of recovery of pneumococci from the lungs rapidly decreases. Of the remaining 114 mice which were sprayed and allowed to live, all survived for 10 days with the exception of 5 which died with pneumococcus septicemia. These observations afford evidence that virulent pneumococci may reach the lungs through inhalation, but that in all but a relatively few animals these inhaled organisms are effectively disposed of. The anatomical and immunity reactions concerned in this defensive mechanism are now being investigated. In many experiments various attempts were made to reduce the resistance of the experimental animals, both before and after exposure to infection, by such methods as chilling, etherization, intraperitoneal injection of foreign sera. In no instance, however, did these measures materially alter the course of events already described.

In an attempt to trace the pathway of infection from a

known portal of entry Dr Stillman has injected pneumococci into the peritracheal tissues, and beneath the nasal mucosa of guinea pigs and followed by cultural methods the route of invasion to the lungs. Of the animals injected 31 were killed in from 1 to 3 days after infection and pneumococci were recovered by cultural methods as follows: from the tracheal mucosa 4 per cent, peritracheal lymphatic nodes 50 per cent, spleen 46 per cent, heart's blood 35 per cent, and lungs 32 per cent. Pneumococci were isolated directly from the lungs in 4 animals in which the heart's blood was sterile. A number of guinea pigs similarly injected survived. Several of these survivors were sacrificed 3 to 5 days after infection and in no instance were pneumococci recovered at autopsy. This work has been complicated by the occurrence in 67 per cent of the pigs autopsied of Gram negative bacilli of two distinct varieties. These secondary organisms have been recovered almost exclusively from the lungs and often from lungs which appeared entirely normal on gross inspection. These organisms probably belong to a group similar to the Gram negative bacilli which have been described by previous investigators as the cause of spontaneous epidemics of pneumonia in guinea pigs.

The second problem, namely the study of the anaerobic filter-passing group of Gram negative organisms associated with mild upper respiratory tract infections is being investigated by Dr Avery and Dr Morgan. In this study we have been fortunate in having the hearty cooperation of Dr Olitsky and Dr Gates, whose important contributions have added much to the knowledge of a hitherto unrecognized group of microorganisms of the respiratory flora. Several weeks were spent in becoming familiar with the biologic characteris-

tics of a strain of Bacterium pneumosintes originally isolated by Dr Olitsky and Dr Gates in the pandemic of influenza in 1918-19. During the recent epidemic of acute respiratory disease opportunity was afforded to put into practical service the technique and methods developed by these investigators for the isolation of organisms from the filtered and unfiltered nasopharyngeal secretions of patients suffering from so-called influenza. From 9 cases in which the clinical diagnosis of acute influenza was made, positive cultures of organisms evidently closely allied to B. pneumosintes have been recovered from the nasopharyngeal washings in 4 instances. These strains have certain characters which aid in identifying them with the group of organisms of which B. pneumosintes serves as a type. All possess in common the following characteristics: they are small, Gram negative bacilli, strictly anaerobic, and were cultivated directly from the filtrates of nasopharyngeal washings after passage through Berkefeld candles "V" - that is they were filter-passing in the form in which they existed before artificial cultivation.

Variations in morphology and cultural reactions suggest that these strains differ in certain characters from the type culture of B, pneumosintes. Further study of the cultural and immunological properties of these recently isolated organisms is necessary, however, before any certain opinion can be given as to their identity with the original strain. It is interesting that in two instances a positive culture was obtained by primary isolation from filtered washings directly on blood agar plates by the use of an anaerobic jar, thus eliminating the possibility of chance contamination from kidney tissue, ascitic fluid, or animal passage. Whatever relation

these strains and others that may be subsequently isolated may bear to one another or to the original B. pneumosintes, and whatever may eventually be proved as to their causal relationship to acute respiratory disease, there is little doubt that they constitute a group of organisms hitherto unknown. It is worthy of note that by identical methods of study of mixtures of the sputum and nasopharyngeal secretions from 8 patients suffering from acute lobar pneumonia of pneumococcus origin, organisms of this new type have not been encountered in a single instance.

Specific Soluble Substance of Pneumococcus.

In conjunction with Dr Heidelberger a study is being continued on the chemical nature of the soluble, specifically precipitable substance which is excreted in the urine of patients suffering from pneumonia of pneumococcus origin. This active substance derived from the infecting organism passes the kidney unchanged in specificity and appears in the urine in a form which reacts only with antipneumococcus serum of the same type as that of the infecting pneumococcus. It was soon found that this specifically reacting substance is not protein in nature, that it is stable in boiling solutions, that it is not dialyzable, and is precipitated from solution by acetone and alcohol. The methods of isolation and purification of the material now being studied depend on these facts. Proteins are removed by boiling the urine with dilute acetic acid and the neutralized and concentrated filtrate is poured into 10 volumes of acetone, the aqueous solution of the resulting precipitate is dialyzed until salt-free, and reprecipitated first with acetone and then with absolute alcohol. The product so obtained contains practically no

free amino nitrogen, but on hydrolysis yields about 50 per cent of the total nitrogen as amino nitrogen and 20 per cent as ammonia.

A product with practically identical properties is obtained by dissolving washed pneumococci in antiformin and purifying as in the case of rabbit. It has recently been found that a further inactive fraction can be removed by precipitating fractionally with acetone. The active substance is not precipitated by mercuric chloride in neutral solution and is therefore not a polypeptide or proteose.

The serologic type specificity of this reacting substance remains unimpaired by these chemical procedures; this fact affords a delicate biologic test for detecting the active substance throughout the various chemical manipulations incident to the search for its structural constitution. It is hoped that further study may reveal the chemical nature of this substance, with which the type specificity of pneumococcus is so intimately bound.

Accessory Growth Substances in Plant Tissues.

The study of the properties of blood upon which depends the ability of the so-called hemoglobinophilic bacilli to grow in this medium, has shown that these properties are related to at least two factors which can be separately studied. Both of these factors are present in plant tissue, (potato and banana), and sterile, unheated plant tissue can replace blood in the cultivation of B. influenzae. These observations have now been extended; yellow and white turnip, carrot, beet, parsnip, and sweet potato, when added to fluid media have been found to possess the same growth

stimulating action as white potato.

Dr. Morgan and Dr. Avery have found that these vegetable tissues not only permit the cultivation of the so-called hemoglobinophilic organisms, but that they also greatly favor the growth of other entirely unrelated organisms. For instance, in the case of pneumococcus, not only is there a marked acceleration of growth, but a seeding too minute in itself to initiate growth in plain broth alone, will amply suffice to induce abundant multiplication in the same medium to which small pieces of sterile, unheated vegetable have been added. Moreover, in the plant tissue medium the zone of hydrogen ion concentration within which growth can be initiated is considerably extended beyond the acid and alkaline limits of the optimal range in ordinary bouillon. In addition certain other bacteria, which ordinarily fail to grow in the presence of free oxygen, multiply in a medium containing fresh plant tissue even though no precautions are taken to exclude air. It is evident, therefore, that the presence in media of certain substances contained in fresh plant tissue not only supplies the necessary factors for growth of the hemoglobinophilic bacilli but furnishes the necessary requirements for the cultivation of other bacteria which multiply only under certain restricted conditions. One such condition is the reaction of the medium which in the presence of plant tissue may be made to vary over a much wider zone without retarding growth; another condition is oxygen tension which similarly seems to require for sensitive organisms much less accurate control in the presence of plant tissue than in its absence.

The exact nature of the substances contained in plant tissue upon which these properties depend is not yet determined, but the studies so far made, suggest that they are related to the presence of certain oxidizing and reducing enzymes in fresh plant tissues, as well as to the presence of so-called accessory food substances.