

REPORT OF THE DIRECTOR OF THE HOSPITAL

October 21, 1921

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In the past year the Hospital has had the advantage of having the most mature and experienced staff in its history. While during the early years of the hospital the staff consisted chiefly of young untrained men, the oversight and direction of whose work was almost entirely in the hands of the Director, during the past year there have been included in the staff several men of mature years whose training and experience have fitted them to carry on independent research and to direct the work of others. As a result the work in the Hospital has gradually become more or less separated into that of several divisions, more or less analogous to the divisions of the Laboratories of the Institute. The Director of the Hospital now shares the responsibilities of the work with several associates, each of whom is responsible for the work carried on in his department. It is well recognized that there are greater difficulties in the development of this kind of organization in the Hospital than in the Laboratories, but it is hoped that with close cooperation between the different divisions there will occur no loss but a great gain in efficiency.

During the years since its organization the Hospital has served as a training place not only for its own men, those who now constitute its staff, but it has also served to train men to occupy academic positions in internal medicine in the universities. Especially during the past year, on account of the reorganization of the departments of medicine in several medical schools, this demand for men trained here has resulted in the departure of a number of the

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most valued members of the staff. Doctor Blake, who has been engaged in important studies concerning measles, was called to Yale University to become Professor of Internal Medicine in the medical school which has been undergoing reorganization. Doctor Stadie, who has been a member of the Hospital staff for three and a half years, also left to go to the same institution as Assistant Professor of Medicine, and Doctor Peters likewise was called to the same place and accepted a similar position. While Doctor Peters occupied only a voluntary position in this Hospital, being sent here by Vanderbilt University, of the faculty of which he was a member, nevertheless, on account of his ability and industry, he had become an important member of the staff and his departure meant a very distinct loss.

Doctor Blake also took with him Doctor Trask, who had been cooperating with him and assisting him in the study of measles. Doctor Trask had been on the Hospital staff for two and a half years and had developed into a most capable worker. Doctor Austin, who has been resident physician in the Hospital, has been appointed Professor of Research Medicine at the University of Pennsylvania, and Doctor Glenn Cullen has been appointed Associate Professor of Research Medicine in the same institution. The appointments of these two men become effective on January 1, 1922, and they will remain at work in our Hospital until that date.

These changes make serious inroads upon the effective staff of the Hospital but several new appointments have already been made and it is hoped that the new organization will soon become welded into an effective force.

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Doctor Christen Lundsgaard of Copenhagen has been given an appointment on the staff of the Hospital, and it is expected that he will arrive about November first to take up his new duties. For the present he will live in the Hospital and will act as Resident Physician. He previously worked in this Hospital, in 1917, carrying on studies of much importance in the field of abnormalities of respiration. He had had a long experience in internal medicine in the Rikshospital at Copenhagen and has been the first assistant in the University Clinic of Professor Faber. Doctor Hugh Morgan, of the Johns Hopkins University, has been appointed an assistant resident physician, Mr. James Neill has been appointed assistant in the chemical laboratory, and Dr. A. B. Hastings has been appointed an assistant, to carry on work along the lines of that now being done by Doctor Cullen. Other appointments will be made as suitable men are found to fill the vacancies in the staff.

With the arrival of Doctor Lundsgaard it is planned to extend the studies of nephritis and to prosecute this work along new and more comprehensive lines.

#### Acute Respiratory Disease.

The study of acute respiratory disease has been continued but along somewhat different lines. The treatment of cases of Type I pneumonia with specific immune serum has been continued with results agreeing with those previously reported. This is only an incidental part of the study, however, since it is believed that the efficacy of this serum has now been well demonstrated and its further employment, as well as its manufacture, should be left to others. The efforts to produce serum effective against the other types of pneumonia have

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not proved successful or promising and it is believed that the successful treatment of these other forms will have to be attained by some other and new method of approach. Consequently during the past year attention has been given to the study of certain fundamental properties of the bacteria concerned in the etiology of pneumonia and to a more detailed investigation of the functional abnormalities occurring in patients suffering from this disease.

Doctor Avery and Doctor Cullen have continued their studies on the ferments present in the bodies of pneumococcus, which were described at some length in the previous report. These investigations have shown that by means of sterile solutions and extracts of pneumococci, it is possible to correlate many of the functional activities of the living cell with the enzymotic processes of the intracellular substances removed from the growing organism.

Further study has demonstrated still other activities of these pneumococcal substances. These specific intracellular agents exhibit other properties in the presence of different substrates. For instance, when allowed to act on blood, active solutions of pneumococci are strongly hemolytic, causing complete dissolution of the red blood cells, and under proper conditions may effect important changes in the blood pigment, transforming the hemoglobin into met-hemoglobin. These substances partake of the nature of endohemotoxins and may prove to be concerned in certain blood changes clinically associated with pneumococcus infection in man.

During the past year it has been found that in addition to the enzymotic and hemotoxic properties above referred to, in the presence of bacterial substrates consisting of heat-killed pneumococci these active enzyme-containing solutions cause complete and

prompt lysis of the dead bacteria. This bacteriolytic enzyme manifests extraordinary specificity, exerting its dissolving action only on pneumococci and not on hemolytic streptococci or staphylococci. On green-producing streptococci, which may be more closely related to pneumococci than either of the other two organisms, the bacteriolytic enzyme of pneumococcus exerts a lytic action which, however, is never so active or so complete as in the case of the homologous organism itself. Investigation of the bacteriolytic property of the intracellular substance of pneumococcus has shown that this enzyme, like those concerned in protein, fat and carbohydrate cleavage, manifests its optimal activity over a hydrogen ion concentration similar to the zone optimal for the biological activities of the growing organism itself.

In connection with the investigation of these intracellular enzymes, a study is being made of autolysis of pneumococci. It has been found, when washed pneumococci from actively growing cultures are suspended in solutions of various salts, that the extent and rapidity of self dissolution of the organisms is dependent upon the hydrogen ion concentration of the mixture. Autolysis is most rapid and complete over the zone of pH 6.5 - 7.5; within which range lie the optima of the protease, lipase and invertase of pneumococcus. In fact within this zone, all types of enzymes of pneumococci thus far described can act simultaneously. This fact recalls the observation of Derby that autolysis of animal tissue proceeds furthest at a reaction where the various enzymes can function simultaneously.

In the course of this study, observations have been made on the effect of autolysis on the heat precipitability of pneumococcus protein. It has been found, that under the influence of heat,

precipitation of the autolysate occurs at a definite reaction, and moreover, that the point at which precipitation with pneumococci, Type III, occurs, is different from the point at which precipitation of pneumococci of Types I and II occurs. The reaction point of precipitation is also different from the zone of acid agglutination of these groups as determined by Gillespie.

Doctor Avery and Doctor Thjotta have been undertaking studies on bacterial nutrition, which have dealt specifically with certain accessory substances concerned with the growth of hemophilic bacilli. Particular attention has been given thus far to the nutritional requirements of *Bacillus influenzae*, since this organism belongs to a group of bacteria which heretofore have not been grown except on media containing blood or blood derivatives. The reason for the peculiar sensitiveness of these bacilli to the presence or absence of even minute traces of blood in culture media has been the subject of much discussion and investigation. Closer analysis of the growth requirements of these organisms, however, has shown that this so-called hemophilic property has been based on a lack of knowledge of their actual nutritional needs.

The substances in blood, upon which growth of *Bacillus influenzae* depends, have been traced by experimental methods and found to be dependent upon two separable and distinct factors, both of which are requisite for growth and each of which is separately inactive. Study of the growth stimulating action of these substances and their chemical and physical properties has brought out certain facts as to their biological significance in the cultivation of *Bacillus influenzae* in particular, and their relation to bacterial nutrition in general. Both of these substances differ in character

one from the other in ways suggestive of their separate functions. One of these, the so-called V factor, is a vitamine-like substance which can be extracted from red blood corpuscles, from yeast and vegetable cells; it is relatively heat labile, readily absorbed from solution by charcoal, and similar in its growth promoting action to the known vitamins. The second substance, the so-called X factor, in blood is heat stabile, present in greatest concentration in red blood cells, absorbed from solution by charcoal, and effective in such small amounts as to suggest its catalytic nature.

It has been found further that these growth accessory substances which occur in blood are also present in plant as well as in animal tissue. These observations on the growth of the so-called hemophilic bacilli on blood-free media have demonstrated that substances of bacterial and vegetable origin (potato) can function in the same manner as the growth inducing factors of blood.

From the results of this investigation it seems not unreasonable to assume that nutritional deficiency in the cultivation of other bacteria may be overcome by the addition to culture media of the appropriate growth accessory substance.

Doctor E. G. Stillman has completed and published his study on the biological classification of hemophilic bacilli. This work has made possible the recognition of distinct varieties of organisms closely related biologically, yet differing quite sharply from one another in their biochemical reactions. Within this group of hemophilic bacilli, *Bacillus influenzae* is recognized as the type organism. With the limits of this group more clearly defined bacteriologically, Doctor Stillman has undertaken a study of the occurrence and distribution of *Bacillus influenzae* in the noses and throats of normal

individuals and of patients suffering from acute respiratory disease. While it is recognized that this bacillus may be of doubtful significance in the etiology of clinical influenza, its importance as a secondary organism in respiratory infections in general is little questioned. A study therefore as to the incidence of Bacillus influenzae, especially in association with acute lobar pneumonia has been made. It has been found that this organism occurs in the throats of about 30 per cent of normal persons. In 30 cases of lobar pneumonia, on the other hand, Bacillus influenzae was recovered from the throats of 80 per cent of the patients. The marked increase in the incidence of this organism in association with disease due to pneumococcus infection suggests that possibly Bacillus influenzae may be one of the contributing factors which allow the non-invasive pneumococcus to penetrate the lower respiratory tract.

Doctor Blake and Doctor Trask.

During the past year a most interesting and important investigation concerning the transmissibility of measles to monkeys has been carried on by Doctors Blake and Trask. Owing to the departure of these men to take up their work in Yale University, mention of which has been made elsewhere, a study of measles will be discontinued in this Hospital for the present. Doctors Blake and Trask intend to continue their studies at Yale University. The following is a somewhat extensive report of the results of their work as far as completed.

Although Anderson and Goldberger had reported the successful transmission of measles to monkeys, and Hektoen had reported the artificial transmission of measles from man to man by subcutaneous injections of blood, others had failed to make such successful transmission

experiments and the latest experiments under the direction of Sellards had been entirely negative. Therefore, at the time of undertaking this work by Blake and Trask, the question of the transmissibility of measles to animals was unsettled. In taking up this problem and in devising methods of attack, Doctor Blake was influenced by the experience gained in his studies concerning the production of pneumonia in animals. He decided that it would be advisable to use comparatively large amounts of material thought to contain the virus, and second, that it would be advisable to inoculate this material in what it was thought to be the natural path of infection. Clinical observation has indicated beyond reasonable doubt that the virus of measles is abundantly present in the secretions of the respiratory tract during the prae-eruptive and early eruptive stages of the disease and that the respiratory mucous membrane is the natural path of entry of the virus. The method used in the preliminary experiments, therefore, consisted in the inoculation of the mucous membranes of the respiratory tract of monkeys with unfiltered nasopharyngeal secretions of patients in the early stages of measles. The secretions were collected by irrigation of the nasopharynx with 20 to 40 cc. of sterile 0.85 per cent salt solution. The monkeys were inoculated with 5 to 10 cc. of these nasopharyngeal washings by intratracheal injection in order to facilitate retention by the animal of as much of the material as possible. When as much as 5 to 10 cc. was injected a small amount was commonly regurgitated and spread itself over the mucous membranes of the buccal and nasal cavities.

By injecting in this way the unfiltered nasopharyngeal washings from cases of measles in the prae-eruptive and early eruptive stages of the disease a relatively constant group of symptoms was

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induced in the monkeys which closely resemble those of measles in man. Of seven monkeys inoculated intratracheally with unfiltered nasopharyngeal washings from seven cases of measles, five developed the symptoms. The same group of symptoms was induced in one monkey by inoculation of the mucous membrane of the nose and mouth with unfiltered nasopharyngeal washings from a case of measles. In these experiments a variety of organisms, largely saprophytic inhabitants of the nasopharynx and mouth, were present in the material inoculated. There is sufficient evidence, however, that these organisms were in no way responsible for the reaction, since the same group of symptoms was induced in two monkeys by the intratracheal injection of nasopharyngeal washings from three cases of measles after the washings had been freed from ordinary organisms of the mouth flora by filtration through Berkefeld N filters.

The characteristic group of symptoms which follows the inoculation of monkeys with the nasopharyngeal washings from patients with measles has been successfully carried through six passages by intratracheal injection of saline emulsions of the skin and buccal mucous membranes of monkeys killed from 2 to 6 days after the onset of the reaction. From the fourth passage monkey the reaction was also successfully induced in three monkeys by means of citrated whole blood injected intravenously. This experiment showed the blood to be capable of inciting the reaction from at least the 7th to 13th days after intratracheal inoculation of the donor monkey, but incapable of inducing it from the 2nd to 4th days. Cultures of the blood showed no growth.

The group of symptoms induced has been constant and definite in character. After an incubation period of 6 to 10 days the animal

becomes listless and drowsy, the conjunctivae become injected, and small, discrete, hyperemic macules appear on the labial mucous membrane. These spots increase in number and may eventually coalesce in the course of 2 to 4 days to form a diffuse, red, granular rash. This rash is usually limited to the labial mucous membrane but may extend to the inside of the cheeks. The individual macules may or may not show the minute bluish white center characteristic of Koplik spots. From one to several days after onset an eruption of small, discrete, red maculopapules appears on the skin, usually coming out first on the face. The rash progressively increases in the number and size of the individual lesions and may in the course of 2 to 3 days extend to the skin of the neck, shoulders, upper arms, chest, abdomen, and thighs. It is constant in character but varies considerably in extent in different animals. By the time the exanthem is fully developed, the rash on the mucous membranes has begun to fade and soon disappears. The exanthem in turn progressively fades, sometimes with a branny desquamation, sometimes without. There may be moderate pigmentation. By the 6th to the 10th day after onset all symptoms have disappeared and the animal again appears well. Coincident with this group of symptoms there is a constant and definite reduction in the total leucocyte count, frequently constituting a true leucopenia. Other symptoms of irregular occurrence are photophobia, diarrhea, and fever. Symptoms of rhinitis and bronchitis have not been noted.

Microscopic examination of sections made from the skin of the animals during the period of eruption have shown that the lesions present resemble exactly those seen in the lesions of the skin in human patients. Numerous attempts were made to obtain cultures of

a virus from the lesions and blood, but it has so far been impossible to obtain cultures of any organism which seems to bear any specific relationship to the disease. The results of these experiments, therefore, have indicated that the disease, apparently identical with measles in man, may be successfully transmitted from man to monkey and from monkey to monkey.

In order to bring still further evidence that the disease produced in monkeys can be truly termed experimental measles, Doctors Blake and Trask have studied the immunity present in the monkeys following the disease produced by experimental inoculation.

Since an apparently permanent immunity against reinfection characteristically follows one attack of measles, the same phenomenon should hold true with respect to the experimental disease if the two conditions are to be regarded as similar. Furthermore, an acquired immunity, if present, should theoretically be efficient against a virus of heterologous source as well as against that of homologous origin, since there is little clinical evidence to show that one attack of measles fails to confer an immunity that is effective against all subsequent exposures. Authentic reports of repeated attacks of measles in the same individual are so few as to be negligible in this connection. In order to test the validity of the foregoing assumptions a series of reinoculation experiments in monkeys which had recovered from a previous attack of experimental measles was carried out.

The result of the experiments shows that one attack of experimental measles confers an apparently complete immunity against reinfection with measles for at least a considerable period. In all probability this immunity is permanent. Moreover, monkeys which have recovered from experimental measles are immune to reinfection

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with the virus of measles irrespective of whether the virus is of homologous or heterologous origin. In this respect experimental measles in the monkey corresponds with measles as observed in human beings, and the result is the same whether the virus is inoculated on the respiratory mucous membrane or is injected intravenously.

However, the exact nature of the immunity produced in monkeys or the immunity developing in man following a natural infection, is still obscure. The way, however, has now been opened to a further study of this problem as well as to the extremely important practical question regarding methods for producing artificial immunity in man. Preliminary experiments by Doctors Blake and Trask indicate that the production of artificial immunity may be quite possible though the studies have not yet reached a stage which will justify drawing definite conclusions. The successful outcome of such an attempt would undoubtedly be of very great value, for although under ordinary conditions measles itself is not a serious disease, yet the complications following measles present one of the greatest hazards of childhood. The dangers of this disease are enormously increased when it occurs among groups of individuals living in unhygienic or crowded surroundings, as in asylums, or as occurred among the soldiers during the war. Knowledge of a method of prophylactic inoculation at the beginning of the late war would undoubtedly have saved many thousands of soldiers from death.

#### Doctor Van Slyke

We have continued the work begun last fall with Doctors Austin, Cullen, McLean and Peters, in collaboration with the laboratory of L. J. Henderson, to ascertain the normal gas and electrolyte

composition of the blood cells and plasma, and the changes in them resulting from changing  $\text{CO}_2$  and  $\text{O}_2$  tensions. The object of the work has been twofold, (1) to elucidate the blood changes that form a part of the respiratory process, and (2) to obtain accurate normal blood pictures more complete than those hitherto available, which may be used as a basis for comparison with the blood pictures in pathological conditions, such as pneumonia and nephritis.

It was found necessary to pay attention to technique before results of the degree of accuracy required for some of the phases of the problem could be obtained. For former purposes, such, for example, as studies of acidosis,  $\text{CO}_2$  determinations on the blood were sufficiently accurate if the error did not exceed  $\pm 1$  volume per cent. For the present work it has been necessary to refine the technique so that the error was reduced to  $\pm 0.2$  volume per cent. Similar refinements proved necessary in the current technique for rapid saturation of blood with atmospheres containing controlled tensions of  $\text{CO}_2$  and oxygen. The necessities for, first, unusual accuracy, and second, rapidity in order to complete operations before extra-vascular changes alter the blood, have required the development of new technique for this entire field of work. The development of the necessary methods for this problem has consumed an unexpected amount of time. Before the close of the past year, however, results of a high degree of constancy were being obtained, and we hope to assemble the desired data before Doctor Cullen and Doctor Austin leave in January.

Doctor Stadie has improved the details of his oxygen chamber, so that the control is simplified and waste of oxygen eliminated. During the pneumonia season a number of severely ill patients were treated in it. The results confirmed those of preliminary experiments

during the preceding year. Cyanosis disappeared when the oxygen content of the air was raised to 40-50 per cent. In cases where oxygen saturation was low the oxygen content of the blood was caused to approach or regain a normal level. Respiration became slower and deeper, and tachycardia was markedly diminished. In short, the symptoms which might be attributed to oxygen want were diminished, and the comfort and clinical conditions of the patient appear to have been uniformly improved. The course of the infection does not appear to have been altered, however. The temperature was not brought down. And if, while the temperature was still high, the patients were removed from the oxygen chamber, they quickly relapsed into about the condition in which they would apparently have been had oxygen not been administered. In order to improve by oxygen administration a patient's chance of recovery, therefore, it seems necessary to maintain him continuously in the oxygen-enriched air until he becomes convalescent. When this is done, it does appear that the oxygen treatment improves the chance of recovery in patients who are unable in ordinary air to keep their blood normally oxygenated. The favorable effect seems to result, not from influencing the course of the infection, but by protecting the patient from the added injury of oxygen want, and from the exhaustion that results from the speeding up of the respiratory and circulatory apparatus in the effort to compensate for incomplete oxygenation. Such protection apparently aids a certain proportion of patients, who would otherwise die, to survive until the natural factors of resistance overcome the infection.

Doctor Binger has developed the lung volume method to such a point that it can be used quite without cooperation from patients,

and can be employed without inconvenience even to those who are ill. As mentioned in the March report, this has been accomplished by having the patient breathe from a spirometer a mixture of oxygen and hydrogen, the hydrogen being accurately measured, the oxygen merely approximately measured in amounts to afford the patient a sufficient supply for the 3 to 5 minute period of the experiment. At the end of the latter, the ratio of nitrogen to hydrogen in the gases is determined, and from it the nitrogen volume and hence the air volume contained in the lungs at the start is calculated. The method has yielded results of interest with heart patients, although the data are as yet not sufficiently complete to generalize. Doctor Binger will this year probably apply the method also to a study of the lung changes in pneumonia, particularly during resolution. The latter problem was the one for which the lung volume work begun with Doctor Lundsgaard was first planned.

Miss Hiller has continued her work on the unidentified basic amino acid of gelatin. It has proved possible to recrystallize it only as the phosphotungstate. The free base has been prepared from the phosphotungstate, and has proved to be an amorphous solid. One half of the nitrogen is in the form of amino groups. When the substance is heated in vacuo at 100° to dry it, it slowly decomposes. Because of the difficult properties of the substance, which presumably have prevented its former detection, the problem of determining the structure is not easy, and will probably require a considerable amount of time.

Miss Hiller at the same time has brought near completion her systematic study of the protein precipitants applicable to analyses of blood and of protein digestion products. The nature and

purpose of this study were indicated in the report of last March.

Doctor Edgar Stillman has carried the work on nephritis through the year, and has collected an amount of data on correlated functional and clinical observations. It is hoped that information thus accumulated may ultimately afford us additional aid in differentiating the types of nephritics and the corresponding types of treatment that are justified. The work is necessarily long, involving as it does systematic following-up and re-observation of patients until sufficient data have been accumulated either to confirm or to alter the present methods of classification and treatment of the disease.

Doctor Swift

Clinical studies: During the past year clinical studies of patients with acute rheumatic fever have been continued. Thirteen such patients have been studied. Special attention has been paid to the effect of the administration of salicylates on the course of the disease, having in mind the question of the specificity of this drug.

In collaboration with Doctor Cohn definite evidence is being collected of the presence of myocarditis and impairment of the impulse conduction during the course of the disease. Electrocardiograms are still being made daily in the acute stage of the disease and at longer intervals in the subacute and chronic stages. With the assistance of Doctor Cullen, a study is being completed of the reaction of the joint exudates. These have been found to range from pH 7.2 to pH 7.4, showing that there is no appreciable acid production in the involved joints.

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Bacteriological studies: Joint exudates and blood of patients have been cultured aerobically and anaerobically, cultures having been made during the year. In no instance did the cultures show growth. Rheumatic nodules found subcutaneously and in the tendon sheaths of patients with acute rheumatic fever have been excised and cultured by the Noguchi anaerobic method; thus far no growth has been observed in these cultures, nor have organisms been observed in sections of the nodules stained with eosin and methylene blue and by the Giemsa method. The supply of such lesions has been limited, owing to their infrequent occurrence in the patients studied. During the coming year it is hoped that a greater abundance of material will permit us to exploit more elaborately this method of attack, for these nodules, which are considered characteristic of the disease, seem to offer the most hopeful method of approach to the etiologic agent.

Transmission experiments: The attempt to transmit the disease to animals has been continued. Last year rabbits and guinea pigs were inoculated with joint exudates and blood of patients. We were unable to reproduce the clinical picture of polyarthritiis, although several of the animals developed a monarthritiis. A histological study of the hearts of these animals is being completed. Certain of the hearts have shown myocardial lesions, the interpretation of which is still unsettled.

Fourteen monkeys have been injected with blood and joint exudate. The results of this work have been confused by a concurrent parasitic infection of the monkeys which manifests itself clinically by fever, leucocytosis, eosinophilia, joint swellings, subcutaneous nodules and blisters on the palms and soles; from these

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latter lesions have been recovered the ova and the adult female of a worm which has been identified by Dr. Stiles of the United States Public Health Service as a member of the super-family trichinelloidea. Dr. Stiles reports that he can find no record of a similar infection in monkeys.

It is probable that this disease has been present in the monkey house for at least three years. In order to continue transmission experiments it seemed necessary to learn more of this disease which simulated in several respects rheumatic fever. During the last three months such a study has been undertaken.

The fully developed female worm, which measures from 1.3 - 1.5 cm. in length, and about 0.5 mm. in thickness, appears just beneath the skin of the palms and soles, giving rise to a papule. The worms recovered at this time are motile and contain many ova. The evidence indicates that the worm burrows beneath the skin, forming a serpiginous blister, and the eggs are deposited. The blister ruptures and the ova are scattered outside the body. Forty to 120 ova have been found in a single blister. These ova are brownish in color, lemon shaped, 70-90 $\mu$  long, and 25-40 $\mu$  wide, with opercular plugs. At the time of rupture of the blister the female worm seems to be partially disintegrated. No male worms have been recovered from the skin lesions. The subcutaneous nodules have been examined histologically, some of them showing the presence of a coiled worm. A few, however, have shown no parasite. A few of the monkeys have been autopsied recently to determine the visceral lesions. Encysted adult worms were found beneath the mucosa of the colon and in the omentum close to the transverse colon; these worms were slightly thicker in the body than the worms found in the skin lesions. Most of them on

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removal from the cysts were actively motile; a few seemed dead. Some of the cysts contained only a brownish substance and no worm. These worms are probably of the male sex. Specimens of these have been sent to Dr. Stiles whose reply has not yet been received.

Salicylate investigation: The non-hemolytic streptococcus is still believed by many to be the etiological agent of acute rheumatic fever, and salicylic acid has been considered a specific remedy. If these views are correct, it would seem that some protection could be afforded against artificially produced streptococcus arthritis by the administration of the drug. We have just completed such a study in rabbits. Fifty-two rabbits were used, one-half receiving salicylates by mouth in dosage comparable to that used in the treatment of acute rheumatic fever in man, the other half acting as control. All the rabbits were injected with strains of non-hemolytic streptococci recovered from cases of rheumatic fever. Polyarthritides developed in both the rabbits receiving salicylates and in the control rabbits. No difference in the frequency of occurrence or in the number or severity of the joints involved could be found in the two series.

Doctor Swift has continued his investigation to determine whether or not the immune bodies formed by injection of non-hemolytic streptococci into rabbits could be enhanced by a simultaneous administration of salicylates. His results have corroborated his previous ones, to wit, that no increase in antibody production followed the administration of salicylates.

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Doctor Cohn

In the early part of the past year, the old laboratories on the third floor of the administration building and on the sixth floor of the Hospital were abandoned and the new ones on the eighth floor of the Hospital building opened. The Hospital building has been re-wired and new wires have been run to the roof of the administration building to connect Doctor Carrel's laboratory with the galvanometer room, as well as to the animal house. These changes have proved to be eminently satisfactory in a technical sense and have afforded the opportunity for considerable increase in the range and volume of our activities.

The problem of the behavior of the heart in acute rheumatic fever has been studied in association with Doctor Swift. It has long been known that the endocardium and the pericardium of this organ are frequently involved in rheumatism, and criteria for appreciating disease of these structures are available. The disorders of these structures have long been regarded as constituting heart disease. But at least of equal importance with them is the reaction of the muscle, which after <sup>all</sup> represents the bulk of the heart. This has until recent times been relatively speaking a silent area. Since the introduction of graphic, and more especially of electric methods, it has become possible to study in certain important details the events which take place here. We have taken advantage of this technique. It was known before that the bundle of His, a thin muscular strand which connects the ventricles to the auricles, is involved in the rheumatic process and when involved causes defects in impulse conduction. The orderly, coordinated, beating of the cavities of the heart is thus seriously compromised; there are gross

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disturbances. We found in addition to the gross changes that alterations of a more subtle nature were in point of fact taking place from day to day, the degree increasing or decreasing. These gave us an insight into the daily progress of the disease in so far as it affects this structure and served as a valuable guide in studying the state of the disease. In a similar way, alteration in the great mass of the ventricular muscle has been investigated. This can be followed by studying the details of the ventricular portion (Q R S-complex) of the electrocardiographic curve. In the same person, such curves usually have a remarkably constant form. Changes of a striking nature were, however, actually found in the curves of at least one patient. While the exact significance of the observations requires further investigation, it is probable that advance in knowledge of the disease process can be made by this method. And not only knowledge of the disease process, but also perhaps a guide to treatment may be found. So long as alterations like these go on, no matter what the other signs show, the course of the infection cannot be regarded as having come to an end. The ordinary rhythmic irregularities in the mechanism of the heart beat were also found. Although these are of interest, they were not unusual, except that by good fortune we were able to photograph a transition from the mechanism of auricular fibrillation to one of normal mechanism.

Recently, in Germany, Frey, acting on a suggestion of Wenckebach, re-introduced the use of a cinchona derivative (quinidin sulphate) in the treatment of cardiac affections, notably fibrillation of the auricles, an affection in which the pulse is completely irregular, with the view to restoring the normal cardiac

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mechanism. In accomplishing this he, as well as others, was successful in more than half the cases treated. Doctor Levy has given the drug to 12 patients in the Hospital of the Institute and like the other observers has succeeded in restoring the normal rhythm in 3 cases. The number of patients it has been possible to treat is insufficient to serve as the basis of a statistical account of the drug's action, but he has been able to make very detailed studies both of the methods of giving the drug, and of the nature of the mechanisms which the drug induces and through which the heart passes on the way back to its normal state.

Concurrently we studied the action of quinidin in dogs. It seemed important to us to do this for two reasons, first, in order to study exactly the behavior of a drug which has so profound an effect in altering the mechanism of the human heart; and second, because quinine has been regarded as having a depressant action, that is to say, an action which reduces the contractile function of the heart muscle. If this were a prominent feature of its activity, its usefulness as a cardiac remedy might easily be lessened. The most striking alteration we found was, contrary to our expectation, an increase in the power of contraction of the ventricles. It is on this account that for clinical purpose we attach significance to our experiments, for if the drug is not a depressant, a residual hesitation to use it may be removed. We have safeguarded our conclusions by making a variety of tests, to exclude the possibility of error due to the nature of the experiments, such as anesthesia and the necessary operative procedures. We wish, however, to be guarded in drawing inferences from our work bearing on the use of quinidin for clinical administration because of the importance and

seriousness of the conditions in which the drug is employed.

The other actions of the drug in dogs, which we found, yield no information of a striking nature except that a fall in blood pressure takes place, at first great and transient - later moderate but permanent during the duration of the experiment. This effect it was necessary to study in detail, because it is itself important and because it may be involved in bringing on the increase in contraction which has been described. In patients, however, a similar fall in pressure was never seen; the drug has no danger from this point of view. Of its relation to the increase in contraction, we can report that a number of control experiments in which the blood pressure was made to fall by other means, failed to duplicate the result obtained with quinidin. Its contractile action then, is exerted apart from its action on blood pressure, and the latter is an effect which, as has just been mentioned, we have not seen in man.

Doctor Levy studied in animals, in a preliminary way, the action of a new strophanthin compound, prepared by Doctors Jacobs and Heidelberger. This drug appeared to be less toxic though therapeutically as effective as the mother substance. In view of the importance of the strophanthin group of drugs in the treatment of patients, it seems desirable to possess them in pure form and to study the action of variant forms with the view to finding ones serving the specific needs of clinical physiology.

Doctor Levy is studying alterations of the size of the heart in pneumonia. This study is important because of the doubt which still surrounds the occurrence of collapse in the course of this disease, and the relation of cardiac dilatation and failure to

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its onset. But it is important in addition to this because apart from collapse, changes in the pulmonary circulation are believed to take place in this disease and to be attended by changes in the size of the heart. If, as experiments in our laboratory show, digitalis acts on the heart during pneumonia, and if, as our experiments also show, this drug increases the contractile power of the heart, additional interest attaches to this study. For should a change in the size of the heart appear to be usual, we have a means at hand, through ability to increase contraction, to bring about relief of this condition.

The method employed has been to make X-ray photographs with great care - all photographs being made as nearly as possible with an identical technique. We are then assured of having plates so nearly comparable that their measurements can be compared day by day. The plates are placed two meters from the target of the X-ray tube; the target is elevated to the level of the substernal angle, the median line of the front and of the back of the chest are in the same line with the target; the exposure is made during normal inspiration.

Doctor Levy has found that if these conditions are adequately met, the X-rays of normal persons do not differ by more than 1.0 cm. in the transverse dimension of the heart's shadow nor by more than 10.0 sq. cm. when the whole area of the shadow is measured. A more accurate method than hitherto available has been devised for outlining the cardiac silhouette. When these results are compared with the situation in ten cases of lobar pneumonia, it is found in nine that there is a distinct increase in both measurements, in the transverse diameter as much as 19 per cent, and in the area

as much as 37 per cent. A similar increase is rare in broncho-pneumonia, that is to say, an increase was found in two of six cases. The size of the heart decreases with the fall in the temperature and the pulse rate, but usually it lags behind these and does not return to the base line until some time, perhaps a matter of weeks, afterwards. Occasionally, during early convalescence, the size falls below that finally attained.

The observations, although still insufficient in number, indicate that the management of convalescence has a bearing on cardiac size - sitting up in bed, especially perhaps if permitted too early, is attended by a return of increase in size. There is a single observation in which it appears that giving digitalis prevented the anticipated delay in the return to normal size. These illustrations point out the practical bearing of this study.

Doctor Binger has worked on a method for measuring the quantity of air in the lungs of patients suffering from shortness of breath, and has now perfected it. The method determines not only the so-called vital capacity or that volume of air which can be expelled from the lungs after maximum inspiration, but also the residual air which remains in the lungs and cannot be expelled even on forced expiration. Residual air is measured by allowing the subject to breathe to and from a spirometer containing a mixture of oxygen and hydrogen. By a chemical analysis of the spirometer contents before and after the patient has breathed, the degree of dilution of the oxygen and hydrogen mixture with the lung air is estimated and thus the volume of the lung air is calculated. By a similar technique the volume of air remaining in the lungs at the end of a usual expiratory movement may be determined. This method has the advantage

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of demanding a minimum of cooperation on the part of the subject and therefore is applicable to patients with severe cardio-respiratory embarrassment - the very type in which a study of lung volumes is needed. Previous methods have not proved satisfactory in this type of case. It has been applied to a series of individuals suffering from heart failure with the view to understanding further the mechanism of their circulatory and respiratory incapacity. A series of observations has been made on normal individuals for control purposes. The measurements obtained have been correlated with certain physiological standards as a further control. It is planned to carry this work further with particular attention to the volume of air content in the lungs in the expiratory phase of normal breathing, and to study its value in relation to the so-called tidal air, which is the amount inhaled and exhaled with each breath. By these relative values it is believed that a more or less quantitative expression for dyspnea (shortness of breath) will be obtained. The method for measuring lung volumes in its present form, we believe, is applicable to the study of pneumonia, in which an investigation of the air content of the lung during stages of consolidation and resolution would be very instructive. So far as we know, previous methods of studying lung volumes have not been practicable for such investigation.

The study of respiration in heart failure has pointed to the intimate relation between circulatory failure in the lung and decreased lung capacity. It has emphasized again a fact long observed at the Rockefeller Hospital that patients suffering from heart failure have a tendency to elevation of temperature. An explanation of this phenomenon has presented itself in a more or less

hypothetical form as being due to impaired heat excretion due to the fact that the blood is stagnating in the internal organs and not adequately brought to the surface of the body. This interpretation of the findings has suggested a field for investigation. Apparatus has been designed and is under construction for measuring by an electrical thermo couple the temperature of the circulating blood in man as well as the temperature of the body surface, and more accurate determinations of rectal and mouth temperatures than are possible with the ordinary clinical thermometer.

RUFUS COLE