worse. Now it has nearly reached the end stage with death certain in a short time. I should say that probably he has a very much reduced renal excretory tissue and probably the process is pretty uniformly distributed throughout the kidney, that it is a pretty uniform type of atrophy affecting all parts of the excretory mechanism and was never in any sense of the word an acute process unless one takes this history of hematuria on one occasion in 1916 as pointing to some severe injury and then the thing quieted down to a slowly-progressing process, causing very extensive atrophy of renal tissue and relatively little change in blood vessels outside the kidney. It is a very different case from the ordinary type of chronic nephritis.

May 26, 1919.—The patient that I showed last Monday with nephritis and marked retention has not made any particular change in the week. Though he has lost ground markedly, there has not been any very striking change in symptoms.

May 28, 1919.—The patient became increasingly stuporous. For a day and a half his breathing was slow and very deep. His vision became very dim though ophthalmoscopic examination showed no eye changes. He had no convulsions and remained conscious until 15 minutes before death. He died at 2:30 p. m. May 28, 1919.

THE MECHANISM OF NATURAL AND ACQUIRED IMMUNITY TO THE PNEUMOCOCCUS IN MAN*

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Intelligent prophylaxis and treatment of any infectious disease necessitates an accurate knowledge of its etiology and pathogenesis. Not only must the infecting micro-organism be known, but we must know how it gains access to the body, how it leaves the body, and how and where it maintains itself outside the

body of the infected individual. We must ascertain the conditions which favor the development of infection after exposure has occurred, and how the body is injured by the infection. We must also know the mechanism by which the body wards off infection, or, if infection has occurred, by which immunity and recovery are brought about. In lobar pneumonia the conditions are peculiarly complicated, and it is only recently that we have reached an understanding of some of the fundamental facts concerning the disease.

It has long been recognized that the pneumococcus is the cause of nearly all cases which are clinically typical lobar pneumonia. There has been a great difference of opinion, however, as to the manner in which the disease is contracted. This has been in part due to the fact that in a considerable percentage of normal human beings, pneumococci are present in the mouth and throat which are not distinguishable culturally from those found in the lung in acute lobar pneumonia. The question naturally arises: why do not these individuals who harbor pneumococci in their mouths all develop pneumonia? It is because the organisms they carry are different in some way from those which cause disease? Are they less virulent, and is the development of pneumonia dependent upon the acquisition of a virulent strain of pneumococcus from an outside source? Or does pneumonia develop because of some reduction in individual resistance to infection which enables the pneumococci which have been leading a saprophytic existence in the mouth to gain a foothold in the lung and give rise to an actual infection?

Definite evidence as to this fundamental point has been obtained but recently by a very thorough study by Cole and Dochez and their associates of the serological and immunological reactions of pneumococci from various sources. They have shown that pneumococci may be divided into four groups or types on the basis of their reactions to immune serum. Of these four groups, three represent distinct clear-cut types. The different strains of organisms belonging to each of these three groups are identical with one another in their serological reactions, but differ absolutely

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from those strains belonging to a different group. Because of the clear-cut differences between organisms belonging to different types and the constancy with which these differences are maintained, they are frequently referred to as the fixed types; and they have been arbitrarily designated by Dochez and Gillespie¹ by the numbers I, II and III, according to their relative frequency as a cause of pneumonia. In Group IV are included all forms which are culturally pneumococci, but which do not fall into one of the first three groups. Most of the Group IV strains thus far studied differ serologically from each other as well as from members of the three fixed types. This group, therefore, represents a heterogeneous assortment of, for the most part, serologically unrelated forms, although recent studies² have shown that several minor groups may be differentiated among them.

Exhaustive studies of the relative frequency of these various types of pneumococci in lobar pneumonia have been made at the Rockefeller Hospital³ and their results confirmed in many other clinics in this country. These studies have shown that between 60 and 70 % of all cases of primary lobar pneumonia are due to pneumococci of Types I and II, which are of nearly equal frequency; that about 15 % are due to Type III strains (*pneumococcus mucosus*); while between 20 and 25 % of the organisms concerned fall into Group IV.

In addition to the serological differences between these types, certain other differences have been made out, which are of the greatest epidemiological significance. Pneumococci of Types I and II, which cause nearly two-thirds of all cases of lobar pneumonia, are usually highly virulent for animals. Furthermore, they cause a high mortality in man, approximately 33 1/3 %. While organisms belonging to these two types may be present for several weeks in the mouths of patients convalescent from pneumonia, they have been found but very rarely in the mouths of normal individuals, except in those who have been in intimate contact with patients with pneumonia of these types.⁴ They do not seem adapted to a saprophytic existence in the mouth. It seems certain, there-

fore, that pneumonia due to organisms belonging to Types I and II can rarely be autogenous in origin, but, as in typhoid fever, the infection must be acquired from an outside source, i. e., from a patient with pneumonia or from a healthy carrier recently in contact with a patient. It is strictly a communicable disease, although only to a slight degree contagious.

On the other hand, pneumococci belonging to Group IV and also the so-called Atypical Type II pneumococci described by Avery⁵, are usually of relatively low virulence for animals. The mortality in man (except for terminal pneumonias in patients with chronic disease) is also low, about half that of Types I and II. It is mainly organisms of these groups which are found in the mouths of normal individuals. It is, therefore, possible that pneumonias of these types may often be the result of an autogenous infection; and this supposition is strengthened by the frequent finding by Clough⁶ of Group IV and Atypical Type II pneumococci in post-operative pneumonias, and in terminal pneumonias in patients debilitated by alcoholism or chronic disease, and by the frequency of Group IV pneumococci as the cause of post-influenzal pneumonia.

Type III pneumococci are peculiar in that they are usually of high virulence for animals, and yet are frequently found in the normal mouth. Although they are a relatively infrequent cause of pneumonia, the mortality in these cases is high, about 60 %. No definite differences have been demonstrated between the strains found in normal mouths and those isolated from patients with pneumonia, either in serological reactions or in virulence for animals. It would seem, therefore, that the normal human body must possess a considerable power of resisting the establishment of infection with Type III pneumococci, but has less power of combatting and overcoming an infection once established than in the case of infection with pneumococci of other types. It also suggests that there may be some difference in the mechanism of resistance to infection with pneumococci of different types. From an epidemiological standpoint, each type of pneumococcus must be regarded as a dis-

tinct species, and receive independent consideration.

The problem of the resistance of man to pneumococcus infection is a double one, and concerns both resistance to the establishment of infection, and ability to overcome an infection which has been established. The former may be called natural immunity, the latter acquired immunity. Since the phenomena associated with acquired immunity in general are more striking and therefore more easily recognized than those of natural immunity, more attention has been devoted to the former subject, and more is known concerning it. A knowledge of the mechanism of such an acquired immunity may be directly helpful in the study of natural resistance, since the latter may depend upon factors which can be more readily demonstrated by the study of acquired immunity.

It has been shown that recovery in pneumonia is not associated with any change in the consolidated lung tissue which is detectable by physical examination or by the x-ray. It is not due to any loss of virulence nor other demonstrable change in the infecting organism. Definite changes, however, have been found in the serum of patients at or near the crisis. It has been shown by a number of observers⁷ that the serum at this time possesses the power of protecting mice from infection with otherwise fatal doses of highly virulent pneumococci, provided one uses in the test the strain of pneumococcus with which the patient was infected, or at least a strain of the same type. These findings have been confirmed by some observations of the author⁸. In my experiments the degree of protective power was much less marked than that exerted by serum from highly immunized animals, but varied from 10 to 10,000 times the M.L.D. Serum obtained from the same patients during the acute stage of the disease showed no protective power, nor did serum obtained from patients who subsequently died of the disease.

Numerous attempts have been made to determine the mechanism of this protective power. It was at first supposed to be due to an antitoxin, analogous to diphtheria antitoxin, but subsequent studies have

not confirmed this view. It was next attributed to bactericidal substances in the serum, which act directly upon the microorganisms, but this view also has been disproven. While normal human serum, as shown by several previous observers,⁹ and confirmed by the writer, often exerts a marked inhibitory action upon the growth of pneumococci as tested by plating methods, this action is not increased in the serum of convalescent patients. Furthermore, this phenomenon is a transient one, and pneumococci after a latent period will usually grow quite readily, either in normal or in immune serum.

The explanation was next sought in an increase in the opsonins in the serum, and a number of observers reported finding an increase in the opsonic index for pneumococci at the crisis. However, the errors inherent in the method make the reported results questionable, and, even if accurately determined, it is doubtful if a rise in opsonic index has any significance. In determining the opsonic index of a patient's serum by the ordinary method one uses a strain of pneumococcus of feeble virulence which is moderately phagocytizable in normal serum, quite without reference to the type of pneumococcus with which the patient was infected. Even if there were an increase in the phagocytic activity of the serum for such an organism, this would not necessarily indicate any increase in resistance to highly virulent strains of the fixed types which are resistant to phagocytosis in normal serum.

That phagocytosis plays an important role in immunity to the pneumococcus, however, is well established. If virulent pneumococci are injected into the peritoneal cavity of an immunized animal, the organisms are ingested by the leucocytes and undergo death and intracellular digestion within the leucocytes. Multiplication of the pneumococci does not occur, and the animal recovers, apparently as a result of this phagocytosis. In a normal (susceptible) animal, on the contrary, the organisms remain extracellular, multiply without restriction and death of the host speedily follows. If an avirulent strain of pneumococcus is used, however, even in the normal animal, the organisms are in-

gested and destroyed by the leucocytes, just as were the virulent organisms in the immunized animal. If the dose is not overwhelming in size the animal recovers. This power of causing phagocytosis of the injected pneumococci is dependent upon the presence of some substance in the serum, which can exert its activity in the test tube as well as in the body. Thus, if we mix in the test tube equal volumes of a culture of virulent pneumococci, leucocyte suspension, and immune serum, the pneumococci will be ingested and dissolved. In a corresponding mixture containing normal serum, no phagocytosis will take place. An avirulent or feebly virulent strain, however, will be phagocytosed in fresh normal serum. There is roughly, at least, a fairly close parallelism between the virulence of a pneumococcus and its resistance to phagocytosis in normal serum.

Attempts to demonstrate phagocytic activity for highly virulent strains of pneumococci in the serum of patients have been hitherto almost uniformly unsuccessful. However, little attention was paid in most of these experiments to the type of pneumococcus with which the patient was infected.

A few years ago the writer⁶ demonstrated such phagocytic activity in the serum of a small number of patients taken after crisis for the homologous strain of pneumococcus. This finding was confirmed by Lister¹⁰ in South Africa. The writer has recently reported the results of a further study¹¹ of a series of 40 cases of lobar pneumonia in which the phagocytic activity of the serum in each case was tested with the homologous strain of pneumococcus which was isolated from the patient whose serum was being tested, and also with other strains of pneumococci of the same type, and of different types. In 85% of the patients who recovered, the serum at or after the crisis or lysis showed well marked phagocytic activity for the homologous strain of pneumococcus, and as a rule for other strains of the same type, whereas it was quite inactive toward pneumococci of different types. The serum of these patients during the acute stage of the disease was quite inactive, as was the serum of all but one of the patients who

died. This phagocytic activity was equally well marked in patients recovering from infection with virulent pneumococci of Types I, II and III, and with the less virulent forms belonging to Group IV. In a smaller series of cases the writer⁵ had previously shown that there was a parallelism between this phagocytic activity and the capacity of the serum to protect mice. Furthermore, in the body of the protected mouse, as in the test tube, phagocytosis and intracellular digestion of the ingested organisms took place. It, therefore, seems probable that this property which the serum had acquired of causing phagocytosis of the virulent pneumococci with which the patient is infected plays an important role in the immunity which develops in man at crisis.

Agglutinins have also been demonstrated in the serum at crisis by a number of observers, notably by Chickering,¹² and his findings have been confirmed by the personal observations of the writer.¹¹ Furthermore, Blake¹³ has shown that the serum at crisis very frequently, although apparently less constantly, contains specific precipitins, similar to those present in immune serum.

Very possibly other unknown activities of the serum may be concerned. In any case, it has been shown clearly that the serum of patients recovering from pneumonia in most instances has acquired in some degree those properties which are manifested much more actively by the serum of immunized animals, and there can be little doubt that this activity of the serum is one essential factor in recovery.

It seems quite certain, however, that other factors are concerned than the activity of the serum. This has been pointed out particularly by Cole¹⁴ on the basis of his experimental work, especially on the fact that while a small amount (0.2 c. c.) of potent immune serum will protect mice from a dose of 0.2 c. c. or less of a highly virulent culture of a Type I pneumococcus, no amount of serum will protect from doses of culture much larger than this. Some unknown factor must be supplied, in this experiment, by the tissues of the mouse, which is adequate if the infection is not too large, but which does not suffice if the infection is excessive, even

although a great excess of protective serum is present. The writer has observed one patient who died of pneumococcus sepsis, notwithstanding the fact that his serum shortly before death and after the onset of the sepsis caused well marked agglutination and phagocytosis of his own organism. Furthermore, in a number of other cases, I have found that organisms (belonging to Group IV) which were cultivated from the blood of patients who subsequently died of the disease, were readily phagocytal in normal serum.

One essential factor is probably the presence of an adequate number of active leucocytes. Winternitz¹⁵ and his associates have shown that animals whose leucocytes had been reduced in number by benzol were rendered abnormally susceptible to pneumococcus infection. Clinically a low leucocyte count is an unfavorable prognostic sign in patients with a serious infection, although the reverse is not necessarily the case. We are not certain that the leucocyte of the circulating blood is the only cell concerned in phagocytosis, nor even the most important one. Doubtless the activities of other tissues are also essential.

The importance of these facts in the serum treatment of pneumonia has been pointed out by Cole.¹⁶ The fact that in natural recovery from pneumonia the same antibodies are elaborated by the patient as are present in artificially produced immune serum, supports the assumption that recovery may be hastened by the therapeutic administration of such serum. The failure of such serum to protect animals from very large doses of culture emphasizes the importance of the early institution of serum treatment in Type I infections. It also explains in part the therapeutic failure of Type II serum, since this serum will not protect animals from as large doses of culture as will Type I serum. It seems probable that any further marked advance in serum treatment must await the discovery of the nature of these essential activities of the body tissues, and the elaboration of appropriate methods of stimulating them.

While our knowledge of the mechanism of recovery from pneumonia is far from complete, still less is known as to the

causes of natural resistance to infection. The conditions may differ in detail, with pneumococci of different types. In the case of Group IV and Atypical Type II organisms, the forms usually found in normal mouths, there must be a comparatively effective means of resistance, and infection may be precipitated by a temporary disturbance which in some way lowers this resistance of the host. In the case of infection with organisms of Types I and II, which are rarely found in normal individuals, exposure to infection is essential; but here, too, a considerable natural resistance to infection must exist, since relatively few of those in contact with patients with Type I or Type II infection contract the disease, although, as shown by studies at the Rockefeller Hospital,¹ about one-eighth of the individuals so exposed become carriers of pneumococci of these types for an average period of 3 to 4 weeks.

Why do some individuals exposed to infection contract the disease while the majority escape? Is it because of differences in local conditions in the lung or differences in the antibacterial activities of the blood or tissues? We would be in a better position to answer this question if we knew exactly what happens between the entrance of the pneumococcus into the mouth and the development of the consolidation in the lung.

The consensus of opinion seems to favor the view that the organisms reach the lung by direct passage downward through the bronchi. It seems very probable that, in addition to the presence of the organisms, local changes in the lung play an important role in determining the development of a consolidation. The well known predisposing effect of chilling can most simply be explained in this way rather than by assuming that it reduces any protective powers which may be exerted by the blood or leucocytes. Meltzer¹⁷ has suggested that local circulatory and secretory changes may be brought about by chilling, as a result of which the finer bronchi may be plugged with mucus, and thus a condition spontaneously be produced analogous to that of the lung distended with culture fluid in the experimental animal.

Some writers have advocated the view that pneumonia, like typhoid fever, is a general infection from the start, that the organisms reach the lung through the blood stream, and that the usual development of a local lesion in the lung is due to some especial vulnerability of that organ to the pneumococcus.

It is not impossible that both modes of infection may occur. In either case it seems probable that the activity of the tissues and of the blood constitutes an important mechanism of defense, which is defective or insufficient in those individuals who develop pneumonia. This would be particularly significant if we are to regard pneumonia as a general infection from the start.

In the case of the Group IV pneumococci present in normal mouths, phagocytosis is probably an important mechanism of defense. These organisms, even those isolated from patients with pneumonia, are usually readily phagocytizable in fresh normal serum. In so far as one can draw conclusions from the results of animal experiments phagocytosis would offer a plausible explanation, although not necessarily a complete one, for the usual resistance to infection with these organisms. In the case of individuals who acquire the disease, there might be some transient reduction in this phagocytic activity of the blood, or the organisms might, as a result of special local mechanical conditions, penetrate into some region where they would be protected from this antibacterial action of the blood, and hence be able to multiply until a sufficient number of organisms had accumulated to overpower the defensive forces of the host and produce disease. A bronchus plugged with secretion might constitute such a focus.

In the case of virulent organisms of Types I, II and III, this explanation does not apply. These forms of pneumococci are usually entirely resistant to phagocytosis in normal human blood in the test tube experiments. That conditions in the body may be more favorable for phagocytosis is, of course, possible, but we have no evidence for such an assumption. That there is some defensive mechanism present seems highly probable in view of the

existence of normal carriers of these strains, especially of Type III.

Since the immunity which develops with recovery from pneumonia is often associated with the appearance in the serum of definite protective power for animals, it seemed to the writer that a similar, although probably less marked protective power might be demonstrable with normal human serum, or with serum from those individuals who may possess a well marked natural resistance to pneumonia. It has previously been shown, particularly by Neufeld and Haendel,¹⁸ that some specimens of normal serum may exert such protective power, but no systematic studies of normal serum have been reported.

The writer recently undertook a study of the protective power of normal human serum against pneumococci of Types I, II and III. All of the sera studied were from normal individuals who had not suffered from pneumonia recently, nor received pneumococcus vaccine. The cultures used were of very high virulence, one ten-millionth of a cubic centimeter killing the control mice regularly within forty-eight hours. The tests were carried out in the usual manner by mixing in a small syringe 0.2 c. c. of the serum and 0.2 c. c. of diluted culture, the actual quantity of the original culture varying from 0.01 to 0.0000001 c. c. The mixtures were injected immediately. As a control a similar series of mice was injected with the same quantities of culture, but without serum. The mice were observed for ten days, and those surviving for this period were regarded as protected.

Serum from 20 individuals was tested in this way with each of Types I, II, III. Definite protective power was demonstrated in 4 sera for the Type I strain; in 8 sera for Type II; and in 8 sera for Type III. There was no one serum which protected definitely against all three types. Most of them protected only from one strain; 2 sera protected from Types I and II; and 2 from Types II and III. The degree of protective power in some was slight, 10 M. L. D. In others it was comparatively high—1,000, 10,000, and with one serum 100,000 M. L. D. These

figures compare favorably with the protective power of the serum from vaccinated or convalescent individuals.

That this protective power is not due simply to a direct injury of the organisms by the concentrated serum is shown by the fact that incubation of the mixture of serum and culture for one-half to six hours before injection did not increase the protective power, and especially by the fact that mice could be protected by subcutaneous injections of serum from subsequent intraperitoneal injections of organisms.

The mechanism of this protective action I was unable to determine. These sera caused no agglutination of the organisms against which they were active; nor could any appreciable degree of phagocytic activity be demonstrated. It was suggested by Neufeld and Haendel¹⁸ that this protective power of normal serum might be due to its slight bactericidal properties. This point has been studied at my suggestion by Miss C. Van Winkle. While she also has been able to demonstrate that normal serum does apparently exert a definite transient inhibitory effect upon the growth of pneumococci of these types, this activity was no more marked in the sera which showed protective power than in those which did not. Attempts to demonstrate precipitins in these sera have also been negative. It would seem, therefore, that the mechanism of this protective power must be somewhat different from that of immune serum.

As to what the significance of this protective power may be, one must speak with the greatest caution. It seems very probable that it indicates a definite power of resisting pneumococcus infection. That it indicates a state of absolute security against infection is improbable. It may explain in part, at least, why individuals who harbor pneumococci of Types I and II in their mouths (contacts), and also those harboring Type III pneumococci do not more frequently develop the disease.

The assumption that this protective power of the serum indicates an actual resistance to the disease is strengthened by recent observations on the serum of vaccinated individuals. Attempts to produce immunity to pneumonia by the vaccination

of human beings on a large scale have been reported by Lister¹⁹ in South Africa and by Cecil and Austin,²⁰ and Cecil and Vaughan²¹ in the United States Army. The production of an effective immunity is pretty clearly shown by the reduction in the incidence of pneumonia due to the types of pneumococci contained in the vaccine, among the vaccinated individuals. Lister demonstrated agglutinative and phagocytic activity in the sera of the vaccinated individuals similar to that which develops after spontaneous recovery. He found that this activity of the serum may persist for months. The American writers mentioned also found agglutinins in the serum of most of the cases examined, but made no observations as to phagocytic activity. They found that many of these sera also showed definite protective power for mice, most marked with pneumococci of Type I and Type II. The degree of protective power reported was about as great as that found by Dochez,⁷ and by the writer,⁸ in the serum of patients convalescent from the disease. So far as reported, specimens of serum from the same individuals, tested before vaccination, with one exception showed no protective power.

Undoubtedly other factors than the activity of the serum are concerned in natural immunity, as has been shown to be the case in acquired immunity. While this protective power of the serum, therefore, is probably not an accurate quantitative index of all the defensive forces of the body, nevertheless it is generally regarded, and probably rightly so, as the most reliable test of immunity now known which is applicable to man.

While our knowledge of the mechanism of acquired immunity in man is very incomplete, that of natural immunity is most meager. A more thorough insight into these processes is essential both for the elaboration of more efficient methods for the specific treatment of pneumonia, and for the institution of effective prophylactic measures to prevent the spread of the disease.

BIBLIOGRAPHY

1. Dochez, A. R. and Gillespie, L. J.: A Biologic Classification of Pneumococci by Means of Immunity Reactions. *J. Am. M. Ass.*, 1913, LXI, 727.
2. Olmstead, Miriam: An Antigenic Classification of the Group IV Pneumococci. *J. Immunol.* 1917, II, 425.

3. Avery, O. T., Chickering, H. T., Cole, R., and Doebe, A. R.: Acute Lobar Pneumonia, Prevention and Serum Treatment. N. Y., 1917, Rockefeller Institute for Medical Research.
4. Doebe, A. R., and Avery, O. T.: The Occurrence of Carriers of Disease Producing Types of Pneumococcus. J. Exper. Med., 1915, XXII, 165.
5. Avery, O. T., A Further Study on the Biologic Classification of Pneumococci. J. Exper. Med., 1915, XXII, 284.
6. Clough, Mildred C.: A Study of the Incidence of the Types of Pneumococci Isolated from Acute Lobar Pneumonia and Other Infections, and an Analysis of the Cases Classified by Types in regard to Mortality, Complications, Associated Diseases, Bacteriemia, and Leucocytosis. Bull. Johns Hopkins Hosp., 1917, XXVIII, 247.
7. Doebe, A. R.: The Presence of Protective Substances in Human Serum During Lobar Pneumonia. J. Exper. Med., 1912, XVI, 655.
8. Clough, P. W.: The Development of Antibodies in the Serum of Patients Recovering from Acute Lobar Pneumonia. Bull. Johns Hopkins Hosp., 1915, XXIV, 255.
9. Todd, H.: Die bakterizide Wirkung des Blutes, Plasmas, und Serums auf Pneumokokken, und ihre Bedeutung für die Immunität. Arb. a. d. k. Gsndtsamte., Berl., 1911, XXXVI, 419.
10. Lister, F. S.: Specific Serological Reactions with Pneumococci from Different Sources. S. African Inst. Med. Research, Johannesburg, 1914, No. 2.
11. Clough, P. W.: Phagocytosis and Agglutination in the Serum in Acute Lobar Pneumonia: the Specificity of These Reactions and the Regularity of Their Occurrence. Bull. Johns Hopkins Hosp., 1919, XXX, 167.
12. Chickering, H. T.: Agglutination Phenomena in Lobar Pneumonia. J. Exper. Med., 1914, XX, 599.
13. Blake, F. G.: Antigen-Antibody Balance in Lobar Pneumonia. Arch. Int. Med., 1918, XXI, 779.
14. Cole, R.: Pneumococcus Infection and Immunity. N. York M. J. (etc.), 1915, CL, 1, 50.
15. Kline, B. S., and Winteritz, M. C.: The Role of the Leucocyte in Experimental Pneumonia. The Relation of the Number of Organisms Injected to the Mortality. J. Exper. Med., 1915, CL, 1, 50.
16. Cole, R.: Report of Studies Concerning Acute Lobar Pneumonia. J. Am. M. Ass., 1917, LXIX, 595.
17. Metzger, S. J., quoted by Cole, R.: Pneumococcus Infection and Lobar Pneumonia. Arch. Int. Med., 1914, XIV, 56.
18. Neufeld, E., and Haendel: Ueber die Entstehung der Krisis bei der Pneumonie, und unter die Wirkung des Pneumokokken-immunserrums. Arb. a. d. k. Gsndtsamte., Berl., 1910, XXXIV, 166.
19. Lister, F. S.: An Experimental Study of Prophylactic Inoculations Against Pneumococcal Infection in the Rabbit and in Man. S. African Inst. Med. Research, Johannesburg, 1916, No. 8.
20. Cecil, R. L., and Austin, J. H.: Results of Prophylactic Inoculation Against Pneumococcus in 12,519 Men. J. Exper. Med., 1918, XXVIII, 19.
21. Cecil, R. L., and Vaughan, H. F.: Results of Prophylactic Vaccination Against Pneumonia at Camp Wheeler. J. Exper. Med., 1919, XXIX, 457.

A THERAPEUTIC STUDY OF BENZYL BENZOATE IN BRONCHIAL SPASM OR ASTHMA

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The writer has for a number of years been engaged in an extensive and intensive pharmacological study of opium, and more especially of the so-called "minor" opium alkaloids, individually and in combination with each other and with the principal opium alkaloid, morphin. As

the result of that work, it soon became evident that the minor opium alkaloids can be regarded as "minor" only in respect to their small quantitative content in crude opium, but not in respect to their pharmacological action. Indeed, it was shown that these alkaloids can and do modify the effects of morphin very markedly when given in combination with it. Thus it was pointed out that there is a distinct difference in the analgesic effect produced by morphin, on the one hand, and by opium, on the other, due to the presence of the minor alkaloids in the latter.¹ Again, important differences have been shown to exist for the same reason between the pharmacological action of morphin and opium on the respiratory center,² the vomiting center,³ and other centers in the medulla.

One interesting feature disclosed by the pharmacological studies just mentioned is the fact that while opium and its alkaloids exert their most marked effects upon the central nervous system, nevertheless they produce also distinct and important pharmacological effects upon peripheral structures, and more particularly upon smooth muscle organs. The action of the opium alkaloids upon smooth muscle was first studied by the author in connection with a pharmacological study of the ureter, because excised rings of that organ permit of an accurate analysis of the action of drugs upon the rhythmic contractions or peristaltic movements and the tonicity of smooth muscle.⁴ It was soon established from studies upon the excised ureters of lower animals and of man, as well as from observations of the ureters in lower animals *in situ*, that the opium alkaloids in respect to their action upon that organ can be divided sharply into two classes: the pyridin-phenanthrene group, of which morphin is the principal member, on the one hand, and the benzyl-isquinolin group, of which papaverin is the chief representative, on the other. The morphin group was found to stimulate the contractions of the ureteral preparations and increase their tonicity, while all the members of the papaverin group were found to inhibit the contractions of the ureter and lower its tonus.