PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE ON RESPIRATORY DISEASES FROM JANUARY, 1920, TO JUNE, 1921 *

PHILIP MOEN STIMSON, M.D.
NEW YORK CITY

INTRODUCTORY

Bacteriology of Normal Throats.—Bloomfield¹ found by examinations of cultures made from a number of throat swabs from each of several healthy people that the organisms present, as revealed by this method, fell into two groups: (a) the true normal flora including non-hemolytic streptococci and gram-negative cocci, and (b) pathogenic or nonpathogenic organisms which are accidentally introduced and are present usually only a short time in a given individual. He felt that a true picture of the normal flora of the healthy throat was obtained only by making repeated cultures from the same individual.

Moss, Guthrie, and Marshall,² in a study of the experimental inoculation of healthy human throats with avirulent diphtheria bacilli, concluded that these organisms retain their characteristics despite long residence in the human throat or transfer from one human being to another, and further that they are devoid of pathogenic importance for man. Accordingly, they stated that the carrier of avirulent diphtheria bacilli does not constitute a menace to the health of the community.

Otteraaen³ found that hemolytic streptococci are frequent inhabitants of the throats of normal individuals as well as of persons suffering from acute infectious diseases. However, these streptococci are not virulent so far as indicated by the results of animal inoculation and phagocytosis experiments.

* Received for publication Dec. 22, 1921.

* From the Department of Pediatrics of Cornell University Medical College.

* This review was originally undertaken by Dr. Louis C. Schroeder, but after reviewing more than fifty articles, he was forced by pressure of other work to relinquish this study. He very generously contributed his notes to me for which I make grateful acknowledgment.

1. Bloomfield, A. L.: The Significance of the Bacteria Found in the Throats of Healthy People, *Johns Hopkins Hosp. Bull.* **32**:33 (Feb.) 1921.

2. Moss, W. L.; Guthrie, C. G., and Marshall, B. C.: Experimental Inoculation of Human Throats with Avirulent Diphtheria Bacilli, *Johns Hopkins Hosp. Bull.* **32**:37 (Feb.) 1921.

3. Otteraaen, A.: Hemolytic Streptococci in the Throat in Certain Acute Infectious Diseases, *J. Infect. Dis.* **26**:23 (Jan.) 1920.

In another article, Bloomfield⁴ showed that influenza bacilli quickly disappear from the normal mucous membranes of the mouth, nose and pharynx, after introduction of a pure culture on the tongue, on the nasal septum behind the vestibule, or into the nasopharynx. He suggested that the presence of the Pfeiffer bacillus in so-called healthy people may result from the persistence of a chronic focus in a sinus or in a bronchus, or from contact with an acutely infected person. With this view, Wollstein and Spence⁵ heartily agreed.

Incidence of Respiratory Disease.—Zahorsky⁶ noted that in his private practice the greatest actual number of cases of acute respiratory diseases sufficient to have the attention of a doctor occurred in infancy, with a decline in number each year to from 4 to 6 when there was a definite increase in the incidence, the time corresponding to the beginning of school life. After this period, the number of cases fell off rapidly. His figures, however, may, perhaps, be influenced by the nature of his practice which may be largely one of infants, so that he would be less apt to see respiratory disease in older children, even as he is quite unlikely to see it in adults.

COLDS AND ACUTE RESPIRATORY DISEASE IN GENERAL

Floyd⁷ divided "common colds" roughly into the following clinical types: (a) acute rhinitis; (b) acute pharyngitis, followed by rhinitis and laryngitis; (c) acute laryngitis, followed by tracheitis, bronchitis and pneumonia; (d) acute tracheitis, followed by bronchitis and laryngitis.

The acute rhinitis is characterized by sudden swelling of the nasal mucous membrane with a watery discharge, fullness in the head, and general malaise. The organism commonly found in the secretion belongs to the staphylococcus group, and somewhat less frequently the hemolytic streptococcus has appeared.

The acute pharyngitis is characterized by redness and swelling of the fauces and of the posterior wall of the pharynx, pain on swallowing, dry cough and fever. The infection may extend into the nose or larynx. Almost invariably the initial infection is produced by a member of the streptococcus group.

The types of cold beginning with laryngitis or tracheitis and followed by a rapid extension over the respiratory tract are closely related,

4. Bloomfield, A. L.: Fate of Influenza Bacilli Introduced into Upper Air Passages, Johns Hopkins Hosp. Bull. **31**:85 (March) 1920.

5. Wollstein, M., and Spence, R. C.: The Bacillus of Pfeiffer in Inflammations of the Respiratory Tract in Children, Am. J. Dis. Child. **19**:459 (June) 1920.

6. Zahorsky, J.: The Resistance to Acute Disease of the Respiratory Tract in Children, Am. J. Dis. Child. **21**:183 (Feb.) 1921.

7. Floyd, C.: The Common Cold in Relation to Certain Microorganisms and Its Treatment with Bacterial Vaccines, Boston M. & S. J. **182**:389, (April 15) 1920.

and are generally caused by the same microorganism. Aside from the local symptoms, the type is accompanied by considerable muscular pain, and the term "grippe" is commonly applied to it. The pneumococcus of Group IV, or occasionally of Groups I or II, is predominant. Occasionally, however, the hemolytic streptococcus has been the original invader. The early fall and winter colds are generally of the first types; the early and late spring colds are of the last two types.

Bloomfield⁸ defined the uncomplicated cold as "a mild disease manifesting itself by a constitutional reaction and by hyperemic phenomena of the upper air passages without local suppurative complications. The duration is brief and there is a tendency to leukopenia." On clinical grounds, he advanced the view that the common cold is an infectious disease analogous to influenza, featured by the frequent development of complications in the upper air passages, such as sinus infections, tracheitis and otitis. A review of the literature furnished him no convincing evidence that any known organism is the primary cause of the cold. The cultural studies in this report failed to show in uncomplicated cases any variation in the flora which enabled one to select any organism or group of organisms as the cause of colds. On the other hand, where clinical complications occurred, pathogenic organisms were definitely associated with them. He felt, therefore, that the primary cause of colds is probably an organism as yet unknown, and certainly not one of the usual pathogens, such as streptococci, pneumococci, *B. influenzae*, or staphylococci. But the primary cold, whatever its final cause, alters the mucous membranes in such a way as to allow secondary bacterial invasion and consequent frequent development of local complications. The cultures clearly indicated that such complications are due to a variety of bacteria, such as those just mentioned.

Wollstein and Spence⁵ noted that the influenza bacillus was not an inhabitant of the normal respiratory tract, but that at a time when an epidemic of influenza prevailed, it was present in more than 50 per cent. of all cases of inflammations of any part of the respiratory tract. At such times, this bacillus was found very commonly present in the sputum in cases of common colds with or without bronchitis, though these cases may be unaccompanied by general or systemic symptoms and have no relation to influenza.

After an elaborate study, Mudd, Grant, and Goldman⁹ recognized the following causes of acute inflammations of the pharynx, tonsils, and nose:

1. The filtrable virus of Kruse and Foster, inducing apparently a clinical entity, a type of acute coryza. According to the experiments

8. Bloomfield, A. L.: Variations in the Bacterial Flora of the Upper Air Passages During the Course of Common Colds, Johns Hopkins Hosp. Bull. **32**:12 (April) 1921.

9. Mudd, S.; Grant, S. B., and Goldman, A.: The Etiology of Acute Inflammations of the Nose, Pharynx and Tonsils, J. Lab. & Clin. M. **6**:175 (Jan.), 253 (Feb.), 322 (March) 1921.

of its discoverers, this is of relatively high virulence, and may cause infection practically independently of the action of exciting factors.

2. Various bacteria, including the pneumococcus, streptococci, *B. rhinitis*, *B. diphtheriae*, Friedländer's bacillus, *B. influenzae*, and probably also *M. catarrhalis*, *B. septus*, *M. paratetrageus*, *Staphylococcus aureus*, and possibly others, seem to be capable of inducing infection of variable extent, duration and symptomatology.

3. Protein sensitization, the basis of vasomotor rhinitis and of true bronchial asthma, the underlying cause also of a relatively infrequent subgroup of acute recurrent "colds."

4. Various systemic diseases, drugs, mechanical and chemical irritants, chronic nasal affections and reflex neuroses.

These authors believe that one factor by which resistance to bacterial infection may be lowered is excessive chilling, probably not by lowering the body temperature but through causing a vasoconstriction and local ischemia in the mucous membranes of the nasopharynx.

Paunz¹⁰ commented on the frequent discovery in child cadavers of inflammatory and suppurative processes in the sinuses communicating with the nose. In older children an acute infectious disease is generally responsible for the sinusitis but in infants even coryza or tonsillitis may develop this complication. In six of his eleven cases, the sinusitis followed coryza, including one 6 weeks old infant.

Prophylaxis.—Preventive measures against acute respiratory diseases require the intelligent cooperation of every individual in a community, according to Overton.¹¹ The attitude of each person must be to report sickness rather than to conceal it, to suspect suspicious signs rather than to ignore them, to impose some degree of self isolation rather than to mingle closely with others, and to observe personal hygiene rather than to assert an excessive degree of personal liberty and independence. The preventive measures against acute respiratory diseases are the same as those against other communicable diseases and include the discovery of the cases in their early stages, their isolation to some degree and the careful and strict disposal of the excretions of their noses and mouths.

Sobel¹² especially urged keeping young children well away from others with respiratory infections, and considered the home the place where most emphasis was needed on this subject. He stressed the proper care of the young children to increase their resistance to such infections, and noted that wet and cold both lower this resistance markedly. He urged the proper treatment of mild infections, such as

10. Paunz, M.: Complications of Sinusitis in Children, *Jahrb. f. Kinderh.*, **93**:313, 1920; *Abstr. J. A. M. A.* **76**:147 (Jan. 8) 1921.

11. Overton, F.: Some Epidemiological Points Regarding Acute Respiratory Disease, *Am. J. Pub. Health* **10**:431 (May) 1920.

12. Sobel, J.: The Prevention of Respiratory Diseases in Infancy and Early Childhood, *Med. Rec.* **97**:817 (May 15) 1920.

colds and bronchitis, to prevent the more severe infections such as pneumonia.

Evidence as to the desirability of keeping children and others with colds away from schools, "movies," and other crowded places is found in the bacteriologic study made by Huddleson and Hull¹³ on the air of an amusement hall. During the height of an epidemic of bad colds, the air of the amusement hall filled with soldiers was so badly contaminated that an average of eighty-two organisms fell on blood agar plates exposed only one minute, while eight days later, after the epidemic had subsided, an average of only sixteen colonies developed on the plates exposed under the same conditions but for a period of ten minutes. In picking colonies indiscriminately from the incubated plates used when the epidemic was at its height, four pneumococci of type IV were found as well as many hemolytic and nonhemolytic streptococci, numerous staphylococci, and gram-negative and gram-positive diplococci. In contrast to this, the types found on the plates used when the epidemic had subsided, were chiefly molds and staphylococci, no pneumococci being found. Sixteen per cent. of the total number were streptococci which showed partial but not complete hemolysis (Alpha type).

Lynch¹⁴ argued for boiling dishes, table silver, mess-kits, and the like to prevent the spread of respiratory diseases, especially in connection with community eating such as army camps, restaurants, etc., and in homes where one case of respiratory disease exists. His work was based on field and laboratory study of many army units of which some boiled their mess-kits and some did not.

Kellogg and MacMillan's¹⁵ experiments showed quite definitely that face masks have a very limited value in checking epidemics of respiratory diseases. Some of their conclusions have been reached by other authors but few have done as carefully controlled experiments. Their final conclusion is that masks have not been demonstrated to have a degree of efficiency that would warrant their compulsory application for the checking of epidemics.

A great deal of work has been done by a number of groups of workers in the study of the prophylactic use of various vaccines against colds, influenza and other acute respiratory infections, and a review of much of the work will be found under the heading of influenza. Park,¹⁶ in reviewing the results of the studies of his co-workers, noted

13. Huddleson, I. F., and Hull, T. G.: Bacteria of the Air in an Amusement Hall, *Am. J. Pub. Health* **10**:583 (July) 1920.

14. Lynch, C.: Prevention of Respiratory Diseases, *Med. Rec.* **98**:799 (Nov. 13) 1920.

15. Kellogg, W. H., and MacMillan, G.: An Experimental Study of the Efficacy of Gauze Face Masks, *Am. J. Pub. Health* **10**:34 (Jan.) 1920.

16. Park, W. H.; Williams, A. W., and Krumwiede, C.: Microbial Studies on Acute Respiratory Infection with Especial Consideration of Immunological Types, *J. Immunol.* **6**:1 (Jan.) 1921.

that the percentage of colds was as great among the vaccinated as among the unvaccinated, and similar results were obtained by other investigators. On the other hand, Floyd⁷ stated that "the production of an active immunity through the use of appropriate bacterial vaccines promises to be of value prophylactically in the control of infections of the upper respiratory tract."

Treatment.—In an article on the treatment of "colds" and "grippe," Fantus¹⁷ recognized chilling as an exciting factor, and therefore did not favor sweating, as a rule, unless great care is taken to avoid damp clothing with subsequent chilling. While "hardening" should be used in prophylaxis, "coddling" is the rule of safety for catarrhal fevers, and he urged stay in bed for three days after the return of normal temperature, and complete stay in bed during the period of fever.

With the possible exception of alkalies, he considered the use of medicines merely symptomatic. Expectoration should be helped by saline expectorants and by fluid. He advocated sodium citrate, from 1 to 2 gm. in lemonade or orangeade every two hours.

McGuigan¹⁸ noted that menthol and peppermint lessen the surface viscosity of the mucous exudates in catarrhal conditions and act similarly on the membranes producing the exudates, thereby relieving the obstruction of nasal breathing in "colds." For this effect the menthol must be in solution or in a condition in which volatility can act. He noted also that similarly the viscosity of a liquid is increased about 2 per cent. for each degree the temperature is lowered. So where the expulsion of mucus is desired, warm moist respired air will greatly aid the expulsion, while cold air will increase the difficulty.

INFLUENZA

A great deal of work has been done in various parts of the country by groups of investigators on the pathogenesis of epidemic influenza. In stating the purpose of the studies of their own group of workers, Park, Williams and Krumwiede¹⁶ defined the problems which attracted the attention of most of the investigators. These problems were four in number:

1. A study of the microorganisms of the upper respiratory tract in "health," in "common colds" and in "influenza." This investigation should include the diligent search for an epidemic microbial strain in influenza cases. Both filtrable and unfiltrable microbes were to be considered.

2. A continuation of the studies of hemoglobinophilic bacilli (group of the influenza bacillus), for the purpose of establishing the relation-

17. Fantus, B.: Therapy of Catarrhal Fevers, J. A. M. A. **75**:1694 (Dec. 18) 1920.

18. McGuigan, H.: Menthol and Peppermint in Acute Catarrhal Conditions of the Respiratory Tract, J. A. M. A. **76**:303 (Jan. 29) 1921.

ship of the influenza bacillus to both pandemic and sporadic cases of influenza.

3. A study of the permanence of type characteristics of influenza bacilli in persons after recovery from respiratory infections. It was considered of the utmost importance to establish as accurately as possible the stability of types.

4. A study of the incidence of common colds, influenza, and pneumonia, following the controlled use of a vaccine made up of different types of bacilli claimed to be the cause of acute respiratory diseases.

Park summarized the results of the studies that were made by himself and his associates. Of the different groups of microorganisms isolated by their procedure, all had the peculiarity that each group was an assemblage of many types. This was equally true for the pneumococcus, the influenza bacillus, the green-producing streptococcus, and the hemolytic streptococcus. They "obtained no evidence of the existence of a common filtrable organism."

In a study of case incidence alone, they found that some groups may be ruled out as being implicated in the epidemic; such as staphylococci, gram-negative cocci, and hemolytic streptococci. They thought more work could be done on pneumococci, green streptococci, indifferent streptococci, and some of the minority groups with a high case incidence.

Coca and Kelley¹⁹ noted that investigators had various opinions as to the bacteriologic causation of epidemic influenza.

1. There are those who think that the influenza bacillus of Pfeiffer is the cause of the disease.

2. Others believe that influenza is caused by a filtrable virus.

3. Some found a "gram-positive streptococcus" or a diplococcus.

Influenza Bacillus.—The influenza bacillus of Pfeiffer has been the subject of much investigation. During the first quarter of 1920, the period of the latest epidemic of influenza in New York City, Wollstein and Spence⁵ studied 1,000 sputum cultures, 294 of which were from adults, nurses and doctors, the rest from children who were hospital patients or dispensary cases. They found the influenza bacillus in 85 per cent. of all the cases of rhinitis and bronchitis that were severe enough to produce systemic reactions, and in 53 per cent. of the cases of ordinary colds, but in only 11 per cent. of their controls. They concluded that the bacillus of Pfeiffer is not specific to influenza in that it is present in from 50 to 80 per cent. of cases of mild respiratory infections clinically not related to influenza. It seemed to grow on any

19. Coca, A. F., and Kelley, M. F.: Studies on Acute Respiratory Infections. VI. A Serological Study of the Bacillus of Pfeiffer, *J. Immunol.* 6:87 (Jan.) 1921.

portion of the respiratory tract which was congested, but proof that it was ever the primary cause of this congestion was lacking. That the local and general symptoms may be influenced by its presence, however, they believe to be true.

Blake and Cecil²⁰ found that in monkeys the influenza bacillus can act as a primary incitant of respiratory infection without the assistance of a preceding or concomitant contributing cause. By intra-tracheal injection of this organism, they produced in normal monkeys an acute infection of the upper respiratory tract, complicated by acute sinusitis, tracheobronchitis, hemorrhagic edema of the lungs, broncheolitis and bronchopneumonia, in fact, a disease apparently essentially identical with influenza with respect to its clinical course, symptoms and complications. They felt that the etiologic relationship of the influenza bacillus to acute sinusitis, tracheobronchitis, bronchiolitis and bronchopneumonia was established, and also that it was reasonable to infer from the results of their experiments that this microorganism was the specific cause of influenza. However, they did not feel that this last conclusion was entirely permissible since it is impossible to determine whether the respiratory disease produced in monkeys with the influenza bacillus is identical with influenza or merely similar to it.

Rosenow²¹ admitted the possibility that the influenza bacillus may play a rôle in the production of symptoms and lesions in influenza, citing this work of Blake and Cecil and believing they were enabled to produce in monkeys influenza-like symptoms and lesions by means of influenza bacilli which had undergone changes and acquired high virulence through repeated monkey passages.

Cecil and Steffen²² found that virulent influenza bacilli, when injected into the nose and throat of healthy volunteers, may excite in them an acute respiratory disease similar in many respects to influenza but falling short of the typical clinical picture. In such cases influenza bacilli, biologically identical with those inoculated, may be recovered from the discharges as long as symptoms persist and often for some

20. Blake, F. G., and Cecil, R. L.: The Production of an Acute Respiratory Disease in Monkeys by Inoculation with Bacillus Influenza. A Preliminary Report, *J. A. M. A.* **74**:170 (Jan. 17) 1920; The Production in Monkeys of an Acute Respiratory Disease Resembling Influenza by Inoculation with Bacillus Influenzae, *J. Exper. M.* **32**:691 (Dec.) 1920; Studies on Experimental Pneumonia: The Pathology of Experimental Influenza and of Bacillus Influenzae Pneumonia in Monkeys, **32**:719 (Dec.) 1920.

Editorial: The Cause of Influenza, *J. A. M. A.* **76**:523 (Feb. 19) 1921.

21. Rosenow, E. C.: Studies in Influenza and Pneumonia: IX. Changes in the Green-Producing Streptococcus Induced by Successive Animal Passage and Their Significance in Epidemic Influenza, *J. Infect. Dis.* **26**:567 (June) 1920.

22. Cecil, R. L., and Steffen, G. L.: Acute Respiratory Infection in Man Following Inoculation with Virulent Bacillus Influenzae, *J. Infect. Dis.* **28**:201 (March) 1921.

time thereafter. This they thought was in sharp contrast to the work of Bloomfield who found that strains of this bacillus isolated from healthy mouths disappeared rapidly after injection into the healthy nose and throat.

Filtrates of influenza bacillus cultures when similarly injected into two healthy volunteers produced neither local nor constitutional reaction. On the other hand, they found that the inoculation of healthy volunteers with virulent hemolytic streptococci may in some cases induce an acute follicular tonsillitis with fever and leukocytosis. But a virulent pneumococcus of Type IV was injected into the nose and throat of two healthy volunteers with impunity. Accordingly, they conclude that it is possible the pneumococci and certain others of the bacteria that are associated with coryza and sore throats, invade the tissue only after some depression in the local and general resistance of the host. The capacity of all these bacteria to act as secondary invaders cannot be questioned, but the experiments reported in this paper indicate that virulent influenza bacilli possess a peculiar power of attacking healthy mucous membrane and of exciting a respiratory infection quite similar in some of its clinical manifestations to spontaneous influenza.

After reporting a case of infection following accidental inoculation with the Pfeiffer bacillus, Park and Cooper²³ concluded that freshly isolated Pfeiffer bacilli are capable of causing infection when transferred in great numbers to susceptible mucous membranes. Strains recovered from infected persons at varying intervals after the accidental inoculation revealed agglutinative characteristics identical with those of the strains which had caused the infection. The varying periods cover the time from shortly after infection to convalescence. This they considered strong evidence that a strain responsible for an infection would reveal identical characteristics during infection and convalescence in the epidemic cases due to its invasion. However, if the epidemic of influenza was due to the Pfeiffer bacillus, they would expect the dominant strains to have similar type characteristics. The fact that just the opposite condition exists they consider strong proof against the primary etiologic importance of the Pfeiffer bacillus in epidemic influenza.

After a study of complement fixation in influenza with *Bacillus influenzae* antigens, Cooke²⁴ found that complement fixation antibodies can be demonstrated in the serum of a considerable number of older

23. Park, W. H., and Cooper, G.: Studies on Acute Respiratory Infections. V. Accidental Inoculation of Influenza Bacilli on the Mucous Membranes of Healthy Persons with Development of Infection in at Least One. Persistence of Type Characteristics of the Bacilli, *J. Immunol.* **6**:81 (Jan.) 1921.

24. Cooke, J. V.: Complement Fixation in Influenza with *B. Influenzae* Antigens, **27**:476 (Dec.) 1920.

children and adults convalescent from influenza, by the use of such antigens, but that these antibodies are much less constantly found in children from 1 to 5 years of age. With the serums tested, however, he could detect no definite antigenic relationship between the sixteen strains of the influenza bacillus. He thought that his results indicate that the bacillus of Pfeiffer is pathogenic and infects many, if not all, patients with influenza. He felt, however, that the complement fixation test could not furnish sufficient evidence to justify the conclusion that this microorganism is the sole etiologic agent in influenza.

Coca and Kelley¹⁹ repeated Park's argument that the most characteristic feature of influenza, namely, its pandemic occurrence, which distinguishes it from all other infectious diseases, requires the assumption of a single etiologic factor in its causation. For this it is not sufficient in order to prove the casual relationship of Pfeiffer's bacillus to influenza that an obligative hemophilic pathogenic bacillus be found in all or nearly all cases of influenza. It is necessary in addition to show with the aid of reliable biologic reactions such as that of agglutination that the cultures obtained from influenza patients that are known not to have been in contact with one another, are identical. Coca and Kelley went on to report that confirming previous work of Valentine and Cooper, a study of eighteen cultures of the bacillus of Pfeiffer isolated from cases of influenza in different localities and at different times, revealed identities in the cultures only when a probability of personal contact existed. From this they decided that on the basis of Park's argument these findings admit of only one conclusion with regard to Pfeiffer's bacillus, namely, that microorganism is not the cause of the disease.

Rosenow²⁵ and his co-workers believed that many epidemics of typical influenza occur that are not due to the influenza bacillus, since this microorganism was found in their studies only occasionally in comparison to certain other organisms. And whereas after the intratracheal injection of influenza sputum or lung exudate, he noted²⁶ the invasion of certain other organisms, invasion by the influenza bacillus did not occur in a single experiment.

Utheim²⁷ found that during uncomplicated influenza, the body does not always form antibodies against its own infecting strain of the influenza bacillus. Of thirty strains isolated from patients with

25. Rosenow, E. C.: Studies in Influenza and Pneumonia: V. Observations on the Bacteriology and Certain Clinical Features of Influenza and Influenzal Pneumonia, *J. Infect. Dis.* **26**:469 (June) 1920.

26. Rosenow, E. C.: Studies in Influenza and Pneumonia: VII. A Study of the Effects Following the Injection of Bacteria Found in Influenza in Normal Throats, in Simple Nasopharyngitis, and in Lobar Pneumonia, *J. Infect. Dis.* **26**:504 (June) 1920.

27. Utheim, K.: Agglutination in Influenza, *J. Infect. Dis.* **27**:460 (Nov.) 1920.

influenza, eleven, or 36 per cent., gave agglutination with the patient's serum. Seven of these instances occurred in cases of uncomplicated influenza and four in cases of influenzal pneumonia. Of the remaining nineteen negative cases, ten were cases of pneumonia. Of the thirty strains, only one was agglutinated by heterologous serum.

Small and Dickson²⁸ concluded that the hemophilic microorganisms (*B. influenzae*) can be grouped by immunologic methods, and they demonstrated four groups into two of which 70 per cent. of the organisms studied fell.

After an elaborate study of agglutination and absorption tests on thirty-six strains of influenza bacilli with twenty-seven immune serums, Bell²⁹ concluded that the influenza bacillus represents a heterogenous group of organisms, though identical strains do occur. The morphology alone was unreliable as a means of dividing this group of organisms into subgroups. He found that a person may carry in the throat three different strains of this organism at the same time. By his serum test methods, he could make no differentiation between the organisms isolated from normal healthy throats within two months preceding the epidemic and those isolated from the throats of influenza patients.

Povitsky and Denny³⁰ also studied the grouping of influenza bacilli and found that in most cases, the organisms obtained from a number of colonies fished in a given case proved to be of one type, or at least, one type greatly predominated. In a minority of instances, the colonies from the same case were not of the same type, as proved by agglutination absorption tests using homologous and heterologous serums. However, in carriers, or when the infection was mild, more than one type of the influenza bacillus was apt to be found in the same case. On the other hand, in several convalescent carriers, tests were made during periods of from three weeks to three months, resulting in the finding of the original type of the influenza bacillus in all but one case, and in another case tests made a year apart proved the original type still present.

So, according to Wade and Manalang,³¹ the problem of the causative agent of influenza and especially that of the importance of the Pfeiffer bacillus, until recently generally believed to be the infecting organism in this disease, seems still far from solution. They referred to many

28. Small, J. C., and Dickson, G. K.: Grouping of *Bacillus Influenzae* by Specific Agglutination, *J. Infect. Dis.* **26**:230 (March) 1920.

29. Bell, H. H.: Relation of Different Strains of Influenza Bacilli as Shown by Cross Agglutination and Absorption Tests, *J. Infect. Dis.* **27**:464 (Nov.) 1920.

30. Povitsky, O. R., and Denny, H. T.: Studies on Acute Respiratory Infections: IV. Further Studies on Grouping of Influenza Bacilli with Special Reference to Permanence of Type in the Carrier, *J. Immunol.* **6**:65 (Jan.) 1921.

31. Wade, H. W., and Manalang, C.: Fungous Development of Growth Forms of *B. Influenzae*, *J. Exper. M.* **31**:95 (Jan.) 1920.

investigators who have cultured minute filtrable organisms and stated that if influenza is a virus disease, as now seems likely, it may be that the influenza bacillus has no primary relation to it. However, this cannot yet be asserted as a fact, for gradually the possibility is gaining recognition that familiar organisms of supposedly fixed morphology may assume a filtrable stage. Their observations then went on to show that the Pfeiffer organism is unstable and the familiar bacillus is but a simple form of an organism capable of complex development.

A Filtrable Virus.—In May, 1920, Olitsky and Gates²² made a preliminary report of the finding of a filtrable substance in the pharyngeal secretions in the early hours of uncomplicated epidemic influenza, which substance induced a clinical and pathologic condition in rabbits similar to influenza in man. They believed they were dealing with the actual transmission of a multiplying agent rather than with a passive transference of any original active substance.

The manner in which the bacteria of ordinary species, such as the pneumococcus, the Pfeiffer bacillus, *Streptococcus viridans*, and others are encountered during the course of the transmission experiments and during the experimental reproduction described justifies the opinion that these microorganisms are secondary in effect. The essential effects are produced by a substance wholly unrelated to these bacteria.

Following the above report, Olitsky and Gates³³ published a series of articles further describing their investigations. In the first one, they cited the criteria used in the selection of their cases of pure influenza as

abrupt onset with chilliness, fever, prostration, headache, and muscular pains especially in the back and limbs. Among the early symptoms were flush and suffusion of the face, injection of the conjunctivae, soreness of the throat, and harsh unproductive cough. In the early stages, no physical signs were detected in the chest; gastro-intestinal symptoms were inconspicuous, and disturbances referable to other internal organs were not complained of or detected by physical examination. These symptoms, although striking, were rarely such as could be measured accurately. However, there was one sign that had a quantitative value, namely the leukocytic picture. Uncomplicated influenza shows a pronounced leukopenia affecting the absolute number of mononuclear cells, chiefly the lymphocytic variety. This is persistent and even resists at times secondary infectious processes, eg., pneumonia, in which leukocytosis is the rule. . . . The symptoms and effects endured for from one to three days, when convalescence initiated by a lytic fall of temperature set in, and recovery promptly followed.

32. Olitsky, P. K., and Gates, F. L.: Experimental Study of the Nasopharyngeal Secretions from Influenza Patients, *J. A. M. A.* **74**:1497, (May 29) 1920.

33. Olitsky, P. K., and Gates, F. L.: Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients: I. Transmission Experiments with Nasopharyngeal Washings, *J. Exper. M.* **33**:125 (Feb.) 1921. II. Filterability and Resistance to Glycerol, **33**:361 (March) 1921. III. Studies of the Concurrent Infections, **33**:373 (March) 1921. IV. Anaerobic Cultivation, **33**:713 (June) 1921. V. Bacterium Pneumosintes and Concurrent Infections, **34**:1 (July) 1921.

At this point it is interesting to note that Rosenow³⁴ concluded after a study of blood counts in men and in animals that the leukopenia in influenzal infection in man may be due to peculiar properties of the bacteria which are now generally regarded as secondary invaders, and not to an unknown virus. Moreover, according to his findings, a persistent marked leukopenia or an increasing leukopenia in influenza predisposes to influenzal pneumonia, and in the latter indicates a bad prognosis.

To return to the work of Olitsky and Gates, they continued to say that with the aforementioned clinical picture as their guide of the pure influenza, they detected, by methods they described, an active substance in the nasopharyngeal washings of five patients in early stages of epidemic influenza during 1918-1919, and in two more in 1920. This active substance was not detected in twelve cases of the same disease in which the onset of obvious symptoms occurred more than thirty-six hours before washing of the nasopharynx was carried out, nor was it found in the secretions of fourteen individuals free from the syndrome of influenza either during the epidemics or the interval between them. They noted that the active agent as it exists in the nasopharyngeal secretions in man and in the lungs of rabbits injected with human secretions, passes through Berkefeld V and N candles. With this active agent, whether in filtered or unfiltered material, they induced in rabbits a clinical and pathologic condition affecting mainly the blood and pulmonary structures, which condition could be maintained and carried through at least fifteen successive animals. The similarity that existed between the effects produced in rabbits in the blood ("changes in the absolute and differential white blood cell count") and the lungs ("certain hemorrhagic, edematous and emphysematous changes") and those occurring in man in epidemic influenza provided these authors with a basis for further investigation as to the inciting agent of epidemic influenza.

Olitsky and Gates next announced³⁵ that using the anaerobic Smith-Noguchi technic, they had cultivated from the filtered nasopharyngeal washings from early cases of uncomplicated epidemic influenza and from the lung tissues of experimental animals, a minute bacilloid body from 0.15 to 0.3 microns in length, of constant cultural characteristics and capable of indefinite propagation on artificial mediums. They stated that this organism grows only under strictly anaerobic conditions, passes Berkefeld V and N filters, and withstands

34. Rosenow, E. C.: Studies in Influenza and Pneumonia: VI. The Leukocytic Reaction in Influenza and Influenzal Pneumonia, *J. Infec. Dis.* **26**:492 (June) 1920.

35. Olitsky, P. K., and Gates, F. L.: Studies of the Nasopharyngeal Secretions from Influenzal Patients: Preliminary Report on Cultivation Experiments, *J. A. M. A.* **76**:640 (March 5) 1921.

the action of sterile 50 per cent. glycerol for a period of months. They gave it the name of *Bacterium pneumosintes* (from πνεύμων, lung, and σίντης, injurer or devastator) since a striking feature of its effect in rabbits is to diminish the resistance of the lungs to the action of ordinary bacteria. This bacterium appeared to the authors to be identical with the active agent previously reported and to be the source of the reactions which occur in experimental animals, rabbits and guinea-pigs, as a result of the intratracheal injection of nasopharyngeal washings obtained during the early hours of uncomplicated epidemic influenza in man. They deferred decision, however, as to the precise relation which the species described bears to epidemic influenza in man, until further experience was obtained.

In two previous papers, Olitsky and Gates³³ stated that in no instance did death occur in the experimental rabbits as a result of the uncomplicated effects of the influenzal agent alone. When death occurred in any of the inoculated animals, concurrent infection of the lungs by ordinary bacteria was present. In fact, their experiments showed that the lungs of animals infected with the *Bacterium pneumosintes* are less resistant than normal lungs to infection with ordinary bacteria, the pneumococcus Type IV, atypical Type 2 streptococci, and hemoglobinophilic bacilli, being most commonly met. They believed that a similarity exists between the conditions under which concurrent infections arose in the inoculated rabbits and those which seem to favor the occurrence of concurrent infections during epidemic influenza in man. They further believed that their observations furnished additional proof of the identity of *Bacterium pneumosintes* and the active agent derived from the nasopharyngeal secretions of patients in the early hours of epidemic influenza.

It is to be hoped that in future papers, Olitsky and Gates will give further information as to the identity and pathogenicity of their interesting bacterium. In the meanwhile, Loewe and Zeman³⁶ have already reported the cultivation of a filterable organism from the nasopharyngeal washings in influenza, and they stated that their organism does not appear to differ from that recovered by Olitsky and Gates. M. W. Hall³⁷ has reported that it is possible by the injection into the circulation of bacteriologically sterile filtrates of sputum from early cases of influenza to produce in animals lesions of a uniform type uncomplicated by the presence of demonstrable bacteria but quite comparable to the so-called primary lesions of influenza reported by many. He believed that his results seem to give support to the theory

36. Loewe, L., and Zeman, F. D.: Cultivation of a Filtrable Organism from the Nasopharyngeal Washings in Influenza, J. A. M. A. **76**:986 (April 9) 1921.

37. Hall, M. W.: A Study of the Lesions Produced by Filtrates of Influenza Sputum, Arch. Int. Med. **26**:612 (Nov.) 1920.

of a filtrable agent as the primary cause of influenza. The active agent concerned is markedly resistant to heat, and probably is mainly intracellular in character, he thought. He further noted that, according to the early reports, the work of Olitsky and Gates in many ways parallels his, with apparently harmonious results.

The theory that influenza is caused by a filterable virus has not been accepted without exception. Williams, Nevin and Gurley,³⁸ of Park's associates, reported an unusually comprehensive procedure for collecting and handling material, and yet stated "the negative results obtained by our procedure for demonstrating filtrable microbes, we consider an indication that the positive results already reported do not bear as wide an application as their sponsors infer."

Branham and I. C. Hall³⁹ reported that in attempting to cultivate filtrable viruses from the nasopharyngeal secretions in colds and influenza, no bodies were found in the cultures which could not also be found in those from normal persons, but they recognized that negative experiments limited to the attempted cultivation of a filtrable virus and including no attempts to reproduce the disease in animals, do not offer conclusive evidence that such a virus is not involved. Nor did they work on cases of influenza during the earliest stages of the disease. In a separate paper, I. C. Hall⁴⁰ stated that the probability of obligate anaerobes developing in the respiratory tract seems slight in view of the excessive air supply, and that his findings indicate that such infections occurred, if at all, only infrequently in the cases of respiratory disease presented for examination during the winter and spring of 1920.

Other Micro-Organisms in Influenza.—Tunncliff⁴¹ noted that from influenza and its complications during the onset and at the height of the 1918-1919 epidemic, various investigators had isolated peculiar green-producing cocci with the characteristics of both a pneumococcus and a streptococcus. These green-producing cocci are oftener lanceolate than round, generally possess a capsule, and produce large moist green colonies on blood-agar plates. She herself succeeded in isolating this

38. Williams, A. W.; Nevin, M., and Gurley, C. R.: Studies on Acute Respiratory Infections: I. Methods of Demonstrating Microorganisms, Including "Filterable Viruses" from the Upper Respiratory Tract in "Health," in "Common Colds," and in "Influenza" with the Object of Discovering "Common Strains," J. Immunol. **6**:5 (Jan.) 1921.

39. Branham, S. E., and Hall, I. C.: Influenza Studies: III. Attempts to Cultivate Filtrable Viruses from Cases of Influenza and Common Colds, J. Infect. Dis. **28**:143 (Feb.) 1921.

40. Hall, I. C.: Influenza Studies: II. A Search for Obligate Anaerobes in Respiratory Infections, an Anaerobic Micrococcus, J. Infect. Dis. **28**:127 (Feb.) 1921.

41. Tunncliff, R.: Observations on Green Producing Cocci of Influenza, J. Infect. Dis. **26**:405 (May) 1920.

coccus from the edematous brain in influenzal broncho-pneumonia, usually in pure culture, but in no instance did she cultivate the Pfeiffer bacillus from the brain. From her serologic experiments she decided that these green-producing influenzal cocci form a group the members of which are closely related immunologically.

Rosenow and his coworkers²⁵ also studied this green-producing streptococcus, finding it in a large series of cases of influenza and influenzal pneumonia throughout four different epidemic waves, more constantly and in larger numbers than any other organisms associated with the disease. Rosenow noted²¹ that the virulency and mortality in animals increased for one or two successive intratracheal injections of this microorganism, and on further animal passage diminished. And after a study of the four epidemic waves as they occurred in Rochester, Minnesota, he found that a similar rise and fall in severity of symptoms, mortality and character of lung lesions occurred as the epidemic waves appeared and disappeared. Accordingly he thought that (1) the change in the type of the disease early and late in the epidemics, (2) the rise and fall in mortality rate in the same epidemic, and in the virulency of different epidemics, and (3) the lesser tendency to leukopenia late in epidemic waves, may all be due, in the main, to changes in virulency and other properties of the green-producing streptococcus isolated so constantly in influenzal infections. He further noted⁴² that whereas these peculiar green-producing streptococci are immunologically quite homogenous at the outset of an epidemic, the strains tend to become more heterogenous after cultivation on artificial mediums, and after repeated animal passages as well as late in influenza and influenzal pneumonia.

Rosenow also studied the four main types of bacteria isolated in this disease as to their invasive powers following intratracheal injection of influenzal sputum. Invasion by the green-producing streptococcus group (including pneumococci), occurred in most instances even when not the predominating organism in the material injected. In some instances, invasion by hemolytic streptococci occurred, but usually only when they were present alone or in predominating numbers. Invasion by staphylococci occurred even more rarely and only when in predominating numbers; and invasion by the influenza bacillus following the injection of sputum and lung exudate did not occur in a single experiment.

Recapitulating, Rosenow wrote,²⁶

Through a painstaking study of the infecting powers of the streptococcus in influenza and influenzal pneumonia throughout several epidemic waves, it

42. Rosenow, E. C.: Studies in Influenza and Pneumonia: X. The Immunologic Properties of the Green Producing Streptococci from Influenza, *J. Infect. Dis.* 26:597 (June) 1920.

has been possible to reproduce in animals by various methods of injection, but particularly by intratracheal injection, the picture of influenza as seen in man. The symptoms both of influenza and influenzal pneumonia have been grossly simulated in these animals as far as possible. Likewise the gross and microscopic changes which have come to be regarded as quite characteristic of influenzal infection have been reproduced. The same varied picture that often supervenes in the later stages of influenzal pneumonia in man such as leukocytosis as evidence of pleural involvement and pleural infection, becomes manifest and the varied pathologic picture in the lung of patients who died late has been noted in guinea-pigs injected intratracheally with these strains. The tendency to involvement of the female generative organs with a high mortality in pregnancy and a high incidence of abortion, of lesions of the heart, abscess in the rectus muscle, and interstitial emphysema, have been noted in the experimental animal quite as they occur in man.

Cooper, Mishulow and Blanc ⁴³ studied the pneumococcus in connection with common colds and influenza-like cases, and found no single variety of this organism dominant in the inflammatory conditions studied. They found no data to indicate that the pneumococcus is the primary etiologic agent in the contagious types of these inflammations. Bakwin ⁴⁴ found pneumococci in seven out of thirty-five antemortem blood cultures in cases of influenzal pneumonia. The remainder were sterile, with the exception of one, which showed a meningococcus.

Influenzal Pneumonia: Pathology.—Bakwin ⁴⁴ made a study of the findings of 106 necropsies on cases of influenzal pneumonia in the American army in France. He noted that the disease was general, affecting not merely the lungs but all the organs, being accompanied by jaundice, cloudy swelling of the parenchymatous organs and heart muscle, and hemorrhages into the pericardium, renal pelvis and other viscera. Changes in the rectus muscle were observed in one-third of the cases, and sphenoid sinusitis was found in twenty out of twenty-two cases examined. Empyema was rare, occurring in less than 4 per cent. of the cases.

Warwick ⁴⁵ reported the case of an infant which was apparently normal at birth but at 3 days of age developed a temperature of 105 F. and died the following day. The necropsy revealed a peculiar hemorrhagic process involving the greater part of both lungs, a pathologic picture which was practically identical with the so-called "hemorrhagic broncho-pneumonia" which was seen so frequently in patients dying

43. Cooper, G. M.; Mishulow, L., and Blanc, N. E.: Studies on Acute Respiratory Infections: II. A Study of the Serological Relationships of Pneumonia from the Upper Respiratory Tract with Special Reference to Common Colds and Influenzal Conditions, *J. Immunol.* **6**:25 (Jan.) 1921.

44. Bakwin, H.: Gross Pathology of Influenzal Pneumonia in France, *Am. J. M. Sc.* **159**:435 (March) 1920.

45. Warwick, M.: Necropsy Findings in New-Born Infants, *Am. J. Dis. Child.* **21**:488 (May) 1921.

of influenza. Since this case occurred early after the outbreak of the 1918 influenza epidemic, it was probably an instance of this disease in a new-born infant, an uncommonly rare occurrence.

Influenzal Types, Complications and Sequels.—Stengel⁴⁶ clinically classified cases as of influenzal pneumonia or lobar pneumonia by a consideration of the history, the character and extent of the physical signs, and by the leukocytic count.

Cases regarded as influenzal pneumonia have invariably shown diffuse physical signs, commonly bilateral, and always much less clearly marked than in lobar pneumonia, and the leukocytic count has usually been below 10,000, while the differential count has commonly shown a relative deficiency in neutrophils, or at least no increase. The development of the signs of pneumonia is somewhat gradual and irregular, following a clear picture of ordinary influenza. On the other hand, the cases regarded as lobar pneumonia have had sudden onset of symptoms of pneumonia and a rapid development of physical signs with clearly marked lobar consolidation. The leukocytic count was above 12,000 and the proportion of neutrophils marked (from 80 to 90 per cent.).

The experiments made as a basis of his studies suggested to Rosenow⁴⁷ that there is a true gastro-intestinal type of influenza, and that green-producing streptococci, similar to those isolated from the respiratory tract, are the chief cause. He went on to say, however, that it is not to be concluded that all symptoms in influenza referable to the gastro-intestinal tract are due to localization of bacteria in its mucous membrane. In certain of his experiments it was shown that the symptoms and findings in influenza are due, in part, to an anaphylactoid reaction; the severe vomiting and diarrhea noted at the outset of some cases may be an expression of this mechanism.

Amesse⁴⁸ wrote in a recent article that he believed that influenza in its acute epidemic form is merely latent at present, yet at the same time the disease is present in occasional dual relation with everyday disease. The observation of such unusual complications of chickenpox, measles, etc., as meningitis and meningismus, complications which occur in influenza also, has led him to believe that influenza may assume different varieties, and that the "unusual features noted in the study of more common disorders justify the impression that we are frequently dealing with a double infection"—presumably of the common disorder and some variety of influenza.

46. Stengel, A.: On the Use of Serum and Blood of Convalescent Patients in the Treatment of Lobar Pneumonia and Influenzal Pneumonia, *M. Clinics N. America* 4:937 (Jan.) 1921.

47. Rosenow, E. C.: Studies in Influenza and Pneumonia: VIII. Experiments on the Etiology of Gastro-Intestinal Influenza, *J. Infect. Dis.* 26:557 (June) 1920.

48. Amesse, J. W.: Unusual Complications and Sequellae in the Acute Infections of Childhood following the Influenza Epidemic, *Colorado Med.* 18: 56 (March) 1921.

Meyer and Lucke⁴⁹ reported seven cases of subcutaneous emphysema following influenza in soldiers. They believed that it arose chiefly as a result of the escape of air from ulcerated or eroded bronchi and its subsequent passage along peribronchial or perivascular channels into the mediastinum. In at least two of their cases, they found marked ulcerative bronchitis and subcutaneous emphysema, both located on the left side.

Fishberg⁵⁰ observed that in many patients attacked by acute epidemic influenza, certain sequels are left in the respiratory tract after the acute infection has run its course. He enumerated subacute rhinopharyngitis, general bronchitis, localized bronchitis resembling tuberculosis and very difficult to differentiate from it, bronchiectasis and pulmonary abscess.

Epidemiology.—The epidemic of respiratory diseases of January, 1920, differed from the epidemic of 1918 in that the total number of persons affected was less, the proportion of acute rapidly fatal cases was smaller, and the period of the epidemic was shorter.⁵¹ In an elaborate statistical study of the 1918 epidemic of influenza in Connecticut, Winslow and Rogers⁵² noted that the epidemic cost the state about 7,700 lives and was by far the most serious sanitary calamity from which Connecticut has ever suffered. Apparently the case rate in affected communities varied from 200 to 400 cases per thousand of population, and the fatality rate between two and four deaths per hundred cases. "The rapid spread of the disease throughout the state and the fact that quarantine completely protected isolated groups of individuals (so long as the quarantine was rigidly maintained) indicates clearly that it was transmitted by human contact, perhaps supplemented in certain cases by the use of infected food and utensils."

Treatment.—Sterling⁵³ noted that quinized malarial patients in hospital in Italy were practically immune to the epidemic raging around them. Accordingly he made a plea for the use of 15 grains of quinin hydrobromid on retiring, as a prophylactic measure against epidemic influenza.

49. Meyer, J., and Lucke, B.: Subcutaneous Emphysema; A. Complication of Influenza Pneumonia. Report of Seven Cases, *Am. J. M. Sc.* **159**:417 (March) 1920.

50. Fishberg, M.: Pulmonary Sequels of Influenza, *Am. J. M. Sc.* **161**:365 (March) 1921.

51. Editorial: Influenza of 1918 and 1920, *J. A. M. A.* **74**:736 (March 13) 1920.

52. Winslow, C-E. A., and Rogers, J. F.: Statistics from the 1918 Epidemic of Influenza in Connecticut, with a Consideration of the Factors which Influenced the Prevalence of this Disease in Various Communities, *J. Infect. Dis.* **26**: 185 (March) 1920.

53. Sterling, A.: Quinine as a Prophylactic and Specific for Influenza, *Pennsylvania M. J.* **23**:719 (Sept.) 1920.

Holt⁵⁴ analyzed the statistics of the Visiting Nurse Service of the Henry Street Settlement during the influenza epidemic of October and November, 1918, where 162 nurses visited and reported on 10,655 cases of influenza and pneumonia under the care of physicians in the patients' homes. One thousand, six hundred and twenty-five cases are left out of his final tabulation, the cases having been mild and not requiring subsequent visits, or terminated before the arrival of the nurse, or for some other similar reason. Of the remaining 8,740 cases, the mortality was as follows:

Type of case, influenza; number treated, 6,243; deaths, 115; mortality per cent., 1.6. Pneumonia: number treated, 2,497; deaths, 485; mortality per cent., 19.4. Totals: number treated, 8,740; deaths, 600; mortality per cent., 6.9.

Holt added that cases of simple influenza and of influenzal pneumonia are accordingly best treated in the patients' homes or when separated as much as possible. His figures also indicated that the frequency and the severity of the complications are much increased in proportion as patients are crowded together.

At the Mare Island Naval Station, the final development of the treatment of influenza which gave the best results, has been set down by Neilson⁵⁵ as follows: (a.) Absolute rest in bed. (b.) Thorough and constant alkalinization either by mouth or by Murphy drip. (c.) Sodium salicylate intravenously, only in cases not complicated by pneumonia and then only when pain, restlessness, and high temperature, evidenced severe toxemia. (d.) Magnesium sulphate intravenously in pneumonia cases showing bad general condition, high temperature, and falling white count. (e.) Blood transfusion from immune donors (citrate method with whole blood) in pneumonia cases showing cyanosis, rise in temperature (either when first seen or after failure to react permanently to magnesium sulphate intravenously), and a falling white count. (f.) Stimulation used more sparingly, and only when indicated for special purpose or in selected case. Whisky, digitalin, or camphor, used as stimulant. (g.) Sodium iodid in a simple cough mixture to relieve a troublesome dry cough. (h.) Magnesium sulphate by mouth for catharsis. (i.) Carbohydrate diet.

The death rate at this station among those receiving the more specific forms of treatment was lower than the death rate given in any statistics that have come under the observation of the writer, from other points at which the disease was of an equally severe type.

54. Holt, L. E.: Home versus Hospital Care of Cases of Influenza, *Med. Rec.* **97**:731 (May 1) 1920.

55. Neilson, J. L.: Treatment of Influenza, *U. S. Nav. M. Bull.* **15**:259 (April) 1921.

Hogan⁵⁶ gave details of the preparation and administration of the magnesium sulphate-calcium chlorid mixture spoken of by Neilson, and stated that there had been only 16 per cent. of deaths in fifty severe cases of influenzal pneumonia treated with this mixture against a mortality of 40 per cent. in similar cases treated symptomatically only.

Rosenow⁵⁷ used an immune serum prepared from one strain of the green-producing streptococcus, and treated twelve patients with influenzal pneumonia, of whom eleven were critically ill at the time of serum treatment. Five recovered. In all cases in which specific agglutination was obtained, marked improvement followed the injection of the serum, and in no case were good effects noted at a time when agglutination tests were negative. Of the seven deaths, two were caused by hemolytic streptococci, two by a strain of green-producing streptococcus immunologically different from that of the serum, and three of the patients were moribund at the time of treatment.

Stengel⁴⁶ treated nine patients all seriously ill with influenzal pneumonia, by the intravenous injection of from 30 to 70 c.c. of blood serum from patients recently convalescent from the disease, and all recovered, but a tenth patient, moribund on admission, failed to survive.

Immunity.—Jordan and Sharp⁵⁸ made a statistical study of several thousand men at the Great Lakes Naval Station and at Camp Grant, to find out which men, attacked in the 1920 epidemic, had been attacked in the 1918-1919 epidemic and which had not. Their results indicate that no marked immunity to influenza exists from twelve to fifteen months after a previous attack.

The use of vaccines as a means of producing artificial immunity against influenza has been studied by a number of observers. McCoy⁵⁹ decided that the Pfeiffer bacillus alone or in combination had no practical uses. Park¹⁹ remarked that the evidence of immunologic response to the vaccines by his co-workers was apparent only in the lessened incidence of pneumonia. The percentage of colds was as great among the vaccinated as among the unvaccinated. The pneumonia incidence was much less. The greater multiplicity of types of microbes believed to be capable of exciting common colds over those usually exciting pneumonia is possibly the explanation of the apparent uselessness of

56. Hogan, J. J.: Intravenous Use of Magnesium Sulphate and Calcium Chloride in Severe Pneumonia Complicating Influenza, U. S. Nav. M. Bull. **15**:277 (April) 1921.

57. Rosenow, E. C.: Studies in Influenza and Pneumonia: XI. Therapeutic Effects of a Monovalent Antistreptococcus Serum in Influenza and Influenzal Pneumonia, J. Infect. Dis. **26**:614 (June) 1920.

58. Jordan, E. O., and Sharp, W. B.: Influenza Studies: I. Immunity in Influenza, J. Infect. Dis. **26**:463 (May) 1920.

59. McCoy, G. W.: Application of Vaccines in Public Health Work, Am. J. Pub. Health **10**:666 (Aug.) 1920.

the vaccines employed in this series in preventing minor respiratory infections while apparently affording considerable protection against pneumonia. The vaccine that Von Sholly and Park⁶⁰ used in this work contained 2,000 million per c.c. each of pneumococcus Types I and II, and 1,000 million each of pneumococcus Type III, *Streptococcus hemolyticus*, *Streptococcus viridans*, and the influenza bacillus.

Similar results to those of Von Sholly and Park were obtained by Jordan and Sharp⁶¹ who stated that rhinitis and bronchitis developed with about equal frequency in the vaccinated and unvaccinated groups. Their figures suggested a favorable conclusion regarding some slight prophylactic value for pneumonia, but that any considerable degree of protection against influenza was conferred by the vaccine, seemed unlikely.

On the other hand, Gay⁶² noted a rising enthusiasm among writers as to the value of mixed vaccines containing various strains of influenza bacilli, pneumococci, streptococci and staphylococci, not only to diminish the incidence of influenza in a community but also for decreasing the pneumonic complications of the disease.

(To be continued)

60. Von Sholly, A. I., and Park, W. H.: Studies on Acute Respiratory Infections: VII. Report on the Prophylactic Vaccination of 1,536 Persons Against Acute Respiratory Infections, 1919-1920, J. Immunol. **6**:103 (Jan.) 1921.

61. Jordan, E. O., and Sharp, W. B.: Influenza Studies: IV. Effect of Vaccination against Influenza and Some Other Respiratory Infections, J. Infect. Dis. **28**:356 (April) 1921.

62. Gay, F. P.: The Use of Vaccines in the Prevention and Treatment of Influenza and Its Sequels, J. A. M. A. **76**:244 (Jan. 22) 1921.