The greater tendency to the development of pneumonia in influenza among the unvaccinated group as observed in this series is in keeping with the lower incidence of this complication (4.7 per cent.) in 11,325 cases of influenza in which the vaccine was given after the onset of the symptoms, as compared with the incidence (8.7 per cent.) in 41,788 cases in which the vaccine was not used. The average mortality in the cases in which the vaccine was used in treatment was 1.4 per cent.; in those not treated it was 2.1 per cent.

From these results considerable weight may be attached to the opinion of nearly all the 430 physicians who have used the vaccine and who have reported on this point, an opinion in agreement with our own observations, that is, that the attacks of influenza if contracted following vaccination are milder and of shorter duration.

SUMMARY

The immunologic and animal experiments reported⁷ elsewhere indicate that the mixed vaccine used by us contained the important bacteria as they occur in influenza and the accompanying pneumonia, and that a relatively large number of strains of the green-producing streptococci which appear to have a specific relationship to the initial attack were included. The reports included results obtained under the most varied conditions, from many communities covering a wide range of territory. In some communities the mortality rate was excessively high, in others comparatively low. The number of persons inoculated is sufficiently large to make the statistical figures fairly accurate. The period of observation was from three to seven months. The incidence of influenza and pneumonia as reported to us is probably far from exact, but the percentage of error should be about the same in the vaccinated and unvaccinated groups. Indeed, if a difference exists, the number of cases reported among the vaccinated might be expected to be proportionately higher because, even though no protection was promised, the fact that influenza occurred after the vaccinations were taken would naturally lead to a higher percentage of reports to the physician who gave the inoculations. The average incidence of influenza and pneumonia in the group inoculated three times is about one-third that of the uninoculated group.

The average mortality rate in the uninoculated, as reported to us, approximates the mortality rate (5.4 per cent.) of sixteen large cities of the United States as given in *Public Health Reports* for February 7. The average mortality rate in the group inoculated three times is about one-fifth that of the uninoculated. A definite although a smaller degree of protection appeared to be afforded to those who took only one or two inoculations. From a study of a series of hospital cases of influenza it is found that the tendency to the development of pneumonia in the vaccinated is about one third as great as among the unvaccinated, and that the mortality in the former is about one fifth as great as in the latter. The number of completed vaccinations in pregnant women is not large enough to give exact figures, but the results indicate clearly that a definite degree of protection was afforded in this group of individuals.

7. Rosenow, E. C.: The Experimental Production of Symptoms and Lesions Simulating Those of Influenza with Streptococci Isolated During the Present Epidemic, Study II, *J. A. M. A.* **72**: 1604-1608 (May 31) 1919. The Occurrence of a Pandemic Strain of Streptococcus During the Pandemic of Influenza, Study III, *ibid.* pp. 1608-1609.

It appears from all the facts at hand that by the use of a properly prepared vaccine it is possible to rob influenza of some of its terrors.

The preliminary results from the use of more than 500 doses of this vaccine suspended in oil, the immunologic studies and the results from the use of pneumococcus lipovaccine reported by Fennel⁸ and by Cecil and Vaughan⁹ suggest strongly that both the degree of protection and the duration of the immunity may be materially increased by the use of lipovaccine over that reported in this paper from the use of the saline vaccine.

STATUS OF PROPHYLACTIC VACCINATION AGAINST INFLUENZA *

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When we consider the tragic experience through which the country and, indeed, the world, has passed during the last year, we realize that a great advance in preventive medicine would be made by the discovery of a prophylactic agent which would enable health authorities to control effectively epidemic influenza or the pneumonia that so often occurs as a complication. Perhaps at the outset it may be profitable to take stock of what we know about the etiology of influenza and the etiology and pathology of influenzal pneumonias.

OPINIONS AS TO ETIOLOGY OF INFLUENZA AND INFLUENZAL PNEUMONIA

Though the organism described by Pfeiffer in 1891 has long been known as the influenza bacillus, there really never has been convincing evidence of its relation to influenza, and the data that accumulated during the epidemic or epidemics here and abroad this past year have not contributed any confirmation to the view that this germ is the cause of the disease.

In this connection it should be borne in mind that it is quite possible that there are a number of organisms, varying greatly in pathogenicity, which are grouped under the name of Pfeiffer's bacillus. We have only to recall the great differences that exist in other groups, in which organisms having common cultural and morphological characteristics vary greatly in disease-producing properties, to realize that the rather vague limitations of what is called the influenza bacillus may cover a number of more or less closely related organisms.

French and English workers have claimed to have produced influenza by means of a filterable virus; this would, indeed, definitely eliminate Pfeiffer's bacillus; but we must bear in mind that attempts to produce the disease in man artificially in this country, by means of both filtered and unfiltered secretions, have in practically every instance been negative. Similar attempts by means of cultures of the so-called influenza bacillus have been negative.

8. Fennel, E. A.: Prophylactic Inoculation Against Pneumonia, *J. A. M. A.* **71**: 2115-2120 (Dec. 28) 1918.

9. Cecil, R. L., and Vaughan, H.: Results of Prophylactic Vaccination Against Pneumonia at Camp Wheeler, *J. Exper. M.* **29**: 457-483 (June) 1919.

* Read before the joint meeting of the Section on Pharmacology and Therapeutics, the Section on Pathology and Physiology and the Section on Preventive Medicine and Public Health at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

When we turn to the views on the etiology and pathology of influenzal pneumonia, we find a rather general opinion that the pneumonia is due to Pfeiffer's bacillus or to the secondary invasion by organisms of acknowledged pathogenicity, particularly the various types of pneumococci, the streptococci, especially those known as hemolytic, and, less commonly, Friedländer's pneumobacillus or the staphylococcus.

A few observers are inclined to the opinion that the original cause of the influenza, be it the influenza bacillus or another organism, is also an essential factor in the production of the pneumonia. This view would appear to be entitled to much respect, on account of the rather general opinion among pathologists that the pneumonia following influenza is generally of a type distinct from the pneumonias ordinarily encountered.

A number of interesting papers have appeared on the pathology of influenzal pneumonia, and a complete review of them would be valuable; but, for the present purpose, we may say that, in general, the pneumonias do not conform to those due to the organisms which are usually associated with pneumonia. Lack of definite areas of consolidation, the absence of the usual fibrinous pleural exudate, the extreme wetness of the lungs, and the blood-stained pleural fluid usually found bilaterally, in most cases serve to differentiate influenzal pneumonias from those ordinarily due to pneumococci, as lobar pneumonia. Emphasis is laid on this point because some workers have hoped that immunization against lobar pneumonia, which appears to be practicable, might prove of great value against influenzal pneumonia; but if the lung lesions of the two diseases are so different, one suspects there may be a material difference in etiology, and that this difference may be of such a nature as to make what appears to be a valuable prophylactic agent in one case of no use in the other.

Rosenow¹ calls especial attention to the fact that "the findings in the lungs, for example, in the so-called acute bronchopneumonia following influenza, are quite unique and are strikingly similar, irrespective of the species of microorganism present." This is quoted to emphasize the point that it is entirely possible that all of these lesions may be due to the primary cause of influenza, and that the various organisms which have been recognized in various cases and various places may really not reach even the dignity of secondary invaders, but may be looked on as leading a relatively saprophytic existence in the tissue damaged by the primary cause of influenza, whatever that may be. With this brief preliminary consideration of these important matters, let us consider the experience with prophylactic vaccination.

VACCINE FROM INFLUENZA BACILLUS AS A PROPHYLACTIC

In discussing this subject, we will give attention, first, to the results obtained from the use of a vaccine made from the influenza bacillus alone, or from other suspected etiologic agent, which aims, to be sure, to prevent the primary disease, and later to a review of the evidence with respect to vaccines which have been devised with the special object of preventing the development of pneumonia or of mitigating its severity.

A vaccine made from the influenza bacillus alone seems not to have appealed sufficiently to European

workers to induce them to try it when the epidemic prevailed abroad. In this country, its use has been confined largely to New England. The early reports on this vaccine were very encouraging; figures were presented which, if taken at their face value, would convince any one of the efficiency of the agent; but, when these figures were submitted to careful analysis, much doubt remained as to whether the vaccine was of any service whatsoever. The chief source of error lay in the fact that the inoculations had been done during the progress of the epidemic, and that the case incidence among the vaccinated was compared with the case incidence in the general population or in the control groups from the beginning of the epidemic. Now, it is plain that if, after the epidemic is well under way, we vaccinate a portion of the persons in a population, the percentage of persons attacked will be smaller among the vaccinated than among the nonvaccinated, because a percentage of the total number of cases will have occurred before the vaccine is given. Not only does this introduce an error by counting in the control, or nonvaccinated group, cases that have occurred early, but also it leaves a select group to be vaccinated, wholly or in part, in which the percentage of susceptibles is smaller than in the original group of which they formed a part.

To make this clear, let us suppose that ten days after an epidemic started in a population of 1,000 persons, an admittedly worthless vaccine was administered to one half of those who at that time remained unattacked by the disease. Let us further assume that on the date of vaccination 20 per cent. of the population had sickened, leaving 800 well persons, of whom 400 were vaccinated. Since the hypothetical vaccine is worthless, the morbidity will be as great in the vaccinated as in the nonvaccinated group. Let us assume this to be an additional 20 per cent. Then the total morbidity in the vaccinated group will be 20 per cent. of 400, or eighty cases. The total morbidity in the unvaccinated, however, if we consider the entire period of the epidemic will be 20 per cent. of 1,000, or 200, plus 20 per cent. of 400, or eighty, which would make 280 cases.

Although the error is now sufficiently clear, we have seen reports which, on the basis of the above figures, if applied to this hypothetical worthless vaccine, make it appear to be a valuable prophylactic. The statement of these reports would be, in effect, that one half of the population was vaccinated, that among the vaccinated only eighty cases developed, while among the unvaccinated 280 cases appeared. Hence the obvious value of the vaccine.

We must also remember that a vaccine can scarcely be expected to exert any appreciable prophylactic effect before from seven to ten days after the vaccine is given, since a week or more is required for immunity to develop. A comparison is fair which considers, among both vaccinated and nonvaccinated, only cases that have occurred, say, ten days or more after the vaccinations are made.

When the influenza bacillus vaccine was submitted to such critical tests as the inoculation of approximately half of the individuals in institutions, or in other large groups, its failure became apparent. A few examples of this are worth citing. Hinton and Kane² were able to vaccinate about half of the patients at an epileptic

1. Rosenow, E. C.: Prophylactic Inoculation Against Respiratory Infections, J. A. M. A. 72: 31 (Jan. 4) 1919.

2. The Commonwealth, Bimonthly Bulletin, Massachusetts State Department of Health 6:28, Nos. 1 and 2, 1919.

colony long enough before the disease became prevalent in the institution to justify the drawing of conclusions from their data. The vaccine used contained 800,000,000 organisms per mil, and a total of 2,000,000,000 were administered to each person. The results were as shown in Table 1.

TABLE 1.—EFFECT OF INFLUENZA BACILLUS VACCINE AS
A PROPHYLACTIC

	Vaccinated		Not Vaccinated (Controls)	
	No.	Per Cent.	No.	Per Cent.
Number of persons	461		518	
Cases of influenza	163	35.4	178	34.3
Deaths	28	17.0	24	13.5

On the basis of this experiment the authors reach the obvious conclusion that the vaccine was without value.

A similar test was made on the naval personnel at Pelham Bay Training Station; here a part of the individuals of a group were vaccinated, the remainder being held as controls. According to the latest available report,³ 9 per cent. of the 554 inoculated persons developed the disease, and 5 per cent. of the 800 who had not been inoculated developed it.

Similar failure attended the attempts at immunization of men at the naval base at Paris Island, S. C. It was definitely shown that neither incidence nor severity was influenced by the vaccination. These observations were all on groups large enough to make the deductions of value.

A number of controlled vaccinations, in which influenza bacillus vaccine was used, carried out in institutions by the Public Health Service, gave the rather paradoxical result of showing an increased percentage of attacks among the vaccinated, but more deaths among the nonvaccinated. This result was obtained with a vaccine directed against the primary disease, not against the complicating pneumonia. The results are shown in Table 2. These figures illustrate the fallacy of giving much weight to the results of a small set of observations in work of this sort.

TABLE 2.—RESULTS OBTAINED BY INFLUENZA BACILLUS
VACCINE IN INSTITUTIONS

	Vaccinated		Not Vaccinated (Controls)	
	No.	Per Cent.	No.	Per Cent.
Number of persons	484		842	
Cases of influenza	153	31.6	223	26.4
Deaths	0		4	1.8

VACCINES FROM STREPTOCOCCUS AND OTHER ORGANISMS

Another series of vaccinations aimed directly against the supposed causative agent was that reported by Ely, Lloyd, Hitchcock and Nickson.⁴ These workers believed that the epidemic was due primarily to a hemolytic streptococcus which could be detected in the blood and in the lungs. From the fact that the organisms with which these observers worked soon lost their chain-forming properties and, in some instances, the power to hemolyze promptly, they express some doubt as to whether they should be classed as streptococci, and they further assume that there are material differences between different strains. The results of the use of a vaccine prepared from organisms isolated from the cases were apparently most

encouraging, though none of the experiments was controlled in a manner that would definitely establish the value of the preparation. The work of these observers needs to be repeated before the results can be accepted for general application.

When we come to consider the evidence with respect to the vaccines especially designed to prevent the pneumonic complications of influenza, we find again such conflicting reports that one is somewhat bewildered.

The only papers from a foreign source that have come to my notice are those by Eyre and Lowe,⁵ who used a mixed vaccine which contained the pneumococcus, the streptococcus, the influenza bacillus, *Staphylococcus aureus*, *Micrococcus catarrhalis*, *B. pneumoniae* and *B. septus*.

These authors believe, and indeed present rather convincing figures in their first paper⁵ to prove their point, that the use of this vaccine produces lowered resistance, which may last for "from a few hours to two or three weeks," during which period the incidence of respiratory infections would be increased among inoculated groups.

The early experience of the English authors does not refer directly to the prophylaxis of influenza, but it is cited here to show that there may be an element of danger in the indiscriminate use of vaccines in the presence of a rapidly spreading epidemic like influenza in which naturally many persons in the "negative phase" would be attacked.

In a later paper,⁶ the same writers report on the experience with vaccine in the epidemic in England in the autumn of 1918. Stress is laid on the necessity of preparing a vaccine from cultures but recently isolated.

The figures given and the facts presented by these writers are difficult of interpretation and permit of almost any conclusion that one wishes to draw from them, from the optimistic one that fatalities after influenza occur only among the nonvaccinated, to the pessimistic one that fatalities occur only among the vaccinated, though the authors believe the results were good. They frankly reiterate the opinion that for a short time following vaccination there is an increased incidence among the vaccinated, owing to temporarily increased susceptibility, but the writers consider that this risk is justified by the benefit that they believe may accrue later. As inoculations were performed largely during the prevalence of the epidemic, and as the controls appear to include persons who developed the disease prior to the vaccination, the alleged good results may be misleading.

THE POLYVALENT VACCINE OF ROSENOW

Rosenow¹ prepared a mixed, and, at least in part, polyvalent, vaccine from the various fixed types of pneumococci, pneumococci of Group IV, hemolytic streptococci, *Staphylococcus aureus* and the influenza bacillus, all of which had been recently isolated. This vaccine was adjusted to meet the bacterial flora encountered during the epidemic; thus, in a manner it may be said that it was designed to approach an autogenous vaccine, but was intended primarily for prophylactic purposes. Dr. Rosenow felt that this vaccine should be prepared for use in any community from the strains of organisms there prevailing, and that a vaccine adjusted to meet the needs of one local-

3. Notes on Preventive Medicine for Medical Officers, U. S. Navy bulletins, Nos. 50 and 51.

4. Ely, C. F.; Lloyd, B. J.; Hitchcock, C. D., and Nickson, D. H.: Influenza as Seen at the Puget Sound Navy Yard, J. A. M. A. 72: 24 (Jan. 4) 1919.

5. Eyre and Lowe: Lancet 195: 484-487.

6. Eyre and Lowe: Lancet 196: 553-560.

ity might not meet those of another. The figures given for protection are encouraging, but do not lend themselves to critical analysis.

Dr. Rosenow considers the immunity produced by his vaccine to be of relatively slight duration, as some persons were apparently protected during the first wave of the epidemic, but not during the second.

A vaccine, prepared essentially in accordance with Dr. Rosenow's formula, was used extensively in the Middle West with alleged good results, but it was not used until the epidemic was at, or beyond, the crest, and the records are not convincing. Vaccine prepared in the manner suggested by Dr. Rosenow should theoretically have a better chance for success than those we shall next consider, but the practical difficulties of preparing it from locally prevailing strains and adjusting it to meet the changing flora of the respiratory tract in a disease that spreads as rapidly as influenza are obvious.

A specimen of the vaccine which was being used in Illinois was tried in California, under rigidly controlled conditions, without success. The disease did not appear in the institution where the test was made until eleven days after the last injection, but, after the epidemic had swept through it, the results revealed that 37 per cent. of the vaccinated were attacked, against 28 per cent. of the controls, while 4.5 per cent. of the vaccinated population died, against 3.6 per cent. of the nonvaccinated. These are differences too small to be significant. Tests made in other institutions gave similar results, though we need not take the time to consider the details here.

There are several other reports of the use of vaccines prepared somewhat along the lines of Dr. Rosenow's, but the data are not presented in a manner to permit of analysis.

The only report we have on a vaccine directed against the influenzal pneumonias associated with the fixed types of the pneumococcus is that of Cecil and Vaughan,⁷ whose work was conducted at Camp Wheeler and was directed primarily against the usual pneumonias of the camp. Apparently the antipneumococcus vaccine reduced somewhat the incidence of influenzal pneumonia among the vaccinated, though, to use the author's words, "influenza causes a marked reduction in resistance to pneumonia even among vaccinated men." These authors show clearly that the case mortality of secondary pneumonias was not reduced by the vaccination, contrary to the claim so often made, that the vaccine, when it fails to protect perfectly, at least leads to a milder type of the disease. Cecil and Vaughan believe that the results of their experiment with respect to pneumococcus pneumonia were obscured by the influenza epidemic; evidence that the prophylactic action of the vaccine employed against influenza was not striking, since the epidemic should have served to emphasize rather than obscure the results of the beneficial action of a really valuable prophylactic agent.

We must next consider, briefly, the stock commercial vaccines made from about the same organisms that went into the vaccine prepared by Dr. Rosenow. Concerning these there are no accurate figures. So far as I have been able to determine, the preparations have not been used anywhere under properly controlled conditions. What we have to consider are, chiefly, the enthusiastic reports of observers whose faith was bet-

ter developed than their judgment. A strenuous effort was made to secure the endorsement of the federal government for this form of prophylaxis against influenza. Under the direction of the Surgeon-General of the Public Health Service, careful investigators were sent to several communities from which glowing reports were received regarding the great value of stock vaccines, but in no case could the claims be verified. In this connection, we may trace the waning enthusiasm of one man who early in the epidemic reported that "immunization, using mixed vaccines, has proved beyond any question of doubt to be of great prophylactic value . . . why not extend this to all the people?" Ten days later, this man advised us that "we felt there was a strong possibility of it [the vaccine] preventing many cases. . . . At the present time we are not in a position to make any absolute and definite statement." So far as we know, the final reports from this source never have been published, though ample time has elapsed.

People wondered that those in positions of responsibility did not accept the first enthusiastic reports, adopt an attitude of optimism, and recommend the universal use of vaccination against influenza; but, in the light of present knowledge, there seems to have been some justification for an attitude of conservatism.

It must be clearly understood that what has been said above does not apply to vaccination against lobar pneumonia, using pneumococcus vaccine. The evidence on this is favorable, though perhaps the final word has not yet been said. It may be noted here that the very optimistic reports by Lister, who introduced vaccination against lobar pneumonia, are being called into question.⁸ The rather startling suggestion is made by Fennel⁹ that this antipneumococcus vaccine may be useful in combating epidemic influenza, but he admits the "information at hand is fragmentary and not to be seriously considered though possibly significant."

Though the evidence in respect to any vaccine that has been tried offers little to warrant hope that an effective agent has been found, we must not feel unduly pessimistic. The problem of vaccination in influenza is an extraordinarily difficult one. The etiology is uncertain, the influenza bacillus and the streptococci are poor antigens, and the epidemics are so far apart and so rapid in passage that the time to work out a prophylactic agent is very limited.

CONCLUSION

The general impression gained from uncontrolled use of vaccines is that they are of value in the prevention of influenza; but, in every case in which vaccines have been tried under perfectly controlled conditions, they have failed to influence in a definite manner either the morbidity or the mortality.

8. Johnson: *Am. Med.* 25:149.

9. Fennel, E. A.: *Prophylactic Inoculation Against Pneumonia*, *J. A. M. A.* 71:2115 (Dec. 28) 1918.

Making a Skilled Physician.—Hippocrates named six conditions necessary to become a skilled physician: Natural talent, instruction by a competent master, a place favorable to study, education begun in youth, love of work and long application. The first of these conditions is the most important, for where there is not a natural disposition it is useless to attempt to force Nature. Theory should be combined with practice. Want of experience begets either timidity or rashness. Timidity discloses impotence and rashness ignorance.—Tweedy, *Brit. M. J.* 2:598 (May 17), 1919.

7. Cecil and Vaughan: *J. Exper. M.* 29: No. 5, pp. 457-483.