The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 71, No. 26

CHICAGO, ILLINOIS

DECEMBER 28, 1918

PROPHYLACTIC INOCULATION AGAINST PNEUMONIA

A BRIEF HISTORY AND THE PRESENT STATUS OF THE PROCEDURE *

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We have just passed through—or rather, are passing through—a pandemic of disease, the gross and microscopic pathologic anatomy of which seems to be fairly constant in the hands of many observers and investigators, but concerning the etiology of which we continue to remain in much doubt. This pandemic had high incidence and mortality rates. In the great majority of cases, death was directly due to a bronchopneumonia. In those cases in which a bronchopneumonia developed, the death rate was so high as to be the cause of a panic, which made itself evident in the use of a wide variety of unjustified therapeutic and prophylactic measures.

It is too early as yet to draw any definite conclusions as to the bacterial etiology of the disease. Apparently well founded opinions have been advanced by experienced investigators setting forth diametrically opposed views. Since all the evidence is not yet, by any means, collected, conclusions would be premature and probably fallacious. Whether the cause has been the Pfeiffer bacillus, which has taken on extreme virulence, or whether a filtrable virus, or a streptococcus, *S. viridans* or *S. hemolyticus*, or a heretofore unidentified gram-positive coccus, it is too early to say. Whether the pneumococci of fixed or heterogeneous type are the true etiologic factors in this pandemic, which has cost the world so much in suffering, death and economic values, is not to be determined at this time.

It seems, however, to be agreed by competent observers that the disease itself was one of but transient duration, of from three to five days, in uncomplicated cases; bronchopneumonia was the most frequent of the complications or sequelae; and when this condition superimposed itself, pneumococci were found with regularity in the nose, mouth, pharynx and sputum of these patients. Since the mortality in the cases of bronchopneumonias was very high (during the height of the pandemic, 50 per cent. would have been a conservative estimate), ample opportunity for necropsy presented itself. Direct smears from lung tissue, and cultures from lung, bronchi, heart's blood, pleural, pericardial and peritoneal fluid,

and from the spinal canal demonstrated the same regularity of the presence of pneumococci of the fixed and heterogeneous types. The presence or absence of other organisms does not bear on the subject in hand, though it might be said in passing that in a high proportion of cases, when careful technic was used, the pneumococci were found in pure culture. This fact has again stimulated research work on the pneumococcus, and has caused investigators and practitioners throughout the world to inquire, "Just what is the present status of prophylactic inoculation against pneumococcal infections?"

A bird's eye view of this subject presents, first, the great preponderance of the work on therapeutic measures in contradistinction to prophylactic measures, and, secondly, the apparent apathy of the profession as a whole concerning the prophylaxis of a disease that is of such vital and economic importance.

Theoretically, any disease of microbic origin, in which spontaneous recovery is at all possible, should yield to specific prophylactic measures. That recovery from pneumonia is spontaneously possible has long been known. During the years from 1881 to 1885, Pasteur¹ and Sternberg² produced a fatal septicemia in rabbits, and Frankel³ and Weichselbaum⁴ established the causal relationship of *Diplococcus pneumoniae* in lobar pneumonia. This was a great step in advance; but, though a large amount of work was done in the interim, some of which was highly confusing, it was not until Neufeld,⁵ in 1900, determined the diagnostic value of the fact that pneumococci are soluble in bile, that the next step was taken. This knowledge enabled investigators to fix their attention on pneumococci, and rule out those bacterial forms so similar in morphology and cultural characteristics.

It had been noticed, however, that strains of pneumococci from different sources have different properties.

In 1909, Neufeld and Händel⁶ definitely established the fact that some strains of disease-producing pneumococci had truly measurable antigenic properties. By injecting into animals a vaccine of a particular strain of pneumococci they were able to awake in that animal an immunity response. They also devised the method for measuring that immunity by conferring a passive immunity on a white mouse by injecting it with serum from the vaccinated animal, and then subjecting that mouse to an otherwise fatal dose of living pneumococci of the same strain. This fact, concern-

1. Pasteur, L.: Bull. de l'Acad. de méd., 1881, Series 2, p. 94; Compt. rend. Acad. de sc., 1881, 92, 159.

2. Sternberg, G. M.: Bull. Nat. Board of Health, 1880-1881, 2, 781.

3. Frankel, H. Z.: Klin. Med., 1886, 10, 426.

4. Weichselbaum, A.: Med. Jahrb., 1886, n. f., 1, 483.

5. Neufeld, F.: Ztschr. f. Hyg., 1900, 24, 454.

6. Neufeld and Händel: Ztschr. f. Immunitätsforsch., Orig., 1909, 3, 159.

* From the Department of Pathology, Army Medical School.

ing that particular Neufeld strain of pneumococci (which later became the Group 1 of Dochez and Gillespie, or Group C of Lister), is the basis on which prophylactic inoculation against lobar pneumonia is built.

We were then on a footing where rapid strides could be made. A therapeutic serum was the direct outcome of the foregoing discovery, but interests us, in prophylaxis, only in passing. The predominant fact stood out that a certain strain of disease-producing pneumococci could stimulate, in an animal, a specific immunity response to that one particular strain. The word "group" should replace the word "strain," for it was found that the "Neufeld strain" was not limited to a race of pneumococci, but was found as Type I in widely separated cases.

GROUPS OF PNEUMOCOCCI

The logical outcome of this work was an investigation of the groups into which pneumococci might be divided, on a basis of their ability to stimulate *specific* antibody production.

In 1913, Dochez and Gillespie⁷ in America, and coincidentally, though independently, Lister⁸ in South Africa (where lobar pneumonia has been a problem of paramount importance), published their classification of the groups of pneumococci. Dochez and Gillespie used the protection tests of Neufeld, and specific agglutinations to evaluate their results; Lister used phagocytosis and specific agglutinations to arrive at his conclusions.

Dochez and Gillespie divided all pneumococci into four groups:

Group I (the Neufeld strain), distinct in its antibody stimulation.

Group II, culturally indistinguishable from Group I, but specifically distinct in its antibody stimulation.

Group III (*Pneumococcus mucosus*), identified by its morphology and its peculiar cultural characteristics. (Later its specific antibody stimulation was more definitely brought out.)

Group IV, all strains that would not fit into the preceding groups, irrespective of the fact that they stimulated an antibody specific for the strain, or stimulated no antibody. Into Group IV fit many of the saprophytic strains found in human mouths.

Lister was able to carry his classification somewhat farther than Dochez and Gillespie because of the greater multiplicity of groups prevalent in South Africa, and because of his added work in the heterogeneous group.

While the original classification of Dochez and Gillespie still stands, and is now quite familiar to the profession in America, Lister's classification has undergone additions until now he groups them as A, B, C, D, E, F, G, H, J, K, X and unclassified. Group A, numerically most important in South Africa, is unknown in America. Groups B, C and E are identical with Dochez and Gillespie's Groups II, I and III, respectively.

In general, Lister classified the pneumococci into a number of groups, ten in number, into which most pneumococci may be classified according to their group antigenic qualities, another group into which

strains stimulating antibodies only against the specific strain, and an unclassifiable group into which are placed those few strains (3.3 per cent.) that give rise to no antibody production when injected into animals.

The relative importance, as measured by incidence and mortality of the pneumonias caused by these several types, varies from time to time and with localities. This fact does not seem to have been accorded the recognition it might better have received. While Groups A, B and C are of prime importance on the Rand, Group H, in a localized epidemic, suddenly sprang into prominence, and had to be specifically considered in prophylactic measures. The numerical preponderance of certain types of pneumococci in certain localities, during the pandemic, has called attention to this fact. The recent report of Friedlander and co-workers⁹ at Camp Sherman called attention to this phase of the subject. They reported an incidence of about 80 per cent. of Type IV in their pneumonias. An analysis of these IV's and a consideration of them in the construction of a vaccine for use in that particular locality would have been logical. That such an analysis is feasible is indicated by the work of Olmstead,¹⁰ and should be carried farther.

Particular attention is directed to Lister's classification, for two reasons; first, because it emphasizes the need of further investigation and classification within our American Group IV, and, second, because it demonstrates the multiplicity of factors to be considered in specific prophylaxis against lobar pneumonia.

WORK OF WRIGHT AND OF LISTER

It is unfortunate that so great an authority as Sir A. E. Wright, and his co-workers, should have undertaken an extended experiment in the inoculation of a large number of mine workers, in South Africa, at a time that was so unripe.

Between the time that Neufeld established the antigenic value of pneumococci, and the time that Dochez and Gillespie, and Lister established the varieties and specificity of the groups of pneumococci (namely, in 1911 and 1912), Wright and his co-workers¹¹ vaccinated a large number of native South Africans.

In the preparation of their saline vaccine they necessarily did not take into consideration the predominant types against which this measure was aimed. Further, in those cases of pneumonia that developed after vaccination, no cognizance could be taken of the groups to which the etiologic organisms belonged. Their results were evaluated by estimation of opsonic indexes—a method that has fallen into much popular disfavor, and by statistics, employing groups of "controls" for comparison, a method that brought about much argument concerning the method of selection.

In a historical study of pneumococcal vaccination, Wright's work must, of course, be considered; in a critical study of the subject it would be better to consider his work only in passing, lest the inopportune time at which it was undertaken and the paucity of our knowledge at that time befog any conclusions that might be drawn.

Lister's work, however, was built on an entirely different foundation. He was well armed with the

7. Dochez, A. R., and Gillespie, L. J.: A Biologic Classification of Pneumococci by Means of Immunity Reactions, *THE JOURNAL A. M. A.*, Sept. 6, 1913, p. 727.

8. Lister, F. S.: Pub. 2, South African Inst. for Med. Research, 1913.

9. Friedlander, Alfred; McCord, C. P.; Sladen, F. J., and Wheeler, G. W.: The Epidemic of Influenza at Camp Sherman, Ohio, *THE JOURNAL A. M. A.*, Nov. 16, 1918, p. 1652.

10. Olmstead, M.: *Jour. Immunol.*, 1917, 2, 425.

11. Wright, A. E., et al.: *Lancet*, London, 1914, 1, 1, 87.

knowledge of the types that predominated in his field of endeavor, and could take the selection of those strains into consideration in constructing his vaccine. The many technical difficulties of producing large numbers of pneumococci in a concentrated form were somewhat reduced by his apt adaptation of a cream separator for centrifugalizing broth cultures. Above all, his knowledge of the types of pneumococci permitted him to evaluate correctly the significance of those cases of pneumonia that did follow his inoculations.

Forearmed in such a fashion, he was enabled to construct a vaccine, limited to those types most potent in the production of lobar pneumonia on the Rand, namely, Groups A, B and C. He determined by extended animal experimentation that these vaccines intravenously, and subsequently subcutaneously, gave rise to demonstrable antibodies. A limited number of intravenous inoculations in human beings was next tried, but the apparent impracticability of such a method caused it to be discarded, though antibody production was good. A limited number of subcutaneous vaccinations in man then assured him that this method was not only productive of results, but quite applicable to large groups of native laborers. Pneumococcus vaccines are noticeably less toxic than many others we are more familiar with, and, coupled with the fact that the South African native is slightly disturbed by bodily discomfort, Lister was able to inoculate a large number of these natives subcutaneously, each with three doses of a saline vaccine, of high bacterial content, at seven day intervals, without undue disturbance.

He was able to keep a large proportion of these subjects under observation for a period of nine months or longer, and his results are startling. It would be presumptuous to try to sum up such a monumental work in a few words. To those interested in this subject Lister's most recent publication¹² is earnestly commended.

His Crown Mine experiment is of particular interest. During a nine months' period, approximately 11,000 natives were inoculated with a vaccine that included Groups A, B and C. During that time, in these 11,000 vaccinated natives, eighty-two cases of lobar pneumonia resulted, but not a single case was caused by a pneumococcus of either Group A, B or C. Had the prevalence of Groups A, B and C remained constant with the other types, lobar pneumonia cases due to Groups A, B and C to the number of 120 would have developed.

There seems to be no doubt, then, judging from Lister's work, that, if the prevalent types of pneumococci be considered in the elaboration of a vaccine, sufficiently rich to be effective, that vaccine should be almost 100 per cent. efficient for the specific types. (Lister rather inclines to large doses and considers a total of 6,000 million cocci of each group against which protection is sought as the minimum.) Three inoculations at intervals of seven days are necessary, and the local and systemic reactions following the vaccinations are far outweighed by the beneficial results.

As a matter of fact, these published results are so good that one is apt to recall the proverb, "Timeo Danaos et dona ferentes."

12. Lister, F. S.: Publications VIII and X, South African Inst. for Medical Research, 1916 and 1917.

WORK OF CECIL AND AUSTIN

Their true worth is practically vouched for, and the results amply confirmed by the recent work of Cecil and Austin.¹³ They prepared a saline pneumococcal vaccine of Types I, II and III, much after the fashion of Lister. This vaccine, under the direction of Colonel Russell, was used at Camp Upton, to vaccinate 12,519 men. Animal experiments and limited ones in human beings had served to demonstrate that this vaccine had antigenic effect, measurable by agglutinins, and the protection the serum of vaccinated individuals conferred on mice. The vaccination of troops began Feb. 4, 1918, and these troops passed from observation about April 15, 1918, making the period of study about ten weeks. The three inoculations were given at seven day intervals, except in those cases that showed a marked reaction after the first or second dose, in which cases it was discontinued. For the sake of simplicity, their results might be tabulated as in Table 1. Any more critical analysis of these figures or cases serves only to accentuate the apparent efficacy of the vaccine.

It will be noticed that a Type I, II and III vaccine seemed to prevent practically all cases of pneumonia

TABLE 1.—INCIDENCE OF PNEUMONIA AMONG VACCINATED AND UNVACCINATED TROOPS: RESULTS OF CECIL AND AUSTIN*

Pneumonia Cases of Types	Vaccinated, 40%	Unvaccinated, 60%
Type I.....	1†	10
Type II.....	0	9
Type III.....	0	7
Type IV.....	9‡	33
<i>Streptococcus hemolyticus</i>	6	72
<i>Streptococcus viridans</i>	1	34
Undetermined.....	0	7
Total.....	17	172

* Average strength of command, 3,200.

† Developed twenty-four hours after first injection.

‡ In three cases only one injection was given.

due to those types, and caused an apparent protection, not only against Type IV, which might have been suggestive of cross protection, but also against *Streptococcus hemolyticus* and *S. viridans*. The authors offer no explanation of this fact. It is possible that so much foreign protein injected into the human being has caused him to mobilize his ferments and leukocytes, as demonstrated by Jobling and Petersen,¹⁴ to the increase of a natural resistance. It is further possible that this change in ferment-antiferment balance has conferred on the individual, besides the specific immunity, an additional resistance against a large number of other bacterial invaders.

There is little room, therefore, to doubt that saline pneumococcal vaccination is highly efficient for the specific types contained in the vaccine. Within that limitation, it bids fair to rival typhoid vaccination, about which there has for some time been no doubt.

SALINE VACCINE AND LIPOVACCINE

The saline pneumococcus vaccine has the advantage of being an efficient prophylactic. It has, however, certain distinct disadvantages. Production of such a vaccine on a large scale has always been a difficult, trying and somewhat expensive procedure. The time limit on such a vaccine, owing to compara-

13. Cecil and Austin: Jour. Exper. Med., 1918, 28, 19.

14. Jobling, J. W., and Petersen, William: The Nonspecific Factors in the Treatment of Disease, THE JOURNAL A. M. A., June 3, 1916, p. 1753.

tively rapid autolysis, must be short, and this would serve to increase its price, an important consideration when widespread measures are contemplated. It must be given, so that a sufficiently large dose to be effective is administered, in at least three, preferably more doses, at seven day intervals. The difficulties that this offers to the general use of a prophylactic measure are most obvious to one who has worked in the public health field, though the rural practitioner, advocating the saline typhoid vaccine, has had ample opportunity to feel this disadvantage.

While pneumococcal vaccines in general are not so toxic as typhoid vaccines, the fact that quite frequently a saline injection is followed by a sharp reaction militates strongly against its general use.

Almost all of the foregoing disadvantages are overcome by the use of a pneumococcus lipovaccine. A lipovaccine is one in which the bacteria are suspended, not in saline solution, but in an oil or lipid vehicle. By this means autolysis is greatly prevented, absorption is slow, and massive doses can be given at one injection, thereby reducing the number of inoculations to one. Not only does the oil retard absorption, but there is good cause to believe that the lipid substances serve directly to reduce the toxicity. Such a vaccine was first elaborated by Le Moignic and Pinoy¹⁵ for triple typhoid vaccine, and has been adapted by the Army Medical School¹⁶ to a wide variety of vaccines.

As early as December, 1917, a pneumococcus lipovaccine had been elaborated at the Army Medical School.¹⁷ Colonel "W" received the first dose, and, along with Capt. "C," the other subject, responded by the production of agglutinins. The reactions to the vaccine were so mild that Colonel "W" repeated the vaccination on the two succeeding days, the third dose being followed by a slight chill. In each of these doses he received the total of three saline doses.

The work on the pneumococcus lipovaccine was somewhat delayed, owing to the fact that a triple lipovaccine had to be perfected, one that subsequently came into use in the Army to the exclusion of the saline vaccine.

Animal experiments with the pneumococcus lipovaccine of Types I and II seemed to show some protection as a result. A direct systematic comparison was then made between two types of saline vaccines, one of the latter being the one in use, at that time, at Camp Upton, which was to show, at a later date, such excellent results.

In these tests, one of the lipovaccines, which could be given in one dose and which caused only a slight reaction, was found to be so far superior to the other three types that it was made on a slightly larger scale and altered by the addition of Type III and used, to the extent of about 25,000 doses, in the military camps. This was a vaccine of high bacterial content, but the reactions following were very mild. The reports, following its use, and the coincidental pandemic, with the attendant pneumonias, confirmed the wisdom of adopting this vaccine as a general but voluntary measure in the Army, a step that had been taken some time previously.

It is to be emphasized that this was not a vaccine, developed over night, as a prophylactic against influenza; it was a vaccine aimed at pneumococcal infections, developed systematically at a time considerably antedating the present pandemic.

This lipovaccine seems to overcome all the difficulties associated with a saline vaccine except the expense and ease of production. It is somewhat more laborious to produce such a vaccine, and the use of oil and the mechanical equipment necessary make it more expensive.

UNITED STATES ARMY VACCINE

The particular type of vaccine in use in the U. S. Army is made as follows:

The three types of pneumococci are grown separately in a beef infusion broth, incubated not more than eighteen hours, and the organisms recovered by the use of a continuous feed type of centrifuge, a perfection of the type used by Lister. On this centrifuge, spinning at a rate of 40,000 revolutions a minute, depends the effective removal of the pneumococci. The organisms are thus secured in the form of a heavy mass of about the consistency of library paste. This mass, under glass hoods and under aseptic conditions, is then smeared in thin layers over the bottoms of Petri dishes, which are next covered with an earthenware top. In these Petri dishes the bacterial material is then brought to complete desiccation in a 53 C. incubator, liberally supplied with unslaked lime. The average water loss is about 80 per cent. This drying process is a matter of only a few hours, and little morphologic change in the organisms takes place, since they may again readily be suspended in saline and present themselves as gram-positive cocci of sharp, clear staining characteristics.

This material, now dry, readily flakes off from the glass, and is pooled, again under the hood, into one container. It is then measured out by weight to establish the dosage. The decided advantage of the use of weighed quantities of dry bacterial material to determine the dosage is, after a moment's thought, quite apparent. Many of the fallacies attending dose determinations in saline vaccines are obviated by the use of weights. It has been found that a unit of dry bacterial mass represents a fluctuating number of bacteria, depending on the virulence of the organisms, cultural environment and time of incubation.

The Army vaccine contains dry material equal, in round numbers, to 10,000 million of each type. Those figures are, of course, only relative, and it must be insisted on that dosage by weight is constant, while dosage by count is notoriously fluctuating and inaccurate.

After the dry material has been carefully weighed under sterile conditions, and calculated so that each cubic centimeter of the finished vaccine will contain 0.83 mg. of each type, the bacterial flakes are placed in a sterile grinding jar, along with sterile steel ball bearings, the jar is placed on a mill, and during the course of twenty-four hours the bacterial mass is ground to a fine, amorphous powder. At the end of that time a mixture of anhydrous lanolin and cottonseed oil, in a proportion of 1:2, is added, so that the completed vaccine shall contain 2 per cent. of lanolin. The mass is then thoroughly emulsified by grinding twelve hours, at the end of which time cottonseed oil is added to make the final dilution, along with 0.5 per cent. chlorbutanol as a preservative. The grinding is then continued twelve hours. The oil and the lanolin-oil mixture has been sterilized by autoclaving at 15 pounds for thirty minutes.

This completed vaccine is then subjected to rigorous cultural tests, and is finally injected into animals, to insure sterility. It is then ampuled and distributed for use. Its administration is a simple matter if a needle of 23 gage or any larger bore is used. While sedimentation does occur, cottonseed oil is only so slightly viscid that an even suspension is easily attained by slight shaking.

Several commercial firms are now actively producing, or preparing to produce, a vaccine modeled on the foregoing plan. Supervisional tests, by the gov-

15. Le Moignic and Pinoy: *Compt. rend. Soc. de biol.*, 1916, **79**, 201, 352.

16. Whitmore, E. R.; Fennel, E. A., and Petersen, W. F.: *An Experimental Investigation of Lipovaccines*, *THE JOURNAL A. M. A.*, Feb. 16, 1918, p. 427.

17. Whitmore, Fennel and Petersen: *Abstracts of Bacteriol.*, 1918, **2**, 16.

ernment, of sterility will be a relatively simple matter; tests to evaluate the antigenic efficiency of the vaccine will be attended by greater difficulties. These, however, no doubt will be met.

It might be interesting to mention that the Army Medical School has manufactured and sent out for use during October and November, 1918, more than two million doses of this vaccine. The magnitude of this undertaking is better understood when one recalls that Lister, the master himself, said that the manufacture of 40,000 doses for the British government on short notice was out of the question.

RESULTS OF VACCINATION

Much had been hoped for when the tabulated results of this widespread vaccination would have been available. The abrupt cessation of the war, and the rapid demobilization that must follow, will withdraw from observation this large number of vaccinated men. Much valuable information, however, should come to light in the due course of time. Laboratory methods that have stood the test of time were used to test the value of the vaccine, and the results have been found particularly gratifying.

Such a vaccine as is issued by the Army has been injected into human beings, and tests have been made. Ten weeks after injection, 0.2 c.c. of the serum of these subjects almost regularly protects a mouse against 1,000 times a dose of living pneumococci that would otherwise be fatal.

Preliminary clinical reports seem to be highly satisfactory. Some of the unexpected results, such as made their appearance at Camp Upton, seem to be following the use of the lipovaccine. While a specific immunity against the three types of pneumococci in the vaccine was all that was hoped for, a certain freedom from respiratory diseases in general seems to have followed its use. Absence of bronchial symptoms in influenza, after vaccination, was noticeable. While the information at hand is fragmentary, and not to be seriously considered, it may be a straw to show the direction of the wind. For example, fourteen women war workers living in one house were exposed to about the same conditions. Twelve were vaccinated at the beginning of the pandemic in Washington, and remained well and on duty throughout that pandemic. The two unvaccinated ones both contracted influenza. Of a number of men on duty in a Washington fire department, two refused the vaccine; these two alone of that company contracted influenza. Such apparent nonspecific protection seems somewhat visionary until one recalls the fact that even normal brain substance increases resistance against rabies, a disease of specific origin. Vaughan¹⁸ noted this resistance following the injection of his protein split products, Zinsser and Dwyer¹⁹ have discussed it, Joblin and Petersen²⁰ observed it after serotoxin injections, and Teague and McWilliams²¹ noted it after typhoid vaccine shock.

The studies of Joblin and Petersen²⁰ and of Scully,²² Culver²³ and Petersen²⁴ endeavor to explain the modus operandi of this increased resistance.

18. Vaughan, V. C.: Protein Split Products, Philadelphia, Lea and Febiger, 1913.

19. Zinsser, H., and Dwyer, J. A.: Jour. Exper. Med., 1914, **20**, 387.

20. Joblin and Petersen: Jour. Exper. Med., 1914, **19**, 480.

21. Teague and McWilliams: Jour. Immunol., 1917, **2**, 167.

22. Scully, F. J.: The Reaction After Intravenous Injections of Foreign Protein, THE JOURNAL A. M. A., July 7, 1917, p. 20.

23. Culver, H.: Jour. Lab. and Clin. Med., 1917, **3**, 11.

24. Petersen, W. H.: Serum Changes Following Protein "Shock" Therapy, Arch. Int. Med., November, 1917, p. 716.

Studies have been made at the Army Medical School to note the relationship between triple vaccination and streptococcus infection. Medlar²⁵ shows that triple typhoid vaccination does not predispose to streptococcus infection and might seem to increase the resistance. Smith's²⁶ study of cytologic changes after the same vaccination might explain some of the nonspecific protection noted.

It is true that to demonstrate increased protection after the injection of foreign proteins it is customary to use large doses intravenously; it is possible that such small doses as 25 mg. (the total content of the Army vaccine) might serve to establish a relative immunity.

In connection with the nonspecific value of a vaccine, and in relation to the particular vaccine issued by the Army, Table 2 might be of interest. Mice, vaccinated with a saline and a lipopneumococcus vaccine, along with control mice, were subsequently

TABLE 2.—RESULTS IN A SERIES OF MICE INOCULATED WITH PNEUMOCOCCUS VACCINE, TESTED TO DETERMINE THEIR RESISTANCE TO HEMOLYTIC STREPTOCOCCUS TWO MONTHS AFTER VACCINATION; SEPT. 15, 1918

Series No.	Date of Vaccine Inoculation	Vaccine	Amount, C.c.	24 Hour Broth culture*	No. of Inoculations	D.	A.	D.	A.	D.	A.	Per Cent. Dead	Per Cent. Alive
1	7/16/18	Saline pneumo.	1/4	1/25	5	3	2	4	1	5	0	100	0
13 mice	7/24/18 8/ 1/18		1/4 1/4 1/4	1/50 1/50 1/100	4 4 4	1 3 0	3 3 4	1 1 1	3 3 3	1 3 1	0 1 3	75 25 75	25 75 75
2	7/16/18	Lipo-pneumo., unheated	1/4	1/25	4	4	0	4	0	4	0	100	0
12 mice				1/50 1/100	4 4 4	2 2 0	2 2 4	3 0 0	1 4 4	1 3 0	1 4 4	75 0 100	25 0 100
3	7/16/18	Lipo-pneumo., heated 53 C. (Army)	1/4	1/25	2	1	1	1	1	1	1	50	50
7 mice				1/50 1/100	3 3 2	1 1 0	2 2 2	2 2 0	1 1 2	1 2 0	1 1 2	66 33 0	33 100 100
Control			—	—	—	—	—	—	—	—	—	—	—
4			—	—	—	—	—	—	—	—	—	—	—
26 mice				1/50 1/100	6 20	2 1	4 19	3 3	3 17	3 4	3 16	50 20	50 80

* Twenty-four hour culture, low virulence *Streptococcus hemolyticus*.

injected with low virulence *Streptococcus hemolyticus* cultures. It would seem that the lipovaccines render the mouse more susceptible to large doses of streptococci, but render it more resistant to smaller doses. Since the latter case more closely simulates the natural mode of infection, the experiment, limited though the series is, may help to explain some of the so-called "cross protection" results. The more gradual absorption of the lipovaccine might account for the difference between it and the saline vaccine.

"MUSHROOM" VACCINES VERSUS PNEUMOCOCCUS LIPOVACCINE

Consideration of the many "mushroom" vaccines that sprang up over night during the pandemic, and which, besides a multiplicity of other organisms, were made to contain a questionable number of pneumococci, is purposely omitted. That they may have served some purpose in a specific immunity is possible, but hardly probable. In these justly called "shotgun vaccines" the content of the individual groups must necessarily have been so small as to be

25. Medlar, E. M.: Personal communication to the author.

26. Smith, J. W., Jr.: Personal communication to the author.

unable to lift the patient over the threshold of appreciable immunity.

That the vaccines may have had some nonspecific value, comparable with that of the vaccine used at Camp Upton, cannot be denied. However, the burden of the proof rests with the originators of these vaccines, and their value should be weighed on the merits of the vaccines alone. Such a judicial decision is, at this time, of prime importance. We have not passed through the pandemic of influenza with its sequelae; we are passing through it. If the history of the last great pandemic²⁷ is to be of any value, it should teach us to be on the alert for the recrudescences that must occur throughout this year, as well as in the following three or four years.

It is a better policy to use one instrument, if one is thoroughly familiar with it, limited though its uses may be, than to use a wide variety of unfamiliar, complicated ones.

We feel that pneumococcus lipovaccine is such an instrument. We feel that we have definite assurance that it will prevent infection by Types I, II and III. Epidemiologic studies of localized epidemics, that would justify the addition of purely local types to the vaccine, are to be encouraged. The lipovaccine is such that much additional pneumococcus material may be added, without increasing its toxicity.

The advantages of such a vaccine—its lack of toxicity, its simplicity of administration, and the high degree of immunity conferred—should, during the remainder of this winter, and during the next several years, when we shall most probably be called on to combat recrudescences of the pandemic, with its attendant pneumonia, be a useful weapon. Not only should it have its place in the Army, but also it should be seriously considered by those physicians in charge of industrial ventures, such as mines, steel mills, ship yards and the like. Such a vaccine must come from a source that is unquestionable and one that is capable of massive production. Such a demand from civilian sources might be satisfied by the Army, if the necessary arrangements could be made, until the supply would be forthcoming from normal channels.

CONCLUSIONS

1. Prophylactic pneumococcus vaccination is successful over an extended period of time for those groups represented in the vaccine.

2. A pneumococcus lipovaccine, of slight toxicity, to be given at one injection, has been elaborated, and has had widespread use. Early reports indicate its usefulness.

27. Epidemic Influenza, Therapeutics, THE JOURNAL A. M. A., Oct. 5, 1918, p. 1136.

Maternal Nursing and the Sculptor's Model.—Rickets, a disease of nutrition, still too common with us, is but rarely seen in Italy, where it is the universal custom for mothers to suckle their infants, and whence accordingly come those shapely human forms that are chosen by our sculptors and artists for their models. Mothers unquestionably suffer in health and happiness from the suppression of a function which should form a pleasurable and wholesome episode in their existence, and it has been suggested that the prematurely aged and withered appearance of the married women in the manufacturing districts is in some degree attributable to the check imposed on the lacteal process in them by their employment, when that process has been once fully established.—Sir James Crichton-Browne, *Journal of State Medicine*, May, 1918.

AN EXPERIMENTAL STUDY OF THE SURGERY OF LARGE ARTERIES: ANEURYSM

THE PLACING OF MUSCULOFASCIAL INSERTS WITHIN
AND THEIR USE IN PATCHING ARTERIES

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It is well known that exposure of blood to extravascular tissue favors clotting. This fact is often used, especially in surgery of the brain, for the control of small bleeding points. However, the ability of normally circulating blood within the arteries to withstand the coagulum-producing influence of foreign tissue has not, to my knowledge, been given special study.

The object of this research was, therefore, to investigate the occurrence of clotting about an intravascularly placed piece of foreign tissue (muscle and fascia). The first conception was that such a condition would rapidly produce clotting, and if the tissue placed within the vessel were of appreciable size, thrombosis would likely occur.

The results of this research, however, have not upheld this first conception, and it has been found that relatively large musculofascial inserts may be placed within arteries (as the aorta of a dog) without producing serious obstruction to the blood current.

The breadth of application of this fact to the surgery of aneurysm or the repair of large blood vessels is evident:

1. The wiring of large aneurysms is inaccurate, and even when, by chance and experience, the wire coils properly, the results have been encouraging in only a few cases. Both the wiring operation and Halsted's rings placed proximally to the aneurysm are foreign bodies in the tissues, and comprise the disadvantages of such measures. The use of musculofascial inserts at the opening of aneurysmal sacs for closing the openings, or so placed as to limit the size of a sac or fusiform aneurysm, is a possibility and led to this research. Furthermore, instead of measures such as Halsted's rings about a large vessel proximal to the aneurysm, it was found that tissue inserts may be used to control the volume of blood passing through the vessel and hence to the aneurysm. The great variety of aneurysms was well appreciated, and the fact was well apparent that much work would be necessary for the application of the method to the different forms of sacs.

2. In the repair of injured vessels, direct intimal apposition has been thought necessary. In the light of this research a patch of fascia, muscle or both may be placed over an injured artery, covering a defect without producing thrombosis of the vessel.

3. In the replacement of segments of vessels, pieces of other vessels have always been used. In dogs, by maintaining a certain part of the circumference of a vessel the balance may be built up with fascia and functionates perfectly, and thus an intimal lining is formed. Its source is open to question and is a problem for further research.

4. In some cases a definite plug of muscle and fascia may be placed against a circumscribed opening in an artery.

The subjoined experimental protocols form a preliminary report: