A SUMMARY OF RECENT WORK ON LOBAR PNEUMONIA.¹

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(1) INTRODUCTION.

In connexion with the proposed use of vaccine treatment in the Army in India this coming winter, it was thought it would be of interest to sum up our knowledge of pneumonia and particularly of immunity against the pneumococcus. I shall not attempt more than to mention briefly the most important facts and conclusions reached. There has been such a great deal of work done that it would be tedious to give every reference. Accordingly only single references will be given, and then only for the less known facts, although they may have been established by more than one worker; facts already well known will be mentioned without reference. This summary has been greatly facilitated by the recent reports of the Medical Research Council, of the Ministry of Health, and of the earlier report of the Rockefeller Institute referred to under (A), (B), and (C). These and other works quoted contain valuable lists of references. An alphabetical list of references will be given for all authors mentioned here. Unless otherwise qualified, pneumonia stands for lobar pneumonia throughout this paper.

(2) THE ORGANISM RESPONSIBLE.

(a) In about ninety-five per cent of cases (apart from particular epidemics) the predominant infecting organism is the pneumococcus. Evidence—in from ninety to ninety-five per cent of 1,500 cases (mainly in America) the pneumococcus has been isolated from sputum, blood, or lung by puncture. Since sputum, which may contain organisms other than the predominant organism in the lungs, was used in most of these cases, and since the percentage of pneumococcal findings in positive lung punctures is ninety-nine per cent (Lister, 1924) we may take ninety-five per cent as a conservative estimate. Lung puncture has the small risk of haemorrhage; air embolism, a more serious risk, is avoided if the needle be attached to a syringe and not used alone—(A) q.v. for technique.

(b) Bacteriological diagnosis.—There is no reliable single criterion. Even bile-solubility is a matter of degree, and further, some pathogenic as well as non-pathogenic pneumococci are not bile-soluble (Malone, 1923 a). Bile-solubility in some strains was a variable character (A).

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(3) **Typing.**

*(a)* Standard antisera can be obtained from the Rockefeller Institute, New York. Differentiation is based mainly on agglutination with mammalian antisera in low dilutions—final 1 in 40 for I and II, 1 in 10 for III (C). Precipitin reactions yield parallel results—except sometimes with the (American) subtypes of II (C), and may be done with: (1) the peritoneal exudate of the sputum mouse; (2) the urine of the patient; (3) the bile extract of pneumococcal sputum—Oliver’s method. The last two are rapid “clinical” methods. For this and other technique see (A), (B) and (C).

*(b)* The modification of the American classification proposed by Griffith (B) seems to be the best. In this the fixed types are single types, I, II, and III, while all others are in Group IV. The Americans place some strains as subtypes of II on the strength of agglutination by undiluted serum. French results are often not comparable because another technique (that of Porges) is used, involving the chemical treatment of pneumococci. Type III is *Pneumococcus mucosus*. This is a different organism from *Streptococcus mucosus* (C), but textbooks, e.g., Zinsser (1922a) state the contrary.

(4) **Distribution of Types in Cases.**

*(a)* On the whole the distribution in North America and in Europe seems to be the same, roughly: I, 30 to 40 per cent; II, 20 to 30 per cent; III, 8 to 16 per cent in America, but only 0 to 8 per cent in North-western Europe; IV, about 30 per cent. A good summary is given in (A), but the largest individual result (Cecil and Larsen) of 834 cases is omitted. The commonest types in IV in England are the American II subtypes and Lister’s A (A and Urquhart).

*(b)* The South African distribution (in Africans) is different (Lister, 1917), I or C, 22 per cent; II or B, 16 per cent; III or E, 1 per cent; IV or A, D, F, etc., 61 per cent. Here A which is in IV was the commonest (and most severe) type, forming 31 per cent of the whole.

*(c)* Malone’s (1923b) findings in North-West India—in Indians of various races and mostly from other parts of India, approximate to the African (or rural?) type in the high percentage of IV, roughly: I, 28 per cent; II, 17 per cent; III, 8 per cent; IV, 47 per cent. One type in IV formed 12 per cent of all types. No type in IV agglutinated with antisera to the commoner African IV types.

*(d)* More than one type is sometimes isolated—e.g., in eight per cent of cases (A). I and typical II have not been found together in cases (B)—nor in normal throats (Stillman, 1917).

*(e)* **Remarks.—** We must bear in mind that differences in distribution may be associated not only with place, but also with time, and perhaps with race and class or other environmental influences. Thus rural communities may have a higher proportion of IV than that given above for
American cities (Richardson). In a paper being published I show that Indian soldiers had a higher proportion of IV than Indian non-combatants (followers), and suggest that a high proportion of the fixed types is an index of defective hygiene, particularly in overcrowding; see sections 8 and 9. The possibility of errors in clinical diagnosis must also be remembered, for the IV group is much commoner in broncho-pneumonia. Lastly, particular epidemics—perhaps associated with influenza—have their own types. Thus at Camp Logan ninety per cent of cases (mainly lobar) were due to IV types (Hall and others).

(5) SEVERITY OF TYPES.

Practically everywhere IH is the most severe and IV the least—but see paras. 4(b) and 6. Individual strains of IV may be as virulent for mice and animals as I and II, but usually these fixed types—particularly I—are more virulent for mice than IV strains. The general level of mortality varies so much with countries and circumstances that averages would be misleading. Mortality tables are given in (A).

(6) BRONCHO-PNEUMONIA.

The percentage of cases due to the pneumococcus probably varies greatly; epidemics due to the streptococcus and to other organisms occur, as was the case in American army camps in 1918 and 1919. These were often associated with measles or influenza. One camp reported that the very great majority of cases were due to virulent pneumococci (Hirsch and McKinney). I have not seen adequate figures for endemic broncho-pneumonia—but twenty-two out of twenty-eight cases examined were pneumococcal (A). The percentage due to IV and the severity of IV, particularly in children, is greater than in lobar pneumonia (A).

(7) DISTRIBUTION IN NORMAL THROATS.

(a) The pneumococcus was isolated from the saliva of 43.5 per cent of 485 normal people (A). The proportions of types were roughly: I, 2 per cent; II, 4 per cent; III, 16 per cent; IV, 78 per cent. Whilst in non-contacts the proportion of I and II was less than 1 per cent, in contacts it rose to 25 per cent (C). The figures are mainly from America. What the normal proportion of III is elsewhere remains to be determined. The remarks in 4(d) also apply here. Thus in naso-pharyngeal swabs from 700 soldiers the pneumococcus was present in only 16 per cent (Sailer and others quoted in (A)).

(b) In convalescents the predominant type in the sputum changes in about a month to one of the normal type—even if the infecting type is III, or in IV, a change usually takes place (C). This is more probably due to the overgrowth of a type previously present in small numbers (as found in some cases) during the attack of pneumonia, than to mutation of the predominant type (B).
(8) Type Specificity.

(a) No change in type occurs on prolonged cultivation in vitro on ordinary media—though loss of virulence occurs.

(b) Miss Stryker’s work suggests that when grown in homologous serum what amounts to a change of type occurs, the degree and stability of the change varying directly with the time of growth. The “original” type characters reappear after one or more animal passages. This important work needs repeating with single cell cultures and with several types and sera before conclusions can be made.

(c) An apparent mutation of a IV strain to type I after animal passage is recorded in (A), and another “mutation” by Clough.

(d) Agglutination.—Monovalent fowl antiserum agglutinated pneumococci of all types but in different maximum dilutions (Keys 1918), which tends to show that the difference in types by agglutination is one of degree. M. Clough reports that some strains are agglutinated by all three, I, II and III, antisera.

(e) Protection of Mice.—Only homologous sera protect (C)—but either I, II or III sera served for Clough’s strains.

(f) Curative Action of Serum.—Only homologous sera are advocated, and in practice only I serum for I cases (C). A type-overlapping curative power is claimed for his monovalent sera by Truche, and for antibodies from serum by Cecil and Larsen.

(g) Other Reactions.—(i) Pneumotoxin. The reaction to an intradermal injection of dissolved pneumococci after previous sensitization is not type specific. (Kolmer and Steinfeld, Kolmer and Weiss).

(ii) Similarly, antihæmolytic reactions of immune sera are not type specific.

(iii) Complement-fixation tests are not absolutely type specific.

The last two facts are quoted and the whole problem discussed by Cole and Moore.

(h) Remarks.—The subject is important both for treatment and for prevention. More evidence is required. We must remember that the specificity of immunity reactions is one thing, and the type fastness (or otherwise) of pneumococci is another.

(9) Infection.

(a) The evidence of 7 (a) and (b) allows us to presume that direct or indirect infection occurs from cases.

(b) The dust of ordinary rooms and of rooms occupied by cases gave practically the same relative distribution of types as given by normal and contact throats respectively (C).

(c) I know of no evidence that many cases are due to direct infection from other cases—here and there groups of cases with a common source, often a healthy person, are described. The South African mine cases...
showed no evidence of the importance of direct cases to case infection (Maynard).

(a) In localized "epidemics" different types are often recovered from cases presumably infected from the same source (Zinsser, b). The same happened in experiments on monkeys (Cecil and Blake, b). This does not negative the importance of infection, but suggests the type mutability of pneumococci or (what is perhaps more probable) the type multiplicity of infection.

(b) It is commonly suggested that infection plays a greater part in I and II than it does in IV cases, where auto-infection perhaps occurs. The importance of healthy carriers of I and II is shown by Stillman (1917) and by (A). The carrier condition usually lasts about a month.

(c) There is good evidence, either for indirect infection from cases, or for what I may call "intensive crowd infection," in that local epidemics occur in conditions of crowding, particularly among recruits or labourers when newly brought together. For work on pneumococcus immunity and the suggestion of exaltation of virulence by the transference of organisms at the right stage see Bull, and for an experimental in vitro proof see Bloomfield and Felty, Felton and Dougherty.

(g) Pneumococci, mainly of Group IV, are more often found—in nearly twice as many instances—in individuals suffering from colds or influenza than in quite normal people, and such pneumococci are more virulent. (Gordon).

(h) Suggestions.—Apart from the obvious hygienic measures indicated, it would seem sound to allot recruits more room than seasoned men. Spittoons in barracks might be useful. More windows or skylights in Frontier and Punjab barracks would probably be of use; the latter could be covered over with thick straw mats in the hot weather—pneumococci soon die on exposure to light.

(10) Pathology of the Onset.

(a) Clinical evidence and the seasonal and regional incidence of pneumonia suggest that reflex vasomotor changes in the respiratory passages following chill assist in the production of attacks by producing favourable local conditions—it is unlikely that general immunity is so variable, but evidence is needed.

(b) A great deal of experimental work has been done (see Permar, who gives a list), of which the most important is that of Cecil and Blake (1920 a) on monkeys—the rabbit is too liable to septicæmia to furnish a good analogy for man. Summing up, we may conclude that:

(1) Infection of the upper (supralaryngeal) respiratory passages alone does not produce pneumonia. Unnatural organisms are quickly removed from these regions—Bloomfield quoted by Stillman (1923).

(2) Intravenous or subcutaneous injection does not produce pneumonia.
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(3) Infection of the lower respiratory passages, even in minute doses (given in one cubic centimetre of liquid), causes pneumonia. "Probably this infection must reach at least as low as the bronchi"—C. and B., above. It is more probable that to produce the disease the infection must always reach the lung alveoli, except when direct infection of the tracheal lymphatics is caused by the needle—see Jones and Stillman (1923).

(4) The start of pneumonia is the penetration of the bronchial or lung epithelium and infection of the lymphatics. This is followed by the infection of lymph glands near the root of the lung; from there as a focus an interstitial inflammation spreads outward into one or more lobes.

(c) Accordingly, in man the first important factor is infection of the lower respiratory passages. Clearly this can be direct by inhalation of the sputum spray of others, or indirect by extension from the pharynx, auto-infection. Paragraph 9 (g) is significant of the part catarrhs may play in both processes. Extension may be furthered by reflex vasomotor changes which may assist also in the next process to be discussed.

(d) The second factor is penetration of the epithelium and mucous membrane. The fate of carbon particles suggests that in man the alveolar epithelium is readily penetrated—perhaps by the carrying action of leucocytes. General and local immunity processes (specific and non-specific) here play their part. Possibly specific local immunity is of importance—perhaps epithelial alone, or perhaps of lung tissue generally. Mice could not be infected with sprayed pneumococci that reached the lung (Stillman, 1923), which suggests a natural local immunity.

(11) Pathology of the Course of the Disease.

(a) 30 per cent. of blood-cultures were positive (C). They are sometimes positive very early. They are usually negative at or soon after the crisis. A positive blood-culture, particularly if late in the disease, is a bad sign. Contrary to textbooks, pneumonia should be regarded as a local infection that is continually attempting to become general—and with success sometimes.

(b) A rising leucocytosis (polymorphonuclear) is a good sign.

(c) Recovering cases (before the crisis) show not only a diminution of cocci in the blood, but also in the lung and sputum (Rosenow, quoted in A). Therefore we may not look upon pneumococci in the focus as shut off from the action of the body, though it is possible that within this area a large part of the final destruction of cocci is brought about by their own ferments and products, as suggested by Lord and Nye.

(d) At or soon after the crisis, certain type specific antibodies can be demonstrated in the serum of the majority of cases—except in type III infections, when they are rare. These are agglutinins, precipitins, opsonins, and "protectins"—to coin a word. The persistence of these is very variable—from a few days to four months (Chickering, 1914).
The pneumotoxin reaction is given before the crisis and sometimes for a few days afterwards—see 8 (g).

(f) The first process of recovery is probably associated with immunity reactions leading to the destruction of living pneumococci in the blood, and to the removal or neutralization of their dissolved endotoxins—the effective use of immune serum is followed by the abolition of bacteræmia (C).

(12) Acquired Immunity.

(a) Second attacks are more frequent in those once attacked than are first attacks in those never attacked.

(b) Such attacks are more common in the earlier period after an attack than in the later (Maynard).

(c) This is against Lister's suggestions that such attacks are due to the disappearance of specific antibodies from the blood. It is also against exogenous infection by new types, but is in favour of infection by types already present—perhaps by a strain accompanying the predominant one. It suggests either that infection of the lungs, or that individual susceptibility, is of more weight in determining the onset of pneumonia than specific immunity reactions are in preventing it.

(d) The evidence in 11 (d) on serum antibodies suggests that type-specific acquired immunity is short, but these substances do not represent the whole action of immunity—see later.

(13) Active Immunity in Man.

(a) From the discussion on Lister's prophylactic work (1924), I conclude that no striking benefit in the diminution of total incidence has been proved; further, this is the opinion of some competent local observers. I suggest that the addition of the results for 1917 to the last table in the discussion would clarify matters. Lister notes the very great diminution—abolition in one mine—of A, B and C cases following the use of A B C vaccine, and advances it as proof of success. This argument, based on a redistribution of types, may not be used as proof of benefit. As a controlled result it can be used as a proof of the action of vaccine, plus either type mutability or type multiplicity of infection. It certainly suggests benefit, so that possibly all that was wanted was better controls. Here I must protest against Lister's idea, that, because vaccination may be of indirect benefit to the unvaccinated by diminishing the total infective conditions, therefore the use of the alternate individual method is vitiolated. This is not so, for a good control is obtained for the same infective conditions; whether these as a whole are changed by the vaccine may be deduced from a comparison with a second absolutely unvaccinated control. Maynard's statistical analysis of Wright's results on the Rand leads him to conclude that vaccination has a protective effect, but for not more than about four months—its protective value is greatest shortly after inoculation and progressively diminishes.
(b) The American results at Camp Upton (Cecil and Austin) were good—no cases of I, II and III (the vaccine types) occurred, and the incidence of IV and of streptococcus cases was less than in the unvaccinated. More information is required as to how the statistics were obtained, though these are perhaps accurate since the period of observation was only ten weeks. The controls, unfortunately, were regimental units. On the whole—though not conclusive—these results are very suggestive of benefit for a short time. The controlled results at another camp (Cecil and Vaughan), though not so good and though complicated by influenza, were good on the whole—the results in seasoned men seemed better than in recruits.

(c) Specific antibodies are demonstrable in the serum of the vaccinated—these occur later if a lipovaccine be used than with the ordinary saline suspensions (Whitmore, quoted by Cecil and Vaughan). Lister states that, contrary to natural acquired immunity, these antibodies sometimes persist for as long as eight months.

(d) I conclude that the results so far are no more than very suggestive of a good effect, particularly over short periods, of prophylactic inoculation, and that conclusive evidence of benefit, over say six months, has not yet been obtained.

14) Active Immunity—Experimental.

A great deal of work has been done; as before, that on monkeys by Cecil and Blake, 1920 (b), and by Cecil and Steffen, 1921, 1922, 1923, is most valuable.

(a) After subcutaneous vaccination type-specific antibodies, as mentioned, are demonstrable in the serum—but seldom against III. The intravenous route requires smaller doses than the subcutaneous.

(b) Protective power for mice does not always correspond with the presence of agglutinins and opsonins—a serum might protect and not agglutinate and vice versa (C).

(c) Such antisera are not distinctly bactericidal or antiblastic (Barber)

(d) Subcutaneous and intravenous vaccination produce active immunity against infection by the lungs or by other routes, except with III and some strains of IV, when immunity is often not produced (Cecil and Blake, and Cecil and Steffen above).

(e) Such immunity is not necessarily associated with the presence of the antibodies mentioned. The converse also holds, that serum can be protective and yet the animal be not immune.

(f) The duration of this immunity, so far as I know, has not yet been determined.

(g) A variable degree of immunity to other types is also produced.

(h) Such immunity is more readily produced (in monkeys) against infection by the intravenous route than against intratracheal infection; the importance of local cellular immunity is suggested by Cecil and Blake.

(i) Intratracheal vaccine produces immunity to infection—by the intra-
tracheal route, and this in most cases without any specific protective power of the serum, which suggests cellular immunity (Cecil and Steffen, 1922). It remains to be determined whether immunity can be so produced to infection by other routes.

(j) Specific whole-blood immunity is produced almost as well by intratracheal as by intravenous vaccination, and better than by the subcutaneous route (Smiley and quotations). This is a "bactericidal" action which includes the action of leucocytes. This whole-blood bactericidal action is mainly type-specific, but some destruction of other types occurs; it appears before agglutinins appear (Heist and Solis-Cohen, 1919).

(15) NATURAL IMMUNITY.

(a) Some normal human sera protect mice without agglutinins, etc., being demonstrable (P. Clough).

(b) The blood of Europeans had more phagocytic power for pneumococci than that of tropical Africans; further, Europeans responded better to immunization (Wright, 1914).

(c) Whereas phagocytic mixtures of serum plus leucocytes and of defibrinated or decalcified blood plus leucocytes leave all the ingested pneumococci alive, whole-blood phagocytosis is accompanied by the death of large numbers of pneumococci (Wright, 1912).

(d) Similarly, Heist and Solis-Cohen (1918) report that the difference between the bactericidal action of the blood (including leucocytes) of susceptible and resistant animals could not be demonstrated if the blood were first defibrinated. But with a special technique Robertson and Sia show that the leucocytes plus serum of resistant animals (dog or cat) kill pneumococci, whereas those of susceptible animals (rabbit, etc.), do not. This bactericidal action does not occur if the serum be previously inactivated.

(e) Normal horse serum (as well as immune) inhibits the growth of pneumococci (Barber).

(f) The immunity of pigeons is mainly due to phagocytosis in the spleen and liver and not to serum reactions (Kyes, 1916).

(g) But the serum of fowls protects mice to a moderate extent (Bull and McKee, quoted by Robertson and Sia).

(16) PASSIVE IMMUNITY.

(a) Some evidence has been given in 8 (f). For summaries of data on the effect of treatment of I cases by I horse antiserum see (A) and Langley. I think we can take it as well established that a tested reliable serum, started early and given in large (100 cubic centimetres) repeated doses is efficacious—its use is of course not contra-indicated in late cases. Some sera on the market are useless (A).

(b) Cecil and Larsen tried serum antibody (against I, II and III) in 424 cases with controls. The results were good in I cases, less so in II and IV (so some cross protection). No effect was produced against III.
(c) The reported results of Rye's polyvalent fowl antiserum in repeated small doses (ten cubic centimetres) are good—summarized in (B). Continued use has confirmed this (Capps).

(d) Human convalescent homologous serum has been used with reported good results.

(e) Berger and Montgomery have reported benefit from intramuscular injections of chicken blood.

(17) **Remarks on Immunity.**

More evidence is needed and will probably soon be forthcoming, but meanwhile it is perhaps permissible to indulge in a little speculation.

(a) It is evident that in whole blood we have immunity reactions which differ, either in kind or degree, from those of serum alone, and possibly even from those of serum and leucocytes.

(b) The absence of strict parallelism between the protective power of serum, and the presence of agglutinins and opsonins on the one hand, and immunity on the other, suggests that blood plasma contains a very labile specific or non-specific substance, which may act directly on pneumococci as well as more energetically in combination with specific known antibodies. The double nature of many enzymes offers an analogy. Hektoen and Ruediger claimed that opsonins have a labile component (Zinsser c). Possibly such a substance is produced by leucocytes—for evidence of their extracellular action see Tongs, also Wright (1923) on epiphylactic response. Possibly leucocytes (or other cells) on receiving an appropriate stimulus have the power to modify specifically their normal secretions. Local cellular or tissue specific immunity is at present a "fashionable" probability, but there is no reason to exclude the cells of the blood from this idea.

(c) Whether clotting plays an important part (other than mechanical) in immunity against pneumococci still needs to be determined—important substances may be retained in the clot.

(d) The evidence under 14 (1) shows the need for caution in postulating tissue immunity, because we may possibly be dealing instead with unknown factors in whole-blood immunity.

(e) The testing of whole-blood immunity appears to be one of the most important tests of active immunity, and promises to become a standard test for vaccines. I suggest that similarly it be used to test the efficacy of antisera, by finding the degree of enhancement of the bactericidal power of whole human blood caused by the addition to it of measured quantities of a serum.

(18) **Vaccine Treatment.**

The late vaccine treatment of complications is too well recognized to need comment. Early treatment with vaccine has been well reported on by many observers, chief among whom are:

(a) Wright and others (1914). Vaccination in the incubation period
H. H. King appeared to abort an attack. A negative phase did not supervene with single doses of less than 1,000 million cocci.

(b) Raw (1912) reported benefit, particularly in the absence of complications. Dose from 100 to 150 million.

(c) Wynn (1915) reported good results from early treatment. Several attacks were aborted, although consolidation, etc., took its normal course. Stock untyped vaccine, virulence essential, primary or early cultures best.

(d) Wynn (1922). As above, good results in both lobar and bronchopneumonia were obtained by early treatment with polytype vaccine of virulent strains—forty-nine lobar cases treated within the first three days with only one death, and that in a labour case. The virulence of the strains used is said to be more important than typing. Dosage 100 million, repeated if necessary on each of the next few days. Once a 1,000 million given with good results.

(e) Malone's recent good controlled results (1924) were with homologous rabbit-grown vaccine, following a stock vaccine on the first day of treatment—18 treated within the first three days with 1 death, 17 untreated with 5 deaths. Dose 400 million on each three successive days. No general reaction to speak of.

(f) Lister (1924) reports good results from South Africa, and quotes good results by Girdwood. Dose recommended, 8,000 million cocci repeated once after twenty-four hours. Lister states he has given as much as 20,000 million intravenously to cases and apparently with benefit, despite the provoking of rigors.

(g) In dogs with a pneumococcal septicemia the organisms diminished in numbers shortly after a living vaccine (Bull).

(h) Altered vaccines. Some workers—e.g., Rosenow and Falls—have reported benefit. Their use is usually accompanied by distinct general reactions which possibly may be due only to the large doses employed. It is to be noted that many users of ordinary vaccines in small or moderate doses have reported benefit—an early detoxication, without any particular rise of temperature, etc.

(i) Foreign Proteins.—Many have reported benefit from the use of typhoid vaccines, injections of milk, etc. As typical examples we may take: (1) Miller, who found that in 6 out of 15 cases detoxication occurred after an intravenous injection of 30 million dead typhoid bacilli. The initial general reaction bore no relation to the benefit received. (2) The action of nuclein injections in producing leucocytosis has recently been favourably reported on in pneumonia by Gardner Medwin. Large doses of sodium bicarbonate are said to have assisted.

(19) Remarks and Suggestions on Vaccine Treatment.

(a) Lack of controls with fewness of cases make sound conclusions impossible. Assuming that vaccines and non-specific proteins have been of some use, it would appear that the action of a vaccine in early treat-
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ment is probably at least partially non-specific—the immediateness of the response is against specificity except that some sensitization may have already occurred. Wright's epiphalactic response (of leucocytes) appears to be mainly non-specific. In our present ignorance it is best to use specific vaccines, and for the same reason type-specific if possible.

(b) Immuno-transfusion seems indicated in cases not benefited at once by vaccines.

c) Autohaemotherapy has not yet been sufficiently tried.

d) Dosage.—Remembering the clinical picture of pneumonia, and seeing that moderate or severe general reactions following the injection of foreign proteins, including vaccines and specific antisera, are said to have sometimes had a bad effect, e.g., by Cecil and Larsen, I think it would be sound to lay down for the present that the treatment vaccine dose should be subreational. Further, it should be the dose that yields the best response. This is impossible to decide without experiment and observation. The tendency in South Africa is towards two doses, or even only one early large dose. While I think it probable that two doses (with twenty-four hours between), each of 400 or 500 million pneumococci, given subcutaneously will be found to be as effective as larger doses, and to be free from general reactions, yet since individual idiosyncrasies occur, perhaps smaller doses of 200 or 300 million each would be advisable to begin with until experience with large numbers of cases is gained. I think only two doses would be best. Too small a dose may produce no results at all.

e) The importance of early treatment cannot be too strongly emphasized. Signs of consolidation should not be waited for. No harm will be done if a few be treated for pneumonia when they do not have it, whereas late diagnosis and treatment will vitiate the trial of vaccines. When cases report or are diagnosed after the third day of illness, vaccine should not be given; these late cases should be recorded separately. Wynn's last article should be read by all using vaccines.

(20) OTHER TREATMENT.

(a) The necessity of not overfeeding and of using glucose to replace food by the mouth, given by other routes if necessary, has been emphasized by several. Burkitt reports that 255 cases of mixed pneumonias seen early have been treated without a death on his lines of initial purgation (plus bleeding if indicated), starvation except for glucose, hydrotherapy to keep the temperature below 101°F., alkalis plus much water. Crossman reports benefit from large repeated doses of tincture of garlic—half a drachm every four hours or so.

(b) Quinine and cinchona derivatives have a direct bactericidal action on pneumococci, but there is no good evidence that quinine in large doses is of use in pneumonia—my own clinical impression has been that cases treated by mistake as malaria in the first day or two with full doses of quinine did badly. Quinine in high dilutions stimulates phagocyteosis, but
not in low dilutions, when it poisons leucocytes. (Kolmer, Solis-Cohen and Steinfeld.) Ethyl hydrocuprein (optochin) after trial in seventy-five cases is not recommended for the routine treatment of lobar pneumonia by Moore and Chesney. It follows that quinine is not indicated. I suggest that if given to prevent malarial relapses it should be very cautiously used, if at all, before the crisis, e.g., only in small doses in the first two or three days. After the crisis is another matter.

(21) THE PREPARATION OF STOCK VACCINE.

(a) Types.—I suggest that these should be I, II and III plus the commonest IV type. Their relative proportions should be roughly, according to the local distribution prevalent, e.g., for North India I suggest two parts of I to one of each of II, III and of the commonest type of IV, as found by Malone.

(b) Virulence.—This is still a debated question. So far as the pneumococcus is concerned, most observers favour virulence in strains for the production of good antisera, e.g., Griffith in (B). This does not necessitate virulence for active immunity or for treatment—see Cole and Moore (B), though even here it has been insisted on, Wynn and others—but how much merely as an opinion, and how much as the result of experiments, is not recorded. Harvey and Iyengar's work suggests that generally virulence is not needed for producing active immunity. Cole and Moore point out that it is virulence for man that is wanted, so keeping stock cultures going on human blood or serum media with occasional animal passage might be of use, if there be any advantage in incorporating only virulent strains: for the maintenance of virulence see Gaskell.

(c) Constitution.—Ferry and Fisher have recently shown the antigenic importance of the filtrates of broth cultures and of the washings of pneumococci grown on solid media. Until more is known of antigens and immunity, it is probably best to use a whole unwashed vaccine made from organisms grown on solid media, to avoid the toxicity of the ordinary constituents of liquid media.

(d) Media.—Recent work by Avery, Morgan and Neill (1924) has shown that multiplication of pneumococci ceases from production of acid and of peroxides (probably H₂O₂), and that the latter can be prevented by anaerobic growth or by the addition of fresh unheated animal or plant tissues—potato serves well. So the addition of sterile potato or other juice to suitable solid media, e.g., trypsinated meat agar, can replace the addition of blood or serum. The optimum pH is one of 7·8.

(e) The suspension liquid.—Recent work by Robertson and Woo, Sia and Oswald (D. 1924) has demonstrated that lysis is slower in Locke's fluid or in phosphate solutions than in normal salt solutions, and is slowest if 0·1 per cent gelatine be added. Lord and Nye have shown that the lysis of pneumococci and even solution in bile is due to enzymes. To what
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extent autolysis alters important antigens is a problem demanding attention. Possibly the reported superiority of autogenous vaccines in many instances is due to their being fresher and less autolysed than stock vaccines.

(f) Sterilization.—Evidence is needed for the relative advantages of killing by heat and by antiseptics, and of various antiseptics such as formalin, phenol, etc., as preservatives for vaccines—the histological properties of formalin would seem to indicate its trial for vaccines. The prevention of autolysis should perhaps be one of the properties of a preservative.

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