PNEUMOCOCCAL SEPTICAEMIA

(Pneumonocosis)

Its Incidence and Prophylaxis.

by

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1. Heart blood of rabbit inoculated, intra-peritoneally, with pus from case of empyema in a child—showing pneumococci.

2. Culture of pneumococci on blood-agar taken direct from vein of case of general pneumococcal infection (Case 1.)

3. Bone marrow of inoculated rabbit showing pneumococci inside leucocytes and also free pneumococci (Marrow Juice).
The combined clinical and bacteriological study of the disease known as pneumonia has convinced me that the malady is one which might in a large number of cases be more fittingly described as Pneumococcal Septicaemia, with acute pulmonary inflammation as its most frequent and important manifestation. Sir John Moore, in his book on Meteorology, and also in a recent monograph on Pneumonia, described the condition as "Pneumonic fever." Others speak of pneumococcic infection, toxaemia, septicaemia, or pyaemia. Probably on the analogy of tuberculosis, actinomycosis, and similar infective diseases, the term "Pneumonocosis" would most adequately express the disease in its various manifestations. All the results of recent investigation, whether carried out at the bedside, in the post-mortem room, or in the bacteriological laboratory, point in the same direction.

It is well-nigh impossible to investigate the subject in the bacteriological laboratory without regarding the matter from this point of view. I would submit that the universal adoption of this view, not only by the scientific investigator but also by the hospital physician and the family doctor, would lead to a much more intelligent understanding on their part of the most widespread and fatal of all the acute diseases met with in
civilised countries, and also be of great therapeutic value as serving to put them on their guard against the various complications that are apt to arise in every case, whether the disease be of a mild or of a severe type. It is by the early recognition of such manifestations and by the adoption of prompt remedial measures that grave consequences threatening the life of the patient may frequently be avoided.

It is just as rational to consider Pneumonia as the principal manifestation of pneumonocosis as it is deemed essential to place pulmonary consumption in the category of tuberculosis, though the latter, on account of its being a more chronic disease, spreads as a rule by direct extension by way of the lymphatic channels: still, it is a matter of universal experience that a local focus in the lungs or elsewhere may originate a general blood infection and give rise to an acute general tuberculosis, which is to all intents and purposes a tuberculous septicaemia. Without going quite so far as Netter, who states categorically that there is no pneumonia without the pneumococcus, all modern observers are of opinion that the great majority of acute pulmonary inflammations are the direct result of the action of this specific virus. For the purposes of the present enquiry, we shall consider the term Pneumonia as being synonymous with that of pneumococcic pulmonary inflammation.
Before considering the question of Pneumococcal Septicaemia in man, I have thought it advisable to glance first at pneumococcal disease in the lower animals, as the manifestations observed in some of these thorn considerably light on some of the problems connected with pneumococcal infection.

Although in Nature the pneumococcus appears to be found as a parasite only in the human species, nevertheless the organism is pathogenic to many of the lower animals. Mice and rabbits, as is well known, are highly susceptible, while others, such as guinea-pigs and dogs, sheep, and cats, are only slightly so. The late Dr. Washbourn found that pigeons and fowls were absolutely immune, possibly owing to their high normal level of temperature rendering them unsuitable hosts. He placed man in the category of slightly susceptible animals, while Dr. Robert Muir states that the evidence justifies the supposition that man occupies an intermediate position in the scale of susceptibility, probably between the dog and the sheep.

My own experience has been confined to observation of the effects of experimental inoculation in rabbits, which are, with the possible exception of mice, one of the most susceptible of all animals to pneumococcic infection.

In addition to using loops of pure pneumococcus
culture on blood-agar, emulsified in bouillon, I have employed also as material for inoculation pneumonic sputum, scrapings from pneumonic lungs, spleen juice, and effusions from the pleural and other serous cavities. If a culture of the organism or an emulsified preparation of any of the above-mentioned morbid products containing virulent pneumococci, was injected into the peritoneal cavity of a rabbit, the animal in the large majority of cases died within sixteen hours of pneumococcal septicaemia; while if the inoculation were made subcutaneously, it would die within forty-eight hours from the same cause, though occasionally the life of the animal was prolonged for several days, the duration depending upon the quantity and virulence of the micro-organisms and to some extent also upon the resistance of the individual.

If we consider a case of Pneumococcal Septicaemia in a rabbit from intraperitoneal inoculation, we find that pyrexia occurs almost immediately: the temperature begins to rise from one to two hours after inoculation and attains its maximum three to four hours later, i.e., in about five hours from the onset. It remains at a high level for a few hours longer and then falls rapidly for the next one or two hours, becoming subnormal for about three hours before death. The animal breathes rapidly as the temperature rises, and towards the end there is considerable dyspnoea, the head moving with each
inspiration. The animal does not appear to be ill until the temperature has fallen: it then refuses its food, ceases to move about, and lies crouched up in its cage: there are often convulsive movements of all four limbs just before death supervenes.

I have generally failed to find pneumococci in the blood during the period of early pyrexia: a few, however, can sometimes be observed as early as three hours after inoculation. The number increases slightly during the maximum pyrexia, but it is only when the temperature begins to fall that their numbers greatly increase, and they continue to do so until just before death, when the blood is found to be swarming with pneumococci.

On making a post-mortem examination (which was always made with sterilised instruments) there are generally all the signs present of acute general septicaemia, with no vestige of any local inflammatory exudation at the site of inoculation. Films prepared aseptically from the heart blood taken from one of the ventricles and stained with Jenner’s or MacConkey’s stain, show the blood to be crowded with encapsulated diplococci. There is often evidence of acute general peritonitis, flakes of lymph being frequently found scattered over the peritoneum, while there is varying amount of turbid serum, often sufficient to fill a large capillary pipette: an interesting feature is the

\[ \text{Vide diagram 1.} \]
rolling up of the omentum, which often occurs. If death occurs very rapidly, there may be no visible evidence of peritoneal inflammation.

The condition of the spleen is very variable, both in size and consistence: it may be enlarged and softened, but there is often no visible alteration in its size, appearance, or consistency. I have found it much enlarged and quite hard. I often found the pericardial sac filled with slightly turbid serum. The cerebral meninges sometimes showed evidence of infection, the subarachnoid space over the vertex often containing quite an appreciable amount of turbid fluid passing down between the convolutions. There is sometimes an oedematous condition found in the anterior mediastinum. The fluids obtained from the different serous cavities, as well as the other morbid effused products, are invariably found teeming with diplococci, from which pure cultures can readily be obtained. The serous effusions, particularly that from the peritoneum, are particularly virulent if injected subcutaneously into other animals.

If on the other hand the virus is introduced subcutaneously, there are different effects to record. Inoculation into the loose connective tissue, (e.g., into the loose cellular tissue behind the ear), results in great swelling and oedema, followed later by general septicaemia.
In order to better study the local effects, I followed the plan recommended by Drs. Eyre and Washbourn and had the injections made into the denser subcutaneous tissues of the anterior abdominal wall. The animal often lived for several days, and characteristic local effects at the site of inoculation could be readily observed. If the animal dies very soon, there is practically no local lesion observable, with the exception of a slight haemorrhagic staining of the skin. If, however, the dose be a moderate one, the animal often lives for several days, and in such a case there generally occurs a distinct local swelling of variable size, due to an infiltration between the skin and the abdominal muscles. This infiltration has sometimes a rather gelatinous appearance, and sometimes there is a quantity of yellowish turbid or even semi-purulent effusion, intermixed with semi-solid material. Microscopical examination shows the former to consist principally of fibrinous exudation, and the latter of small-celled cellular elements, though there is usually a mixed cellular and fibrinous infiltration.

Drs. Eyre and Washbourn in 1901 made a series of careful experiments with different strains of pneu-
occi in support of the theory that the strains derived from cases of lobular pneumonia produced a cellular type of inflammation, while those derived from cases
of lobar pneumonia produced fibrinous inflammatory products. I have not had the opportunity of confirming this interesting conclusion or controlling their experiments.

The local and general effects of subcutaneous inoculation I found to vary in different animals, even although a precisely similar dose of the virus was employed. These effects seemed to depend to a considerable extent on the degree of resistance of the individual, as manifested by the local reaction at the seat of inoculation and the degree of phagocytosis in the blood and blood-forming tissues.

Thus at my request Dr. Eyre kindly inoculated four rabbits in my presence with a minute lethal dose consisting of one-tenth of a measured loopful of a virulent blood-agar culture derived from a case of pneumonia in the human subject. The injections were made with careful aseptic precautions into the subcutaneous tissue over the abdomen, which had been previously shaved over a wide area so that the local manifestations might be readily observed. The exact date of the inoculations was March 17th 1904, at 12 noon. Rabbit No. 1. Death occurred during night of March 18th (within 48 hours). I found the temperature 24 hours after inoculation to be 39°C., and though there was a slight local discoloration at this stage, there was no swelling at the site of inoculation. At the
post-mortem the heart blood was found to contain a large number of pneumococci, from which pure cultures were readily obtained. At the site of inoculation there was nothing beyond the slight discoloration of the skin observed during life. There was general peritonitis with peritoneal effusion: the pericardial sac contained one-tenth cc. of slightly turbid fluid: the spleen was hard and much enlarged: the meninges were not examined. The ventricles of the heart contained a quantity of blood-clot. There were thus all the signs of acute general septicaemia, with absence of local lesions.

Rabbit No. 2. Death occurred during night of March 19th (within three days). The temperature 24 hours after inoculation was 40.1°C., and at this stage there was no evidence whatever of a local lesion. At the post-mortem examination the heart blood contained a fair number of encapsulated diplococci, but was not crowded: cultures were obtained on blood-agar. There was a slight local lesion, consisting of an inflammatory oedema, raised perhaps a twelfth of an inch above the normal surface, and consisting chiefly of fibrinous material entangling some small cellular elements. There was very slight peritonitis, and no visible affection of any of the other serous membranes. There was a good deal of blood-clot in the cavity of the right ventricle. In this case there was a well-marked general septicaemia,
with little or no metastatic change, and a slight local lesion.

Rabbit No. 3. Death occurred during the night of March 21st (within 4 days). The temperature 24 hours after inoculation was 39°C. at this stage there was a visible local lesion, consisting of slight inflammatory induration.

At the post-mortem examination the heart blood was found to contain only a few pneumococci. There was, however, a very large local swelling some two inches in diameter and about \( \frac{1}{4} \)-inch thick in the central portion. Between the skin and the abdominal wall there was found a large deposit of fibrin, with a good deal of sero-purulent exudation. There was a quantity of lymph on the surface of the peritoneum and a large amount of sero-purulent effusion, a condition which might almost be described as purulent peritonitis. There was also a fair amount of pericardial effusion. In this case there was a slight septicaemia with a very marked local lesion, and distinct metastasis.

Rabbit No. 4. Death occurred at 8 a.m. on March 23rd (within 6 days). At the post-mortem examination one or two pneumococci were found in the blood after very careful search of several films, and also one or two in the bone-marrow juice. A culture made in the usual way from a loop of the heart blood proved sterile. There was, however, a large fibrinous local lesion, similar to that
found in the previous case, but in addition there was a very marked haemorrhagic discoloration, indicating acute local reaction. There was no pericarditis or meningitis, and practically no peritonitis.

In this case therefore there was a very mild septicaemia with a pronounced local reaction. Of course it may have been that the general phagocytic reaction had been equally pronounced, resulting in the destruction of the bulk of the diplococci, a destruction which might have been complete had the animal lived a day or two longer.

In this series of cases the inoculation with approximately the same strength of virus derived from the same strain of pneumococcus and introduced by the same skilled experimentalist and under precisely the same conditions, was followed by markedly different effects, which appeared to depend to a considerable extent upon the individual degree of reaction, local and general. At a subsequent subcutaneous inoculation of two rabbits with virulent pneumococcal material, one of them entirely survived the effects and was quite well one month after inoculation.

As a rule it may be said that the greater the local reaction the longer the duration of life. It is invariably true that the number of diplococci in the blood is inversely proportionate to the duration of the disease: when the animal dies within 48 hours (as in this case)
Inevitably the case in intraperitoneal inoculations) the blood is always found crowded with pneumococci.

In none of my cases did pneumonia occur. Dr. Washbourn however has observed two cases of pneumonia occurring after intraperitoneal inoculation although death occurred within 48 hours. In one case the whole of the upper lobe of one lung was solid, and there were several patches of lobular pneumonia in the lower lobe. He also observed pleurisy with pneumonia in three cases. Fränkel specially mentions pneumonia as occurring after injection with attenuated cultivations. These cases are all of extreme importance as indicating the fact that pneumonia in animals (and probably also in man) may occur secondarily to blood infection, and not necessarily be the result of inhalation.

Gamaleia states that direct inoculation into the lungs of sheep, rats, and dogs is sometimes followed by pneumonia. He also succeeded in inoculating four sheep by intratracheal injections of pneumococci, having previously weakened the alveolar tissue by the introduction of tartarated antimony: all the sheep contracted pneumonia. In another case, where a sheep was killed one hour after intratracheal inoculation, diplococci were found in the alveoli enclosed in mononuclear leucocytes and polynuclear cells.

Eyre and Washbourn introduced by means of a glass canula an emulsified culture of the pneumococcus.
into the trachea of 25 anaesthetised rabbits. In 7 of them there were definite areas of pneumonic consolidation, while in another there were small greyish solid areas exactly resembling the condition found in broncho-pneumonia in the human subject.

If virulent pneumococci are subcutaneously injected into moderately susceptible animals, such as guinea-pigs, sheep, and dogs, we often get an intense local cellulitis without a fatal result. A similar result has been obtained in a partially immunised rabbit with an attenuated virus: a local inflammatory lesion was produced with no appreciable general effects, the animal making a good recovery. A dose of pneumococci sufficient to kill a rabbit has been injected into the human subject in a case of cancer and has given rise to a similar local inflammatory swelling, with slight pyrexia and rapid recovery, although a case has been mentioned by another observer where the pneumococcic culture was injected into an abdominal tumour and resulted in death from acute peritonitis and probably pneumococcal infection.

Let us now pass to the study of the disease in man. Professor Stengel of Pennsylvania states emphatically what I have already expressed at the commencement of this paper, that a clearer conception of the malady known as Pneumonia would be obtained if the lung process were considered merely as one of the many
manifestations of pneumococcic infection, and that in this manner the clinical course, complicated or regular, would be much more clearly understood. Strong support is given to this view by the constant occurrence of clinical pictures which quite fail to correspond with any type of pulmonary inflammation, and still more by the knowledge that with improvement in technique we are able to recover from the blood of pneumonic patients Fränkel's diplococcus in an increasing number of cases. This suggests the probability of the invasion of the blood in every instance,—in other words, that there is probably always a greater or less degree of pneumococcal septicaemia.

Let us now enquire as to how far the general mass of evidence is in favour of such a view.

There has been an extraordinary diversity of opinion amongst the various investigators as to the proportion of cases of pneumonia in which the pneumococcus can be isolated from the blood. The earlier observers only found the micro-organism in a comparatively small percentage of cases. Even such a modern writer as Dr. Ewing in his recent work on the "Clinical Pathology of the Blood" comes to the following conclusions after a survey of the evidence:

1. When pneumonia leads to metastatic inflammation the pneumococcus is frequently found in the blood.
2. In some cases the blood is invaded just before death.
3. In uncomplicated pneumonia the pneumococcus is rarely found in the blood during the progress of the lesion.

4. When it is present the disease is usually fatal.

The first of these conclusions is naturally quite obvious, as had there been no pneumococcus in the blood there would have been no metastatic inflammations to record. As regards the second, it is correct in so far that there is doubtless a special invasion of the blood due to failure of the protective phagocytic properties of the blood. The experiments already alluded to in rabbits showed that the blood just before death almost invariably swarmed with pneumococci. I have myself obtained a pure pneumococcus culture from the blood taken from one of the intercostal veins of a patient who had died from pneumonia, though it was not obtained during life.

Thirdly, the statement that the organism is rarely found in the blood of uncomplicated cases of pneumonia is probably quite erroneous, and inexcusable in the light of recent researches of Prochaska, Frankel, and others, which Dr. Ewing was aware of and alluded to in his work. As regards the fourth conclusion that the mere finding of the diplococcus in the blood usually heralds a fatal termination, its acceptance would probably increase the actual mortality fourfold. The statement would probably have been much more correct had he made it in connection with the finding of large numbers of diplococci in the blood.
The history of blood examinations in pneumonia is extremely interesting and important as showing the value of accurate technique and the employment of suitable culture-media. Talamon, one of the joint discoverers of the pneumococcus, examined the blood in 25 cases of pneumonia, and found the organism only twice, on both occasions a few hours before death. Friedländer, the discoverer of the pneumonia bacillus, examined the blood in 6 cases of acute pneumonia, and found the pneumococcus but once. Netter examined a large number of cases, but reported only one positive case, which was complicated with meningitis and peritonitis. Sittman records an interesting series of observations, bearing upon the prognostic as well as diagnostic value of pneumococcaemia. Examinations of the blood were made in 16 cases of pneumonia: 6 of these were positive, 5 of which were complicated with metastatic lesions. Of the 10 negative cases, only one proved fatal, while of the 6 positive ones, 4 died. Kohn records 32 cases, with similar results, from a prognostic point of view: of these only 9 were positive, of which 7 died. In the 7 fatal cases, a positive result was only obtained a day or two before death. Kühn's results, as being those of a very skilled observer, are often
quoted in support of the view that uncomplicated pneumonia is but rarely a septicaemia. Preble examined 4 cases of pneumonia, in 3 of which he obtained the pneumococcus in cultures by direct smears of the blood. White (F.W.) reported 19 cases, 3 only of which were positive, and all fatal. Sello confirms Sittman's and Kohn's results. He reported a series of 48 cases, of these 12 were positive (i.e., 25%), with 10 deaths. Of the 36 negative cases, there were 27 recoveries and only 9 deaths. Silvestrini and Sertoli had the most successful series of cases reported up to this time. They found the diplococcus present in 15 out of 16 cases, and in 22 out of 24 investigations. They expressed the view that negative results were to be attributed to failure in technique, but were also of opinion that the number of pneumococci often showed a direct relationship to the severity of the disease. Beco examined 50 cases of pneumonia, with 11 positive results: of these 9 were fatal and 2 recovered, while of the 39 negative cases, 29 recovered. It is interesting to note that in this connection Beco reports a case of pneumonia due to Friedländer's pneumo-bacillus, in which there was a general bacillaemia. Prochaska was the observer who first startled the students of pneumonia all over the world by his marvellous results, which contributed very largely to modify scientific opinions with regard to this important subject.
In 1900 he reported his first series of 10 successive cases of fibrinous pneumonia, with positive results in all cases, and in 1901 he reported 40 additional cases, in all of which micro-organisms were found in the blood. In two instances these were not encapsuled diplococci, but cocci in chains, which were regarded by Prochaska as either streptococci or irregular forms of the pneumococcus. Eight of the 40 cases died, and the rest recovered. He asserts that in none of the cases was there risk of contamination from the skin or outside air.

In 1902 he published a further series of 4 successive pneumonias, in all of which the pneumococcus was found. Of these, 1 was fatal and 3 recovered. Prochaska's method was to remove 10 cc. (formerly he only used 5 cc.) of blood from a vein by means of a glass canula, and sow the greater part in distinctly alkaline broth, and the remainder he poured over agar slopes. The most constant results were obtained in the bouillon cultures. He ascribes his good results to the use of large quantities of blood, to the use of bouillon as a culture medium, and to great care in the examination of the cultures. Positive results were obtained at all stages, in several cases as early as the second day, in one case two days after the crisis, and in one case three days after the crisis. In two cases he found the staphylococcus aureus, and the streptococcus associated with the pneumococcus. One or two of these were cases
of metastatic inflammation. He found no relation between the degree of leucocytosis and the grade of bacteraemia, and no relationship between the latter and prognostic significance, as he believed every case of pneumonia to be accompanied by blood infection.

Londi and Gionini have reported a series of 27 pneumonias in which investigations of the blood during life gave positive results. Fränkel (A.), with whose name the pneumococcus will ever be associated, claims to have verified Prochaska's conclusions. At a meeting of the Verein für innere Medizin in Berlin, he stated that he had very often obtained cultures of the pneumococcus from the blood; they could be found if large quantities of blood (5-10 cc.) were used with a liquid medium such as bouillon, as they seemed to multiply better in liquid culture-media. He went on further to state that since we no longer take 1 cc. of blood for our experiments, but 6 to 8 cc., we find the pneumococcus in the blood in every instance.

Cole examined 30 cases of pneumonia, but was successful only in finding the pneumococcus in 9 instances. His method was to take 10 cc. of blood and add it to 150 cc. of sterile litmus milk. The 9 positive cases all died, while of the 21 negative cases only 4 proved fatal. Dr. Cole's experience therefore makes him conclude that the invasion of the blood by the pneumococcus is a rare occurrence and of grave prognostic significance.
Badnel and Gargano reported an epidemic of pneumonia involving 8 children in one house, many of whom had complications: the pneumococcus was found in the blood of all of these cases. Badnel does not consider the presence of pneumococci in the blood of any prognostic importance. He states that he was found them in 55 out of 57 patients, and as late as 25 days after the crisis: the diplococcus, he says, may localise itself in the blood primarily or secondarily, and he believes that the diplococcaemia is much more grave in the latter eventuality.

In June 1903 Dr. Rosenow reported cultures from 83 cases, with positive results in 77. In March 1904 he reported 145 cases, inclusive of the above 83, and in March 1905, 30 additional cases. Of the total number of 175 cases of lobar pneumonia in which he made blood cultures, the pneumococcus was isolated in all but 15, i.e., over 91%. Usually only one culture (3 to 4 flasks) was required to demonstrate the presence of pneumococci in the blood, though occasionally a second culture was necessary to obtain the organism. In 11 of the 15 negative cases, only one culture was made, there being no opportunity for a subsequent examination. In the remaining 4 cases only was it impossibly by repeated cultures to demonstrate the pneumococcus in the blood, and in one of these 4, a careful search in smears prepared directly from the blood showed undoubted
pneumococci. The cultures with negative results were all made within 24 hours of the crisis, while the positive ones were made at least two or more days before the crisis. Positive results were obtained as early as 12 hours after the initial rigor, and as long as 48 hours after the crisis, though cultures taken after the crisis usually proved sterile. The mortality in the series of 175 cases was high, - 40%, - and the percentage of positive results was equally high in the fatal and in the non-fatal cases.

Kinsey made an examination of 50 cases of pneumonia. The importance of technique is well illustrated by his results. In his first 25 cases he had only 3 positive results, or 12%; while in his second series of cases from the same epidemic, there were 19 positive results out of the 25 cases examined, or 76%. The only difference in the two sets of examinations consisted in the exact dilution used: in the first 25 cases from 8 to 9 cc. of blood were used to 50 cc. of bouillon, making a dilution of about 1 to 6 : while in the second series the proportion of blood to bouillon was made lower, one part of blood being employed to 15 or 20 parts of bouillon. The mortality was not greater in the positive cases.

Technique of Blood Examination. The most satisfactory instrument for drawing blood from the patient seems to be
a glass canula. This was used by Sittman, Prochaska, Fränkel, Kinsey, and other observers. Kinsey employed a glass canula marked in cubic centimetres, to register the amount of blood extracted, and the end of which was drawn through a tube to which was fixed a platinum needle about 6 cm. long, while fixed to the other end was a rubber bulb supplying sufficient suction to draw up the blood to the height desired. The majority of experimenters, following Prochaska and Fränkel, employ bouillon as a culture medium, partly on account of its excellent culture properties, and partly on account of the ease with which it is prepared.

As regards technique, the withdrawal of blood from the patient must be done with the strictest aseptic precautions. The operator's hands must be thoroughly sterilised by scrubbing, soaking in bichloride solution, washing in alcohol, and finally in ether. The bend of the patient's elbow is similarly sterilised. An assistant then exerts pressure on the upper arm, so as to make the veins stand out prominently, and the sterilised instrument is introduced into the median basilic or median cephalic vein and the requisite amount of blood drawn up by the suction of the bulb. When a sufficient quantity is obtained, it is added to a flask of bouillon which is gently agitated, to mix the culture, which is then allowed to grow in the incubator at 37°C.

A careful analysis of the above results,
particularly those of the later observers, compels the unprejudiced student to come to the same conclusion as that arrived at by Fränkel himself,- that if a sufficient quantity of blood be taken, the pneumococcus can be found in the blood of every pneumonia patient; and to agree with the opinion of Silvestrini and Sertoli already referred to, who attributed negative results to imperfect technique or to unfavourable conditions of growth.

If, then, we grant that the virus is present in the circulating blood of all pneumonia patients, we will cease to be surprised at the occurrence of metastases, but wonder rather why we do not meet with complications in every case.

Let us now consider the question of positive blood examination results from a diagnostic and prognostic point of view. Its diagnostic value must necessarily be very limited, but in atypical cases with absence of typical symptoms and physical signs in the lungs themselves, blood cultures may be of great value. Dr. Rosenow reported a case in the Journal of the American Medical Association, issued in March 1905, where the blood culture was the means of deciding in 12 hours whether an atypical pneumonia following pregnancy was due to a streptococcus infection, secondary to infection from the uterus or to a pneumococcus infection independent of the pelvic condition. He mentions further that in 5 of
his series of 175 cases the blood examination was the means of making the diagnosis. It may be of service also in differentiating the disease from typhoid fever, though probably the leucocyte count forms a more readily applicable differential test. It is certainly true that the virus may be discovered in the circulating blood before any definite pneumatic signs develop. Cases of pneumococcal infection of the blood have been observed by Preble and others, in which no physical signs of pulmonary consolidation were at any time demonstrable, and yet the course of the illness, including the pyrexia, was typical of pneumonia. Hospital physicians are familiar with cases - I have a case in point under my care at the moment of writing, - where there have been practically no physical signs in the lungs, until just perhaps at the end, and yet where the nature of the case was never in doubt owing to the appearance of the patient, - the course of the pyrexia, with typical crisis, and the usual symptoms one associates with acute pneumonia. These are sometimes put under the category of central pneumonias. I am much more inclined to believe that in many of these cases there was in reality a primary blood infection, and that the pulmonary changes were secondary. The view that pneumonia is occasionally a secondary localisation of a primary blood infection is gradually gaining ground.

Let us now briefly consider the question of
positive blood examinations from the point of view of prognosis. It is held by a large number of clinicians and it is taught in some of our modern text-books, that the finding of pneumococci in the blood is of grave significance. The above-detailed results of Sittman (1894), Kühnan (1897), White (1899), Sello (1899), Beco (1899), and Cole (1902), certainly strongly support such a view. These six observers report in all 43 positive results, with 37 deaths, i.e., a mortality of 86%, and 139 negative results with 34 deaths, i.e., a mortality of only 24%. The contrast is sufficiently striking to warrant the gloomiest prognosis in positive cases.

On the other hand, the practically cent. per cent. positive results above detailed of Silvestrini and Sertoli (1899), of Prochaska (1900, 1901, and 1902), of Landi and Cionini (1901), of Badnel and Gorgano (1903), of Rosenow (1903, 1904, and 1905), and of Kinsey (1904), by means of modern bacteriological technique, seem to justify the conclusion formed by most of these observers and strongly supported by Fränkel himself, that with modern technique blood cultures are of little prognostic value, because positive in both fatal and non-fatal cases.

Kinsey, however, from his experience of 50 cases, is of opinion that the finding of large numbers of pneumococci is of grave prognostic import. He bases
this opinion on the fact that in his fatal cases the organism was invariably present in large numbers, while with two exceptions only, few pneumococci were found in those positive cases which recovered. Other observers have expressed the same view, which may be taken as being substantially correct.

The divergence of the experimental results and consequent conclusions of the two sets of investigators is so remarkable that I have thought it well to examine their methods carefully, with the view of detecting the reason of this divergence, which may have a valuable clinical significance. The earlier observers who obtained a small number of positive results and these as a rule in fatal cases only all used small quantities of blood. Thus Fränkel himself when he used only 1 cc. of blood obtained only a comparatively small number of positive results, and later when following Prochaska he employed 5 to 10 cc., he was uniformly successful in isolating the pneumococcus. This does not apply to Cole, who obtained the pneumococcus in 9 out of 30 cases, all 9 being fatal. He used quite as large a quantity of blood as the other observers, but, unlike Prochaska, Fränkel, Kinsey, and Rosenow, did not employ bouillon as his culture medium, preferring sterile litmus milk, which is probably not so good a medium for the purpose. It would be well if Cole repeated his experiments with bouillon. It would be very valuable, I think, if future
observers conducted two controlling sets of investigations side by side, on the one hand using a large quantity of blood (say 6 to 8 cc.) with the most suitable medium obtainable (say bouillon), and on the other using a small amount of blood (1 to 2 cc.), either with bouillon or a less suitable liquid medium: 10 cc. of blood drawn from the patient would do for both experiments. It is quite probable that positive results would be obtainable in the second set of investigations only in a limited number of cases, and these possibly mainly in the fatal ones, thus confirming the results of the earlier observers. In this way positive or negative results might become of considerable prognostic value. Streak cultures on solid media (e.g., agar) direct from the blood might also be made with advantage in every case. A positive result would indicate the presence in the circulating blood of large numbers of pneumococci, and would therefore be of some slight prognostic significance. In 47 out of 80 cases examined by Rosenow (i.e., rather more than half) the pneumococcus was discovered in agar smears taken direct from the blood.

Before leaving this subject it will be well to enquire if any relationship can be established between the degree of bacteriæmia and the occurrence of metastases. In as many as 5 of the 6 positive cases in Sittman's series of pneumonias already
referred to, there were lesions found in other organs. Schabad describes a case of pneumococcic septicaemia with involvement of practically all the organs of the body. In this case positive results were readily obtained from agar growths taken direct from the blood. Netter reported only one case of pneumonia with pneumococci in the blood, and in this instance the disease was complicated with meningitis and peritonitis. In Kinsey's series of positive results in cases that recovered, there was found, as already mentioned, only a few pneumococci in the blood with some exceptions. In one of these two (the case of a young girl of 22 years of age) high pyrexia persisted. Numerous pneumococci were found in pure culture, while agar streaks also proved positive. In this case pneumococcic arthritis developed, from which she ultimately recovered. Numerous individual cases have recently been published with various forms of metastases, in which the pneumococcus was readily found in the circulating blood.

Sufficient evidence has been adduced to support the view that in fatal cases and in cases of metastases the blood as a rule contains a larger number of diplococci than in the milder and uncomplicated cases. The occurrence of metastases, as we shall see later, may be due rather to the degree of virulence of the pneumococci than to the actual

Vide diagram 2

27.
number of micro-organisms present in the circulating blood. It is interesting to note in passing that Netter and Levy have found the pneumococcus in the blood of a dead foetus whose mother had died of septicaemia, while Bozzoli has found the germ in the milk of a nursing woman who was attacked by pneumonia.

While Prochaska found no relationship between the degree of leucocytosis and the grade of pneumococcaemia or the severity of the disease, other observers have formed a different opinion. It was Kikadse and von Jaksch who first pointed out the prognostic significance of leucocytosis. They believed that the absence of leucocytosis was an unfavourable prognostic sign. This view, however, in light of recent investigation, must be accepted with some reservation. In an unusually mild case there may be little or no leucocytosis: the absence of leucocytosis, however, and still more hypoleucocytosis in severe cases, must be regarded as prognostic signs of grave significance. Lambert states that some severe cases may show absence of leucocytosis to begin with, but later on a well-marked increase. He believes that a continuously low or decreasing number of white cells is only seen in fatal cases. This view is, however, probably somewhat extreme. Other things being equal, it is safe to regard a high leucocytosis as a favourable sign. A leucocyte count
was made by Rosenow in 40 cases of pneumonia: in the 16 fatal cases the average leucocytosis was only 12,000, whilst in the 24 cases which recovered the average was 20,000. It must be noted, however, that patients with an excessively high leucocytosis seem to be more prone to the development of empyema, arthritis, and other complications, though the hyper-leucocytosis may in reality merely be the first indication that such a complication has actually occurred. In the only four cases out of Dr. Rosenow's series of 175 where he failed by repeated cultures to demonstrate the pneumococcus in the blood, there was in each instance an unusually high leucocytosis, indicating that the negative findings were possibly the result of an active phagocytosis. Dr. Rosenow was able to show that the close relationship that seems to exist between leucocytosis and pneumococcus invasion of the blood in the experimental pneumococcal infection of the rabbit, existed also in the human subject. He made a series of plate cultivations of the blood in pneumonia: in this way he was able to show that the higher the leucocytosis, the fewer the number of visible pneumococci in the circulating blood, and vice versa. Thus in 7 patients with a leucocytosis ranging from 5,000 to 43,000, the number of pneumococci which developed was very small indeed, varying from 0 to 25 growths per cc. of blood.
On the other hand, in the cases where there was hyperleucocytosis or only a moderate leucocytosis, the number of growths on the plates ranged from 100 to 1,350 per cc.

It is curious that no observers, so far as I can find, have described the pneumococci as occurring in the leucocytes in the blood: Kinsey expressly states that he did not find this condition in one instance. Personally I have frequently examined the bone-marrow taken from the thigh bones of rabbits who had died of pneumococcic septicaemia, and almost invariably have had no difficulty in seeing the cocci both in the capsule and in the protoplasm of the oxyphile leucocytes. In one case, where the rabbit was inoculated intraperitoneally with lung scrapings taken from a patient who had died from pneumonia which had begun to resolve, I found many of the oxyphile cells in the rabbit's bone-marrow loaded with cocci, with the granules relatively few in number, looking as if they had been actually replaced by the diplococci. Of course in addition to these, there were numerous free cocci in the bone-marrow.

Having now established the fact of the frequent, if not constant, presence of pneumococci in the circulating blood, let us now enquire whether the organisms themselves vary in virulent properties. The symptomatology, mortality, and tendency to

\[ \text{vide diagram 3.} \]
metastases all exhibit such remarkable variations in different cases, groups of cases, and epidemics, that one is led to suspect essential differences in the characters of the pneumococci. That there are such variations, bacteriologists are recognising more and more. Morphologically, all diplococci may appear to be alike, or may present only minor variations, but as regards infectiousness and virulence, the greatest degrees and varieties have been observed. If this is so, the extreme difficulty of obtaining a universally reliable antitoxin will be at once appreciated. The earlier observers were not of this opinion. Thus Netter, who tested the virulence of cultures immediately after isolation from cases of recent infection in man, found that its degree was remarkably constant in a series of experiments in rabbits. The organisms experimented with were taken from 11 cases of empyema in children, 2 cases of empyema in adults, 3 cases of lobar pneumonia, 2 cases of meningitis, 1 case of cellulitis, and 1 case of circumscribed abscess of the finger. These experiments are, however, open to the obvious fallacy that a sufficient dose (say an ordinary platinum loopful) of a pneumococcus culture, whether the virulence be great, moderate, or only slight, will in the great majority of cases prove rapidly fatal to such extremely susceptible animals as the mouse or rabbit. In fact, with this rough test
the pneumococcus obtained from healthy saliva will apparently prove quite as virulently pathogenic to susceptible animals as a strain derived from a case of acute lobar pneumonia with general metastases.

Foa was so impressed with the manifold pathological conditions met with in pneumococcic infection that he did not think that any one organism could be responsible for them all, and accordingly described two distinct varieties, viz.,

a. Pneumococcus proper, which produces a serous exudation in the subcutaneous tissue, a moderate number of cocci were found in the blood post-mortem, and the spleen was small and soft.

b. Meningococcus, produces no local reaction in the rabbit, the animal died with a large number of cocci in the blood, and the spleen was hard and enlarged. He further found that rabbits immunised against the one variety were not immunised against the other. Later observers have, however, shown that these distinctions are in reality due partly to different degrees in virulence of the pneumococcus, and partly also to varying degrees of resistance on the part of the individual, and thus the same pneumococcus may be the specific organism concerned in the production not only of a lobar pneumonia but also of lobular pneumonia, serous or purulent pleurisy, and pericarditis, otitis media, and suppurative meningitis and
peritonitis. Eyre and Washbourn state that the pneumococcus exists in nature in two forms:—

a. Pathogenic form. This is a very delicate and sensitive organism, capable of cultivation only in a very few culture-media, which must be alkaline in reaction, and readily destroyed by temperatures slightly above or below that of the human body-temperature, living only for a few days in such media as bouillon and agar (though it may live for months in agar smeared with the serum of rabbits), with its virulence steadily diminishing day by day.

b. Saprophytic form. This, though of similar morphological appearance, is much less sensitive and more highly resistant, will grow well upon any ordinary culture medium, acid or alkaline, and at the ordinary temperature of the air. This form is almost non-pathogenic, though capable of transformation into the pathogenic variety by passage through susceptible animals such as rabbits or mice. To this category belong many of the pneumococci found in the saliva and buccal secretions of healthy individuals.

These two observers, believing that the older experiments, already alluded to, of Netter and others, with regard to the virulence of various strains of pneumococci, required to be repeated with more accurate methods of dosage, hit upon an ingenious device
for accurately measuring the inoculation dose of any particular culture of pneumococci. I have frequently used this method. An accurately calibrated platinum wire loop is taken, and with it an exact loopful (with both sides flattened against the sides of the culture tube) is taken of a 24-hours' growth of the pneumococcus from the surface of blood-agar. As soon as the animal is prepared and the inoculation instruments sterilised, this loopful is emulsified with a measured quantity of sterile bouillon and diluted down until the desired dose in a convenient quantity of bouillon for injection (say 1 or more cc.) is obtained. It was found that one-millionth part of such a loopful of a highly virulent culture was fatal to rabbits, whether introduced intraperitoneally or subcutaneously, although in the case of subcutaneous inoculation, the rabbit died at a later period. A strain of pneumococcus of such virulence, that a dose of one-millionth part of a loop inoculated into a rabbit is fatal is considered as being of standard virulence.

Measured in this way, strains of the pneumococcus isolated from various pathological conditions in the human subject were found by these investigators to differ greatly in their virulent properties.

In connection with our study of pneumococccic septicaemia and pyaemia, it will be instructive to quote a few of Eyre and Washbourn's results:
<table>
<thead>
<tr>
<th>Origin of Strain</th>
<th>Virulence (minimal fatal dose of pneumococci)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Meningitis (complicating pneumonia)</td>
<td>Entire blood-agar culture</td>
</tr>
<tr>
<td>2. Sputum of case of pneumonia</td>
<td>2 loops</td>
</tr>
<tr>
<td>3. Sputum of case of pneumonia</td>
<td>1 loop</td>
</tr>
<tr>
<td>4. Saliva of healthy person</td>
<td>1 loop</td>
</tr>
<tr>
<td>5. Meningitis (complicating otitis media)</td>
<td>1/10th loop</td>
</tr>
<tr>
<td>6. Pericarditis (child)</td>
<td>1/10th loop</td>
</tr>
<tr>
<td>7. Sputum of atypical pneumonia</td>
<td>1/100th loop</td>
</tr>
<tr>
<td>8. Lung juice of lobar pneumonia</td>
<td>1/1,000,000 loop (standard virulence)</td>
</tr>
<tr>
<td>9. Broncho-pneumonia (infant)</td>
<td>Ditto ditto</td>
</tr>
<tr>
<td>10. Pericardial pus, case of pneumonia with purulent pericarditis and empyema</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>11. Pus from peritoneum, case of pericarditis, pleurisy, suppurative peritonitis, sero-purulent meningitis, but no pneumonia</td>
<td>&quot; &quot;</td>
</tr>
<tr>
<td>12. Saliva, case of chronic Bright's disease.</td>
<td>&quot; &quot;</td>
</tr>
</tbody>
</table>

These twelve cases are sufficient to show how greatly the different strains of pneumococci may vary in virulent properties. The strains derived from atypical pneumonia and those with metastases as a rule exhibited a high degree of virulence. That these variations in the fatal cases are not due to post-mortem
cultural or degenerative changes inside the body is indicated by the fact that strains showing standard virulence were obtained at post-mortem examinations made at intervals varying from 15 to 40 hours after death. It is only right, however, to say that such an accurate recent observer as Dr. Foulerton, the bacteriologist to the Middlesex Hospital, confirms Netter's results and states that out of 19 cases he found the virulence practically the same in all.

My own few experiments, which I conducted in the bacteriological laboratories of Guy's Hospital under the direction of Dr. Eyre, lead me to support his and Dr. Washbourn's contentions. I had the opportunity of investigating a considerable number of cases of pneumococcic empyemas, and almost invariably found the pus to contain organisms of comparatively slight virulence as tested by experimental inoculation. This result is, however, probably due to degenerative changes taking place in the organisms while contained in the effused pus inside the body, comparable to the daily loss of virulence so generally observed in tube cultures in the laboratory. As regards the latter, a highly virulent pneumococcus can readily be converted by cultivation into an absolutely avirulent type, which is then capable of being cultivated readily in all ordinary culture-media, alkaline or acid, even at a temperature of 20°C. It can be re-converted into
the virulent type by passage through susceptible animals. Cultures even on blood-agar so readily degenerate and subcultures so soon lose their virulence that in order to keep any individual succession of generations at a high standard virulence it is absolutely necessary from time to time to pass the virus through susceptible animals. In this way the virulence may be kept unimpaired for long periods of time. In the body also the virulence tends to be lost or impaired, as is shown by the number of degenerated and devitalised pneumococci that are often obtained from old empyemas and slowly resolving pneumonias. Professor Welch of Baltimore goes so far as to state that the virus inside the body becomes so attenuated that pneumococci derived from inflammatory exudations are sometimes found non-pathogenic to susceptible animals. This is certainly my own experience with regard to some empyemas. I have at present under my care a case of bronchiectatic abscess of one lung, of 4 years' standing, who daily expectorates from 2 to 3 ounces of purulent secretion loaded with pneumococci, and yet enjoys excellent health with no pyrexia and no diminution in body weight. Dr. Michael Foster of San Remo has sent me notes of a large number of similar cases. Fränkel himself believed that the pneumococcus underwent a progressive diminution in virulence as the
course of pneumonia advanced, while Netter went further and stated that the virulence of pneumonic sputum is often suddenly lost at the crisis and remains in abeyance for 2 or 3 weeks, when the virulence may again manifest itself. On the other hand, there are those who assert that the growth of the organism in the tissues is apt to increase its virulence. Dr. Andrew Smith of New York is of opinion that the extensive effusion of fibrin is in reality a "breeding ground" for the diplococci, and this enormous amount of pabulum is probably the explanation of the overwhelming amount of poison manufactured by them in the lung, and from there thrown into the circulation. This may afford a theoretical explanation of the gravity of cases without expectoration. At the same time, in my own experience the severest cases of pneumococcic infection I have met with have been those associated with least pulmonary consolidation. I shall again refer to this point in dealing with the clinical aspects of the subject.

Professor Stangel states that the virulence of the cocci is as a rule directly proportionate to the acuteness of the lesions, though the latter must depend to a considerable extent on the resisting power of the individual patient.

Mortality statistics in regard to particular outbreaks and epidemics go far to support the view
of divergence in virulence in regard to the specific causal agent. One might particularly refer to the unusually severe epidemics which have occurred within the last few years in New York, Chicago, and other large cities in America. In the Chicago epidemic, which was carefully investigated by Dr. Kinsey and Dr. Rosenow, the mortality was as high as 40%—practically double the average mortality in England. As already mentioned, these observers were able to isolate the pneumococcus from the blood in practically all the two hundred odd cases examined by them. Last year in New York acute pneumonia was so prevalent and the mortality so high that in August 1904 a Commission composed of some of the most distinguished American physicians and pathologists was appointed to make a systematic study of pneumonia in New York. As showing the severity of the epidemic, it may be mentioned that 364 deaths occurred in New York from pneumonia for the week ending January 9th 1904, being 143 more than were recorded from the same cause for the corresponding week in 1903. During that week the total number of deaths in the city was 1635, so that pneumonia was directly responsible for nearly one-quarter of the mortality from all causes. Dr. Guilfoy, the Registrar of the New York Department of Health, states that of the 364 above-mentioned deaths, 239 were due to lobar
pneumonia, and 125 to broncho-pneumonia. During the first six months of 1904 there were 8360 deaths from pneumonia, or nearly 20% of the total mortality. The Commission consists of such well-known physicians as Drs. Osler, Billings, Janeway, Biggs, Musser, and Holt, associated with such distinguished pathologists as Drs. Welch, Prudden, and Smith. A symptomatic investigation was to be carried out in connection with the specific cause of the disease, the frequency and varieties of occurrence, the evidence of its contagiousness and communicability by mouth-infection, its seasonal and geographical relations, its appearance in the form of an epidemic and the reason for this appearance, and also the question of prophylactic methods and precautions. It is sincerely to be hoped that much good will result from their labours and much light be thrown on the all-important subject of pneumococcic infection.

We shall now briefly consider the interesting though extremely obscure subject of Pneumococcic Toxaemia, as practically all clinicians attribute the pyrexia, cardiac failure, and the other grave symptoms so characteristic of pneumococcic infection to the immediate action of some toxic substance circulating in the blood.

Of the exact nature of these toxins,
practically nothing definite is known. The difficulty experienced in isolating them is doubtless due to their extreme instability, as they are produced apparently only by virulent pneumococci in the most favourable conditions within the body and are readily broken up and destroyed or removed from the circulating blood. Clinical evidence alone, however, is sufficient to convince us of their existence. Two facts may be mentioned:—

1. The remarkable difference in the condition of a pneumococcic patient before and after the crisis, although the amount of pulmonary consolidation remains practically the same.

2. The symptoms are often most severe when the amount of lung consolidation is quite insignificant.

G. and F. Klemperer claimed to have isolated from cultures in bouillon by treatment with sulphate of ammonia and alcohol a toxic albumose-substance which they termed "pneumotoxin," and also found formic acid in the cultures. When injected this Pneumotoxin produced symptoms in rabbits, and when this toxalbumin substance was obtained not from bouillon cultures but from the blood of animals which had died of the disease, it even produced fatal results.

Rosenow mentions a series of experiments where he cultivated pneumococci in normal blood
serum and in pneumonic serum. In normal bloodserum the growth produced scarcely any appreciable precipitate, while in pneumonic serum a copious sediment invariably appeared, associated with the presence of a distinct acid reaction. He conducted a control series of experiments which satisfied him that this sediment was the direct result of the acids present. He was thus led to make the deduction that the pneumococcus by its growth in the consolidated lung and other tissues of the body and also in the blood of the patient during life, probably produces acids as it does in the test-tubes. He suggested therefore that some of the symptoms of pneumonia may be due to an acid intoxication: this in his opinion explained the great therapeutic value attributed by many physicians to the administration of alkalies in large doses in the treatment of pneumonia. Support is lent to this hypothesis by the fact that a uniformly acid reaction of the lung tissue has been found by various observers in patients dying of pneumonia. Dr. Washbourn in his Croonian Lectures states that the pneumococcus resembles the streptococcus pyogenes (the causal agent in ordinary septicaemia) in producing no soluble toxin, and in this respect is unlike the virus of diphtheria or tetanus. He often injected as much as 20 cc. of filtered broth cultivations into rabbits without causing death. Auld, on the
other hand, states that filtered cultivations in doses corresponding to 1% of the body-weight of the rabbit were sometimes fatal. Sterilised cultures on any medium have very little toxic effect: in fact, Pané stated that bouillon cultures that have been kept until the cocci are dead are only slightly more toxic than ordinary broth. It is possible, however, that toxic substances if produced are not secreted by the cocci themselves, but are formed from the infected tissues by the action of the diplococci. Auld has isolated an albumose-like body from the tissues of infected rabbits by macerating them in rectified spirit for from 4 to 6 weeks and then extracting with water. The spirituous and aqueous extracts were then filtered, concentrated, and precipitated with absolute alcohol. The final precipitate had the characters of an albumose, and on evaporation of the alcoholic filtrate a viscous amorphous substance containing a quantity of organic acid was obtained. A solution of the albumose injected into the thorax produced in the case of one rabbit a lobar pneumonia with pleural effusion, and in another a lobar pneumonia with pleural and pericardial effusion. In a third rabbit a subcutaneous injection of the albumose was followed by a short attack of cellulitis, terminating in recovery on the 6th day. In all
these animals there was a marked rise in temperature. On the other hand, injection of the acid-containing residue (soluble in alcohol) was not followed by any injurious results.

Carnet also describes a toxin which when introduced into an animal's lung gave rise to pneumonic conditions, and also secondarily produces symptoms of cardiac affection, similar to those occurring during the disease in the human subject.

Carnat and Fournier indeed state that definite alteration of the cardiac muscle can be produced in rabbits by the injection of small quantities of pneumococcic toxins, including exaggerated striation, vacuolation, dissemination, and fragmentation of the muscle fibres. In two cases of pneumonia in man they found changes in the heart muscle similar to those produced in the rabbit.

Foulerton and Campbell Thomson found structural alteration in the motor cells of the cerebral cortex in experimental pneumococcic infection. There was no reason, however, in their opinion to suppose that these changes were specific or in any way peculiar to the pneumococcic toxin, but were similar to those occurring in various diseases accompanied by a high range of temperature.

Summing up, it may be said that the experimental evidence in regard to the nature and composition
of the pneumococcus toxin or toxins is by no means conclusive. Still, what actually has been done goes some way to support the clinical evidence, which so strongly favours the belief in the existence of such pyrexia-producing and heart-depressing toxic bodies. The close analogy also between pneumococcic infection and such diseases as diphtheria and tetanus, where we can actually prove without doubt the existence and nature of their respective toxins, is a strong argument in support of such a view. The difference probably mainly lies in the greater stability of the toxins of diphtheria and tetanus, as compared with that of pneumonia. We may conclude therefore that in every case of pneumoccal septicaemia we have a corresponding toxaemia, its degree being precisely proportionate to the virulence of the specific virus. The fact that we meet with cases occasionally where the patients exhibit marked toxic symptoms, and yet very little gross change whether in the lungs or elsewhere, indicates that the toxins are at least in part produced in the blood itself as well as in the pulmonary substance and other fixed-tissue elements.

The consideration of these toxins naturally leads us to the questions of immunisation and the formation of antitoxins. Animals (e.g., rabbits) can readily be immunised against pneumococcic infection in various ways. One method is by inoculation with an
attenuated virus: its attenuation may be produced by cultivation in artificial media. Sputum taken a little time after the crisis also contains attenuated pneumococci, and may be used as an immunising medium. Netter used an emulsion of the dried spleen of an animal who had died of pneumococcal septicaemia. Here the attenuation, as in the virus of rabies, was effected by drying. Probably the best method of immunisation was that advocated by S. and F. Klemperer, which consisted in the intravenous injection of about 12 cc. of a bouillon culture of virulent pneumococci which had been sterilised by being exposed to a temperature of 60°C for one or two hours. They also used virulent sputum treated in the same way. In this case the immunisation was produced by the injection of the toxic bodies derived from the cultures and not by attenuation of the virus. During this process some animals die, but those which recover are rendered immune to subsequent inoculations. In nearly all cases one or two injections of the attenuated pneumococci or of the toxins derived from the cultures are sufficient to produce immunisation. Immunity is established in three days in the case of intravenous injection, and in 14 days in the case of subcutaneous injection. This immunity will last for at least a month.
The Klemperer brothers were the first to show that the blood-serum of immunised animals had protective properties when injected into other animals. Foa and Carboni and also Arkarow and Issaef obtained similar results.

It was thus shown that immunity is accompanied by the development in the blood of antitoxic substances which neutralised the toxins produced by the pneumococcus. These antitoxins were found not only to be efficient for protecting a rabbit against subsequent inoculation with pneumococci, but also to be capable of preventing death from pneumococcal septicaemia if injected within 24 hours after inoculation. They are thus curative as well as prophylactic agents.

In this country Dr. Washbourn was able to confirm these results, and was further the first investigator to immunise a horse and thus obtain a sufficient amount of serum, for the treatment of cases of pneumococcic infection in the human subject. He immunised a pony by employing bouillon cultures sterilised by an hours' exposure to a temperature of 60°C., and also by using living agar and broth cultures. He was in this way able to obtain a serum of very high protective power, the potency being such that 0.03 cc. when mixed with 10 lethal doses of living pneumococci and injected into the peritoneal cavity of a rabbit, prevented death from pneumococcal septicaemia. We shall refer to the use of anti-pneumococcic serum in the case of Man when dealing with the clinical
aspects of the subject.

It may be here mentioned that the Klemperer brothers have shown from examination of the serum of patients convalescing from pneumonia that during the progress of cases of pneumococic infection in man, the serum acquires feeble protective powers.

Wasserman has published experiments which strongly point to the bone-marrow being possibly the main seat of the formation of these protective antitoxins. The finding in my own experiments (vide ante) of such definite evidence of phagocytosis in the bone-marrow would seem to indicate also that the bone-marrow is also one of the chief tissues where the bacteria in the circulating blood are mainly destroyed.

Fifteen years ago (in 1890) Baring and Nessen showed that the blood-serum of a normal rabbit or guinea-pig had no bactericidal action on the pneumococcus, but that on the other hand the serum of a normal sheep and of an immunised rabbit had distinct bactericidal properties. These results have been confirmed in their main contentions by Pane, Eyre and Washbourn, and other observers, some of whom found, however, that the serum of immunised animals varied very much in its bactericidal properties, the effects being sometimes so slight as scarcely to be differentiated from those exerted by normal serum. The agglutinative characters of the serum may be briefly referred to.

\[ \text{Vide diagram.} \]
In normal blood-serum the pneumococcus gives rise to a uniform turbidity, the growth taking the form of diplococci which remain separate from one another. In the serum of immunised rabbits, on the other hand, the appearance is quite different. The pneumococci sink to the bottom in the form of a sediment, while the supernatant serum remains clear; the cocci at the bottom are found clumped together in masses.

Berzaneon and Griffin advocated the agglutination as a useful form of serum diagnosis, comparable to, though of less value than; the Widal test in typhoid. By their method a small quantity of blood was drawn off from a patient and the serum collected in a small tube, which was inoculated with a pneumococcus culture and incubated from 15 to 18 hours. At the end of that time the contents of the tube were examined. If the case were one of pneumococcus infection, there would be a more or less adherent sediment of growth at the bottom of the tube, while the serum above was quite clear; while if the case were some other disease, the serum would be finely turbid throughout.

A careful consideration of the causal factors in connection with the increasing prevalence and mortality of this disease leads one to attribute them in part at least to the influence of epidemic influenza. The accompanying mortality chart of the
town of Philadelphia, extracted from a paper by Dr. E. F. Wells of Chicago, bears out this view.

<table>
<thead>
<tr>
<th>Year</th>
<th>Deaths</th>
<th>Population</th>
</tr>
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<tbody>
<tr>
<td>1876</td>
<td>4</td>
<td>100,000</td>
</tr>
<tr>
<td>1877</td>
<td>3</td>
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</tr>
<tr>
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<tr>
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<tr>
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<tr>
<td>1890</td>
<td>0.005</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Pneumonia mortality in Philadelphia (after Wells). Note great increase of mortality during last decades.

A glance at the chart will show that a marked increase in mortality took place in 1890, the year of the first outbreak in America of Russian influenza, which had commenced its ravages in Europe the year previously. This increase in prevalence and mortality will be seen to have persisted up to the
present time with no tendency to diminution. It is right, however, to note that Dr. Fulton of Baltimore is of opinion that this great increase is more apparent than real: he alleges that the increase is to a great extent due to the fact that a number of pyrexial illnesses are now entered as pneumonia which were formerly classified as bronchitis, congestion of the lungs, etc. As showing the effect of influenza, it is a remarkable fact that the death-rate from pneumonia in males, as shown by the British Registrar-General's returns, rose with a bound from 1206 per million in 1889, to 1731 in 1890, and to 1798 in 1891 (coincidently with the first two general epidemics of influenza), while among females the mortality rose from 848 per million in 1889 to 1165 in 1891. It is probable that influenza exercises a special action in lowering the resisting power of the lung-tissue to the invasion of the pneumococcus. This is borne out by the fact that although pneumonia may attack the strongest persons, yet any condition of depressed vitality, due to fatigue, injury, starvation, alcoholism, etc., renders the person much more liable to the disease. But influenza has been found not only to influence the incidence, but also to greatly modify the course of the disease itself. It is remarkable that probably more cases of metastases occurring in pneumonia have been recorded in the past 15 years during
which influenza has become more or less endemic in Western Europe, than in all the previous literature of the subject. It would seem, indeed, as if the presence in the system of the influenza bacillus discovered by Pfeiffer in 1892 in the purulent bronchial secretion, and later by Cann in the blood of influenza patients, so lowers the resistant power of the patient's blood and tissues that the pneumococcus is able to flourish in remote parts of the body with a frequency unknown before that period. It may indeed be the case that the presence of Pfeiffer's bacillus under certain conditions actually increases the virulent properties of the pneumococcus, as has been observed in the case of other mixed infections. But that as it may, it is undoubtedly true, as a matter of universal experience, that the number of atypical and anomalous cases of pneumonia has enormously increased since epidemic influenza invaded Western Europe and America, and further, that many of these cases, particularly the graver types, much more closely resemble streptococcic septicaemia than any definite type of pulmonary inflammation. I have frequently during the past few years had under my care a successive series of pneumonic cases, none of which exhibited practically any of the classic features either of catarrhal or croupous pneumonia, yet a few of which were rapidly fatal, with symptoms
suggestive of acute bacterial toxaemia. The prevailing form of the disease in recent years since the advent of influenza is one, the clinical features of which are not those of acute lobar pneumonia, but rather a mixture of catarrhal and fibrinous inflammation, the amount of consolidation bearing no definite relationship to the severity of the disease. On the other hand, it is right to state that influenzal pneumonias form a large percentage of the mildest types of pneumonic infection with which we are acquainted.

Evidence is rapidly accumulating in support of the theory that pneumonia is not only an infective disease with a tendency to metastases in the individual, but is also markedly contagious in a degree corresponding to, though even greater than, that in pulmonary tuberculosis. The evidence mainly rests on the comparative frequency of cases of house infection, outbreaks in public institutions, and epidemics in towns and cities. The latter have been already referred to with sufficient detail. As regards house infection, its occurrence is so frequent that instances must occur from time to time in the practice of most hospital and family physicians. During the past year I have met with several cases: in one instance the mother acquired pneumonia, two or three days afterwards one of the children was admitted under my care, and a day or two later one of the other children was
also admitted. Both were suffering from pneumonia, in one case broncho-pneumonia with extensive consolidation proved fatal, and in the other acute croupous pneumonia with high pyrexia, which recovered. I have at the moment of writing under my care at the (London) Royal Hospital for Diseases of the Chest, a little girl with croupous pneumonia who has just had her crisis. She had been an in-patient three months previously with the same disease, and went home quite well: a week before her re-admission her sister was taken ill with pneumonia. It would thus seem that this little patient contracted a second pneumococcic invasion by direct contagion.

The cases of house infection in regard to pneumonia are often indeed so definite that the actual incubation period can be fairly accurately determined. It is found, as a rule, to vary from 1 to 3 days. In the Lyon Medical, April 29th 1889, an interesting series of cases is reported. A shopkeeper's child was convalescing from pneumonia, when a servant-boy developed the disease: he was removed to hospital and another boy engaged to take his place, the latter wearing his predecessor's suit of livery and sleeping in the same bed. Two days afterwards he contracted pneumonia. A third boy was now engaged, who slept for two nights with the second boy, and 30 hours later fell ill of acute pneumonia. The incubation period
Dr. Eustace Callender published a striking series of five successive cases in one household: (1) a girl of 18 years of age had naso-pharyngitis with empyema of left antrum; (2) in 58 hours the girl’s father contracted acute pneumonia which proved fatal on the eighth day; (3) in 69 hours after visiting the latter, a friend was attacked with mild pneumonia; (4) in 45 hours after a visit to the sick-room a domestic servant was seized with acute sore-throat with dysphagia; (5) in 55 hours after exposure, a relative who visited one of the patients contracted acute pneumonia which proved fatal. The average incubation period in this series of cases was 57 hours.

Several epidemics of pneumococcic infection have been reported as occurring in asylums and other public institutions. Of these, one of the most complete reports is that published by Dr. Sinigar, the Assistant Medical Officer of Leavesden Asylum. The sequence was as follows:-

1. In the first week of December 1902, an adult male had left basal pneumonia, the sputum containing numbers of diplococci presenting all the staining and morphological characters of Fränkel’s pneumococcus. The resolution was extremely slow, and a month after the onset there were still physical signs at the left base, while film preparations of the sputum still
revealed pneumococci in large numbers.

2. On Jan. 17th 1902 an outbreak of pharyngeal and bronchial catarrh occurred amongst the male attendants. In all cases there was cough and expectoration of scanty viscid sputum, swarming with pneumococci. In only two cases was there actual pulmonary consolidation, one male nurse having a small area of impaired percussion, while another developed a typical apical pneumonia, from which he recovered.

3. At the end of January the female patients were attacked, six women suddenly contracting acute pneumonia: a week later four fresh cases occurred, one of which was followed by empyema and proved fatal: a week later 20 new cases occurred, 15 showing typical signs of lobar pneumonia, so acute that 12 (i.e., 80%) were fatal, while 5 were cases of acute bronchial catarrh with general aches and pains. During the next week 13 more women were attacked, 9 being cases of pneumonia, with 4 deaths, while the remaining 4 had each a slight pyrexia with general pains.

During these three weeks many precisely similar cases occurred amongst the male patients, 6 of whom died from pneumonia. In this epidemic, lasting for rather more than two months, 13 nurses, 17 male attendants, 43 female patients, and a large number of male patients, were attacked with the disease in one or other of its manifestations. The
epidemic suddenly subsided at the end of February. In all cases the pneumococcus was discovered in the sputum, and on no occasion could the influenza bacillus be detected. The gradually increasing severity of the cases was the principal feature of the epidemic. The effects were thus similar to the increase of virulence observed in the laboratory, on passage of the pneumococcus through rabbits or other susceptible animals. In one case,—that of a previously strong and healthy woman,—who was attacked in the middle of February, the pneumococcic invasion was so acute that she became unconscious in 24 hours and was dead within 48 hours,—a condition approximating in severity to pneumococcic septicaemia in mice and rabbits.

In light of such facts, it is not to be wondered at that the question of Prophylaxis has become prominent during the last few years. As the result of the epidemics already alluded to as occurring in American cities, the public health authorities in Michigan, Rochester (New York), etc., have made pneumonia a notifiable disease, placing it in the same category as diphtheria, typhoid fever, and other infectious and contagious diseases. It would probably be well for the community if notification of pneumonia, as well as of pulmonary tuberculosis,
were made compulsory in this country also. This is more especially necessary in cities and large towns where the prevalence and mortality of pneumonia is so much greater than in the country districts. In the returns of the Registrar-General for Ireland quoted by Sir John Moore in his monograph, the fact is emphasised that while the average annual mortality per 10,000 of the population from pneumonia throughout Ireland in the quinquennium 1894-98 was 7.9, the corresponding figure for the Dublin Registration district was 14.4. In other words, pneumonic affections kill twice as many of the population in a large town as they do in the open country. This difference may partly be due to the lowered resistive power of town-dwellers, but is no doubt largely the result of the infinitely greater facilities of intercommunication among the inhabitants in the streets, theatres, football-fields, public conveyances, and elsewhere. The increase of the urban population at the expense of the rural inhabitants is one of the most noticeable of modern social phenomena. There seems to be an ever-increasing tendency for people everywhere to congregate and mingle together. Though strenuous efforts are now made all over the country, with conspicuous success, to stamp out pulmonary tuberculosis, yet in the case of pulmonary pneumonocosis, a more acute though precisely
analogous infective disease and spread in a precisely similar manner by the ubiquitous specific virus, which has been isolated from the dust of hospital wards, cellars, and elsewhere; and further which exacts an annual death-roll in England and Wales alone of 32,000 persons and is thus the most universally fatal of all acute diseases, no systematic measures are taken in this country with a view to limit the incidence of the disease. My own view in regard to this matter is that the various branches and agencies of the National Association for the Prevention of Tuberculosis should add to their usefulness by advocating that exactly the same prophylactic measures should be taken in pneumonia as are now being carried out with much success in connection with pulmonary consumption.

Dr. E. F. Wells of Chicago lays down the following prophylactic rules:—

I. For the Individual.

1. The nasal cavity, pharynx, and mouth should be kept as clean as possible, and especially free from accumulations of mucus.

2. In coughing and sneezing, a protective cloth, preferably moistened, should be held before the mouth and nose.

3. This is especially necessary in the case of pneumonic patients and in those harbouring the
pneumococcus. In the case of such persons, the sputum should be destroyed before it has become dried.

4. Other individuals (viz., friends) should so far as practicable keep out of range of the extruded pneumococcus-laden secretions of infected persons.

II. For the Public.

1. Plainly and succinctly stated rules embodying the above recommendations should be widely and persistently circulated by the health authorities among the laity.

2. Practising physicians should be furnished with a supply of copies of these rules, with a request that they give a copy or else similar instructions to their patients and clientele.

3. The interest of physicians and humanitarians should be aroused by forming special societies and committees for the purpose of studying the problem and furthering the efforts of the various health bodies.

It seems to me that all these results could be most efficiently and economically achieved by the already established agencies of the Society for the Prevention of Tuberculosis, which now numbers amongst its adherents a large percentage of the members of the medical profession in all parts of the country.
It will now be well to consider the source
and channels of infection in pneumococcal septi-
caemia in the human subject. As the lungs are in
the majority of cases the primary seat of the inva-
sion and in many cases are the only organs where
gross morbid lesions are present, we must look to
inhalation by the air passages as being by far the
most important mode of infection. Much light was
thrown upon the causation of the disease by the
simultaneous discovery in 1880 by Pasteur in Paris
and Sternberg in America of the frequent presence
of virulent pneumococci in the saliva of healthy
persons. The former found it accidentally on
inoculating rabbits with the saliva of a child who
had died of hydrophobia, while the latter made the
same discovery on inoculating his own saliva into
rabbits as a control to some other experiments.
A large number of
with the saliva taken from healthy students in
Philadelphia and Baltimore, with the result that
the organism was found in 20% of the cases exam-
ined. Experimental inoculation in rabbits showed
that there was a great difference in the virulence
of the cocci as obtained from different individuals.
In some its saprophytic existence in the mouths of
healthy people often led to an almost complete loss
of virulent properties. Referring recently at the
54th Annual Meeting of the American Medical Asso-
ciation, June 1904 (Section of Hygiene) to the danger of persons carrying the diplococcus pneumoniae in their saliva, Dr. Sternberg stated that he had made frequent salivary inoculations from his own mouth into rabbits, producing fatal pneumococcic septicaemia, thus showing that he carried this microorganism in a virulent form in his salivary secretions. Netter found pneumococci in 15% of the saliva of healthy persons, Eyre and Washbourn in 30%: Fränkel himself and many other investigators have confirmed these results. In any particular individual the cocci are more numerous at certain times than at others, while occasionally they may be absent altogether.

They are also found in the nasal cavity of healthy people. Von Berser found the pneumococcus in 14 out of 57 individuals examined, i.e., in about 25% of the cases.

The organism is also frequently present on the tonsils and pharynx. Dr. Wells of Chicago examined the throats (in some instances on several occasions) of 135 persons, and found the pneumococcus present in 60 of them, or 45%. In the larger number of instances the diplococci were few in number, while in others they were numerous. In the case of a man who had had pneumonia six years previously, and at the time of examination
was suffering from acute tonsillitis, the virus was present in enormous numbers.

Dr. Wells made the important observation that while in some families the organism could not be discovered in any member of the family, in others, on the contrary, every or nearly every member of the family, including domestic servants, had the pneumococcus in their throats. He further noted that the majority of the families in which the pneumococcus was peculiarly prevalent had had more or less recently one or more cases of pneumonia, while in the case of those families in which the germ was not found, there was as a rule no such history. This observation, if correct, would form a ready explanation of the not-infrequent house-epidemics already alluded to.

It would thus seem that not only are the pneumococci distributed by actual contact, as in kissing, and by means of the dried sputum from infected individuals, but also by coughing and sneezing and consequent throwing-off of minute coccus-laden particles of mucus and saliva into the air, and in this way conducting to the dissemination of the virus, which can lead a saprophytic existence for a considerable time and at a later period become pathogenic. It is quite possible, as I suggested in a paper published last year that
the saprophytic forms found so commonly on the surface of the buccal mucous membrane may after penetration into and growth in the subepithelial tissues of the naso-pharynx, trachea, and bronchi, re-acquire a certain degree of virulence, rendering them capable of producing pathogenic results.

Dr. Bichu, the Director of the Laboratory of the Health Department in Chicago stated in his report to the recently appointed New York pneumonia Commission that his investigations convince him that the cause of pneumonia is generally a mixed infection of different pneumococci. He finds that rabbits injected intravenously with the sputum of a healthy person seldom develop pneumococcic septicaemia, but that an animal injected with the mixed sputa of two or more persons almost invariably does. He believes that although pneumococci are present in the secretions of the mouths and throats of most healthy individuals, they usually remain dormant until mixed with diplococci from other mouths, when they become active and dangerous. This observation has not, as far as I know, been confirmed. If true, even in a modified sense, it might account to some extent for sporadic cases occurring in perfectly healthy individuals, and also for the much greater prevalence in the urban population. In the future it may be found
advisable to recommend the routine use of antiseptic mouth-washes and gargles as a prophylactic measure in the case of all members of a household where pneumonia has occurred, particularly in the case of those brought into actual contact with the patient. The solutions used should have an acid reaction, as we know from cultural experiments that the virulent forms of pneumococci cannot thrive in an acid medium. These measures ought to be stringently carried out in the case of the patients themselves for many weeks after convalescence is established, as the virus is known to exist in the mouths and throats of such patients for prolonged periods. The same precautions should be carried out in the case of obscure sore throats, which are occasionally pneumococcal in character. It is probable also that the continuous vaporisation of such volatile antiseptics as creasote would act as a prophylactic by obtaining access to the tracheal and bronchial mucous membranes, the secretions of which, like those of the upper air passages of healthy persons, frequently contain pneumococci. It would of course be impossible to recommend the general use of such antiseptic mouth-washes, gargles, and inhalations in the case of all persons exposed to chills, depressing influences, and other predisposing conditions.

There is, however, one type of case where the use of
such measures is readily applicable. I refer to post-operation pneumonia. I have recommended and actually employed such measures in the case of patients who were about to submit to a serious operation: I am convinced that if the use of such prophylactic means were included in the ordinary preparation of the patient for operation, we would hear much less of post-operation pneumonia. I was lately discussing this matter with a London surgeon who during the past 12 months has had several deaths from pneumonia after laparotomies with no suspicion whatever of antecedent abdominal sepsis. If in the future pneumonia cases come to be isolated and treated in special hospitals like other contagious and infectious diseases, then it will become an easy matter to destroy the bulk of the pneumococci in the mouths and throats of the patients during convalescence and before they are sent back to their respective homes.

Bazancon and Griffin reported the results of an examination of the tonsils of 40 healthy persons under various conditions. They used the serum of a young rabbit as their culture-medium, and found from a bacteriological examination of the secretion from the tonsils that the pneumococcus was present in every case. This result is very different to those of Wells, already referred to,
as he only found the virus in 45% of the cases. In all such cases there should be experimental inoculation of rabbits or mice with a measured amount of the cultures so that their virulence could be compared with that of a standard culture according to Washbourn's method. In this way the proportion of saprophytic and pathogenic varieties could be fairly accurately determined.

Of still greater importance, however, in connection with pneumococcic invasion is the presence of pneumococci in the lungs of healthy persons. Dürck examined the lungs of 13 children who had died from some other disease, and found pneumococci present no less than 12 times. Polynère also found pneumococci in normal lungs. The existence, then, of the virus in the mouths and throats of healthy persons, and still more its existence in their lungs, seems obviously to have a very important bearing on the origin of pneumococcic pulmonary infection, and accounts, as in the case of tuberculosis, for the large preponderance of cases where the lungs are the main or only seat of the disease. A chill, an attack of influenza, an abdominal operation, or any other depressing cause may at any time lower the resisting power of the lung to the invasion of the ubiquitous pneumococcus; and as there is little or no defence against the invasion once the germs
have reached the alveoli in a virulent form, one can readily understand why pneumonia should be one of the most widespread and common of acute diseases.

Coming now to the question of the mode of absorption and channels of infection in the lung itself, the problem is probably essentially the same as that in tuberculosis and other bacterial affections. The inhalation experiments of Arnold and others, in connection with artificially-produced anthracosis, have shown that bacteria and other particles find their way into the peribronchial and perivascular lymphatics and are also found in the adenoid tissue of the lung in connection with these lymphatics, and in the bronchial glands. The bulk of evidence is in favour of the view that no absorption of particles takes place through the mucous membrane of the trachea and bronchi. However, believes that such absorption does take place, and if this is so, it will account for the cases of pneumococcal infection being secondary to bronchial inflammation. Tchistovitch's experiments indicate that the particles are taken up by phagocytes in a few hours after their introduction, both in the alveoli and lymph-spaces. The first cells to take them up are the lymphocytes, small macrophages, and polynuclear cells, while at a later period come the epithelioid phagocytes, resembling alveolar epithelial cells but not derived from them but from the endothelium.
of the blood-vessels and lymphatics. In the alveolar blood-vessels themselves there are also found a large number of similar polynuclear leucocytes, lymphocytes, and macrophages, which exert a similar phagocytic action inside these vessels.

These experiments are important in connection with the question of septicaemia. Let us contrast pulmonary tuberculosis and pulmonary pneumonocosis. It is probable that in the case of the tubercle bacillus,—an organism of only moderate inflammatory virulence,—in the large majority of cases the germs that have escaped phagocytic destruction in the alveoli and lymph-spaces are retained in the peribronchial and perivascular adenoid tissue and are partially destroyed there, while the remainder pass on to the bronchial glands. It is thus quite exceptional to get a general tubercular blood-infection in the course of pulmonary tuberculosis. On the other hand, such an acute inflammation-exciting virus as the pneumococcus cannot be similarly dealt with when present in large numbers. The few that are present in healthy persons are doubtless being constantly destroyed in this fashion. When, however, a chill or exposure to cold occurs, the temporary congestion of the alveolar capillaries thereby induced and the corresponding slight functional alteration in the
cells lining the air vesicles, render them less potent in resisting the pneumococcic invasion. As a result, acute pulmonary inflammation (pneumonia) ensues, and the cocci multiply rapidly in the inflammatory exudation. The protective mechanism is now no longer effective. The pneumococci are present in such enormous numbers that many escape into the small blood-vessels and so into the general bloodstream, giving rise to a pneumococcic septicaemia. The violent respiratory movements involved in coughing readily lead to rupture of minute blood-vessels in the inflamed lung, and so facilitate the absorption into the bloodstream. The mere presence of rusty sputum of itself serves to indicate the number of minute breaches of continuity that must exist in the alveolar capillaries and small blood-vessels. It may be mentioned that Fränkel and Reiche have found the pneumococcus in the kidneys in 22 out of 24 cases of pneumonia examined post-mortem.

The frequent occurrence, then, of pneumococcic septicaemia secondarily to pneumonia is thus readily understood. It is more than probable that the converse is also true, and that occasionally though more rarely we may get a pneumonia secondary to a general blood infection. I have already alluded to inoculation experiment in rabbits, in which both lobar and lobular pneumonia have been produced.
by intraperitoneal injection of pneumococci, and this too in animals where lung inflammation is probably the least common of all manifestations of pneumococcic septicaemia, as proved by the fact that even intratracheal injections are generally followed not by pneumonia but by pleurisy, pericarditis, or other manifestations as accompaniments of a general pneumococcic septicaemia. Human pneumonia is probably a much more common sequela to general blood infection originating elsewhere, as human lungs appear from all evidence to form an especially suitable nidus for the growth of the pneumococcus.

Amfrecht, on the other hand, has made numerous experiments on the absorption of coloured particles by inhalation, and states that there is no absolute proof that in genuine croupous pneumonia in man the virus is primarily developed in the blood and from there attacks individual organs including the lungs. He bases his view on the assumption that pneumonia begins in the bronchioles and alveolar passages, and from there spreads to the surrounding structures, and also on the fact that Weigert's method of staining shows that the cocci are mainly situated in the cellular alveolar exudation and within the cells themselves. He might have added, however, that there is no absolute proof to the contrary.
Baumgarten and Ribbert believe that in pneumonia in the human subject the pneumonic virus always enters the lungs from the respiratory passages, remains there, and only later may become localised in other organs.

The balance, however, of experimental, clinical, and more especially *post-mortem* evidence is in favour of the view that the invasion of the lung in the course of a general blood infection is by no means an infrequent occurrence. The pneumococcus may enter the body in other ways than through the lungs, as is proved by the fact that we occasionally meet with various pneumococcic lesions in distant parts not preceded by pneumonia, such as otitis, endocarditis, pericarditis, meningitis, peritonitis, arthritis, nephritis, conjunctivitis, and other manifestations which we shall presently deal with in detail.

There is a marked tendency to the occurrence of multiple lesions in pneumococcic infection, in many respects similar to those occurring in the course of septicaemia associated with the streptococcus pyogenes. In fact, clinically the two conditions can often not be differentiated in the absence of an antecedent pneumonia, apart from bacteriological examination of the blood, as the symptomatology is practically identical in both affections.
It will be well to examine the various individual lesions *seriatim*, mainly with the view of arriving if possible at definite conclusions in regard to the source and channels of infection. Let us consider these as far as possible in the order of frequency and importance.

The commonest channel of infection in man is undoubtedly the respiratory tract, thus accounting for the marked preponderance of pneumonia and frequently also of pleurisy, empyema, with occasional extension to the mediastinum and pericardium.

I. PNEUMONIA.

1. Primary. The frequency of pneumonia, both lobar and lobular, as a primary manifestation of pneumococcic infection is so self-evident as to require no comment.

2. Secondary. The evidence of secondary pulmonary invasion is mainly based on three grounds:

   a. The occasional occurrence of single and multiple lesions in the human subject some time (days or weeks) before a pulmonary lesion manifests itself.

   b. The occurrence of cases of pneumonia with resolution of the morbid process followed by metastases, and later on by re-invasion of the pulmonary tissue.

   c. The possibility of the artificial production
of pneumonia in rabbits by subcutaneous or intra-peritoneal inoculation.

It is extremely probable that in double pneumonia the involvement of the second lung is by no means invariably the result of direct extension from the first affected, but may occasionally be the result of secondary blood infection. This, too, is doubtless the explanation of some of the cases of relapse occasionally observed in pneumonia. I have frequently seen, particularly in children, pneumonia of the base go on to resolution, and some days later (and in one case now under observation three weeks later) by consolidation of the other apex. A girl of 13 was under my care at the Royal Chest Hospital last year with signs of consolidation of the left lower lobe; two days later signs of acute pericarditis appeared. The physical signs at the left base entirely disappeared, the pyrexia subsided, and the patient appeared to be rapidly recovering. A few days later she had a relapse, with recurrence of pyrexia, the physical signs of consolidation developed at the right (opposite) apex, she became rapidly worse and died on the following day. At the post-mortem examination which I conducted the following day, I found that the left lung had completely resolved and was quite crepitant. There was, however,
right apical hepatisation, fibrinous pericarditis, and recent vegetations on the aortic valve. Pneumococci were found in the affected lung and pericardium. The occurrence of acute endocarditis indicated a general septicaemic process, and the involvement of the right apex was believed to be the result of a secondary invasion, though of course there was the possibility of direct extension by way of the inflamed pericardium and mediastinal tissues.

The migratory pneumonias described by Dr. Dreschfeld of Manchester probably come under the category of secondary blood infections, and appear to be analogous to the occurrence of scattered miliary tubercles and foci of caseous broncho-pneumonia in acute tuberculosis. These are characterised by the successive invasion of different portions of the lung, while the physical signs disappear from the parts first attacked; the affected portions clear up with great rapidity, while other portions in turn become affected with congestion or consolidation. The course of such a case may be prolonged for several weeks. Sir Richard Douglas Powell states that this migratory pneumonia probably coincides with the pythogenic form described by Murell.
which is characterised by a more insidious onset, a more fluctuating type of temperature, an incomplete crisis, the physical signs of imperfect consolidation, the asthenic condition of the patient, and its peculiarity in attacking successively different portions of the lung. In fatal cases, and such cases are frequently fatal, Dr. Dreschfeld found the affected portions of the lung teeming with capsulated diplococci. Last year I was called by a friend to see in consultation a well-developed athletic man of 22 years; he was said to have had influenza some weeks before coming under observation. There was a high, remittent, pyrexia, the evening temperature rising to 104° and even 105°F., there was marked dyspnoea, an anxious expression of face, and a rapid, feeble pulse. There was acute abdominal pain and some distension and loss of movement, suggesting peritonitis. A surgeon was sent for, but decided not to operate, in view of the weak condition of the patient. There was some cough and expectoration. The sputum contained pneumococci, while the blood obtained from the lung by an exploring syringe also contained pneumococci; the blood taken from the lobe of the ear was found to be sterile. There was a moderate degree of leucocytosis. There were areas of dulness and bronchial breathing in the right upper lobe, and
smaller patches elsewhere: some of those patches cleared up, to be replaced by other similar patches in the left lung. The temperature continued to be of high remittent type until the 12th day, when he succumbed from cardiac failure. A post-mortem examination could not be obtained. Netter as the result of the analysis of 121 post-mortem examinations states that in adults lobar pneumonia was the primary seat of pneumococcic infection in 65.95% of the cases.

II. Pleurisy and Empyema.

Pleurisy and empyema occurring in the course of pneumonia are probably always pneumococcic in origin, and when occurring on the same side are the result of direct extension from the underlying lung. They may also develop on the opposite side of the chest. I saw 4 such cases in 1900, and, though probably in the great majority of cases these are also the result of direct extension, they may occasionally be due to secondary blood infection. Foulerton states that the initial pleural effusion which occurs to a greater or less extent in probably every case of lobar pneumonia is in the majority of cases due at first to the irritation of toxins passing through from the neighbouring infected portions of the lung,
and not to the presence of the cocci themselves in the pleural sac: in support of this view he states that, with one exception, he has never been able to find the pneumococcus in a non-purulent pleural effusion sufficiently extensive to require tapping.

As physician and pathologist to the Royal Hospital for Diseases of the Chest, I have had opportunities of investigating a large number of cases of sero-fibrinous pleurisy and empyema. My observations have confirmed the generally-accepted view that the large proportion of empyemas in children are pneumococcic in origin, while a much smaller proportion of those in adults are due to the same organism. Foulerton finds that 75% of adult empyemas are streptococcic in origin, and 25% pneumococcic, while in the case of children the exact converse is the case. In pneumococcic empyemas in adults I have generally found either clinical or post-mortem evidence of preceding or intercurrent pneumonia, though this has not invariably been the case. In children, on the other hand, there is frequently no such evidence, the empyemas being not uncommonly primary, and the only discoverable manifestation of the pneumococcic infection, though in children also there are often preceding or intercurrent croupous or catarrhal pneumonia. In searching for the
pneumococcus I used the inoculation method in all doubtful cases, in addition to cultivation on suitable media. Rabbits were in all cases employed, as being extremely susceptible to pneumococcal infection. The routine method adopted was to inject about 1 cc. of the pus, either into the peritoneal cavity of the rabbit or into the subcutaneous tissues of the abdomen, which had previously been shaved and carefully disinfected. The needles were also boiled before use. If the pneumococcus was present in the exudate, the animal usually died within 18 to 48 hours in the case of intraperitoneal inoculations, and in from one to several days when the pus was injected into the subcutaneous tissue. The blood from the rabbit's heart was then examined, and was generally found crowded with encapsulated diplococci: cultures were also made from the blood, the medium employed being blood-agar prepared according to Dr. Washbourn's formula. It is frequently possible to tell whether the pus obtained on exploration of the chest is pneumococcic or streptococcic in origin by the characteristic naked-eye appearances, which are quite different in the two varieties. In the case of pneumococcic empyemas the pus generally consists of a yellowish-grey fluid of a uniform thin consistence throughout on immediate
withdrawal, but on being put into a test-tube and allowed to stand, it is found that the pus sinks to the bottom of the glass, and within a very short time we have a greyish-deposit of pus, occupying from one-quarter to one-third of the whole, the upper two-thirds or three-quarters consisting of almost clear though slightly turbid supernatent fluid. This appearance stands out in marked contrast to that presented by streptococcic pus, which is of uniformly thick, yellowish consistence throughout, and does not alter materially on standing. This auto-sedimentation is so characteristic of pneumococcic pus when obtained from the pleural or peritoneal cavities that in the absence of facilities for accurate bacteriological examination, its presence may be taken as almost certainly indicative of the presence of pneumococci. The clinical value of this fact cannot be over-estimated, as the prognosis is so much more favourable in the pneumococcic variety of empyema. Some of the empyemas investigated were of mixed bacteriological origin: in those cases were the empyema had ruptured into the lung, and in those where the pus had not been examined until 24 hours after death, (as in those empyemas only discovered post-mortem), the presence of the accompanying streptococci or other organisms was probably due to secondary invasion.
As regards the frequent occurrence of primary empyema in children, Drs. Eyre and Washbourn's experiment by intratracheal inoculation in rabbits proved that the pneumococci may actually enter through the lungs and yet produce metastatic lesions without leaving a trace of inflammation in the lung itself. The method they employed was to anaesthetise a rabbit and pass a catheter through the larynx into the trachea: 1 cc. of a broth cultivation of the pneumococcus was poured down the catheter. The animal was killed some time after. There was usually found pleurisy and pericarditis, but, with one or two exceptions, no pneumonia.

It may be concluded then that the source of infection in the great majority of empyemas is by way of the respiratory passages and lungs, and that occasionally the infection is through the general blood stream. That the latter hypothesis is correct is proved by the ever-increasing number of reported cases where empyema has developed secondarily to other manifestations, without any lung involvement. My friend Dr. Langdon Brown, in his analysis of 39 cases of multiple pneumococcal infection at St. Bartholomew's Hospital, states that empyema appeared to be the starting point of a general pneumococcal infection in 8 cases (i.e., 20%), and occurred as a complica-
tion of such an affection in 7 cases (i.e., 17.5%). Empyema was the primary lesion in 8.53%.

III. Bronchitis.

We shall dismiss this subject in a few words, as the rôle it plays in originating pneumo-
ococcal septicaemia is extremely small.

The pneumococcus can frequently be ob-
tained from the bronchial secretions of patients who have died from some other disease. Marfan states that in all the cases of bronchitis he has examined, he has invariably found the pneumococcus in the secretions. A certain degree of bronchitis is, of course, present in all cases of lobar pneumonlia, but in a certain proportion, acute bronchitis may be a serious complication. In an analysis I made of 45 successive cases of lobar pneumonia admitted into King's College Hospital in 1900, I found that 7 were complicated with severe bron-
chitis. Menetrier at a meeting of the Société Médical des Hopitaux de Paris in December 1904 records an extremely rare case of membranous pneumococcic bronchitis in a boy of 2 years of age: for a period of two months he expectorated arborescent membranes loaded with pneumococci which were obtained in pure culture, and the inoculation of which into mice produced fatal pneumococcic septicaemia.

I have especially noted the presence of
pneumococci in cases of chronic bronchiectasis. I have notes of some ten cases, partly occurring in my own practice and partly in that of Dr. Michael Foster of San Remo, who has made a special study of this question. In all of these, pneumococci in large numbers were found. I have alluded to one of them in referring to the question of the various degrees of virulence of the pneumococcus in the human body.

The reason that trachitis and bronchitis so seldom give rise to general infection is a physiological one, all experimental investigations going to prove that their mucous membranes are not absorbing surfaces. Nasal, tracheal, and bronchial catarrh, however, on account of their frequency as independent affections, play a not unimportant part in maintaining the viability and virulence of the pneumococci normally present in the buccal and other secretions of healthy persons, and so predispose to the occurrence of pneumonia, besides constituting a course of contagion to other persons. Capillary bronchitis or bronchiolitis, on the other hand, is frequently the origin of a general infection, but this is due to the fact that capillary bronchitis is always accompanied by a greater or less degree of alveolar inflammation, or, in other words, broncho-pneumonia. In Netter's 121 post-mortems bronchiolitis and broncho-
pneumonia were the primary lesions in 15.85% of the cases. In Dr. Longden Brown's series of cases (loc. cit.), broncho-pneumonia was the primary seat in 9 instances, or 22.5%.

IV. Pericarditis.

Professor D. A. Welsh, of Adelaide University, states that in his experience most cases of fibrinous pericarditis with sero-purulent effusion are due to pneumococci, whether an antecedent pneumonia can be traced or not. Pericarditis occurs in the course of pneumonia in a proportion varying from 0.5 to 5% of cases. Both clinical and post-mortem evidence, as well as experimental investigation, prove that in the large majority of cases the involvement of the pericardium is by means of direct extension from the lungs by way of the pleurae and mediastinal tissues. A considerable number of my own cases of pericarditis complicating pneumonia have been in connection with pneumonias involving the left lung, as in the fatal case above recorded, but Dr. Kingston Fowler states that an analysis of a large number of cases convinces him that it is not, as is generally supposed, especially frequent as a complication of left-sided pneumonia. Bryant records a case where he had the opportunity of carefully studying the spread of the infection to the pericardium, in
which the lymphatics were undoubtedly the channels of infection. He made a post-mortem examination on a case of right pleuro-pneumonia, and found the right lung adherent to the adjacent part of the pericardial sac by means of recent lymph. There was commencing pericarditis, but only the outer two-thirds of the pericardium covering the right ventricle were involved: the most advanced changes were found in the outer part of the right ventricle, which was covered with small flakes of lymph: then internal to this came an area of pericardium, dull and granular in appearance: then a zone showing increasing vascularity: and finally the pericardium covering the outer third of the right ventricle: while the whole of the left ventricle was smooth and shiny, and appeared to be perfectly healthy.

I have seen several cases also where purulent pericarditis has occurred as a complication of empyema, and one case where acute pericarditis with sero-fibrinous exudation was followed left-sided pneumococcic pleurisy with sero-fibrinous effusion.

The intratracheal inoculation experiments in rabbits, already described, also point to pericarditis as frequently occurring by direct extension from the pleurae, pleurisy and pericarditis usually
occurring together. On the other hand, in the case of rabbits dying from pneumococcic septicaemia as the result of intraperitoneal or subcutaneous inoculation, I frequently found pericarditis and no trace of pleuritis, the serous inflammation being thus secondary to general blood infection.

In man, too, cases have been recorded, though very rarely, where pericarditis has been the only manifestation of infection to be found post-mortem. I do not happen to have seen such a case, though I have observed a considerable number.

Among 48 cases of pneumococcic infection in children, investigated by Netter, in one only was pericarditis considered to be the primary localisation, while among the 121 fatal cases examined after death, there was not one such instance.

A most valuable paper on suppurative pericarditis in children has been published by Dr. George Still. The pericardial fluid was examined bacteriologically in 3 cases, and in 11 of these the pneumococcus, generally in pure growth, was discovered. In several of the cases with accompanying pleurisy or empyema, it was observed that the patch of lymph or loculus of pus was so situated that a direct infection of the pericardium seemed very unlikely, if not
impossible: the presence of suppurative meningitis in 7 of the cases made it almost certain that in these at least a blood infection had occurred, and he was strongly of opinion that the pneumococcal pericarditis was in some of the cases the result of a similar blood infection, rather than of direct extension from the pleura.

V. Endocarditis.

This is essentially a streptococcal lesion, as there is practically no other channel by which the infection can be conveyed to the heart valves, unless associated with acute pericarditis. Its present therefore is conclusive evidence of the presence of some septicaemia. It was Dr. Osier who in the Goulstonian Lectures first drew attention in this country to the comparative frequency of ulcerative endocarditis as a complication of pneumonia. In Montreal he found that 11 out of 23 cases of infective endocarditis were associated with pneumonia. Of 103 fatal cases of pneumonia, there were 16 with acute endocarditis, 11 of these being of the malignant form, and 5 being associated with acute meningitis. The condition is common in elderly persons. There was a percentage of 16 in Dr. Osler's fatal cases. This percentage is higher than is usually recorded; the more generally accepted percentage is 0.3% of all cases, and 4% of fatal ones.
As I myself in a comparatively limited number of cases of fatal pneumonia have observed the condition post-mortem in three successive cases, I believe Dr. Osler's statistics are more nearly correct. In a number of my own cases there were simply numerous tiny recent vegetations on the anterior mitral valve or in both, though occasionally there were large warty excrences with or without ulceration.

It is said that a characteristic feature of pneumococcic endocarditis is the large size and broad base of the vegetations and their marked tendency to ulcerate. In Dr. Osler's 16 fatal cases, 5 were warty and 11 ulcerative. The endocarditis often occurs early in pneumonia, and soon after its onset ulceration may occur or it may be delayed for several weeks. The pneumonia may even run its course to the crisis with nothing to draw attention to the heart, and often a few days after apparent convalescence signs of embolism with pyrexia supervene: on the other hand, disintegration of the valves with evidence of general septicaemia before the pneumonia has run its course may occur, and in such a case death takes place in a few days. The occurrence of purulent meningitis and arthritis is frequently
observed in cases of pneumococcic endocarditis.

Dr. Preble has reviewed 50 cases published since Netter's paper in 1885, where 82 cases were referred to. The percentage of pneumococcic cases in all forms of infective endocarditis is 22. As regards the valves affected, he found that out of the 141 cases recorded, the aortic valves were affected alone in 56, the mitral valve in 40, the aortic and mitral in 20, the tricuspid alone in 12, the aortic, mitral, and tricuspid in 5, the pulmonary in 5, the mitral and tricuspid in 2, and the aortic and tricuspid in 1. The left-sided lesions therefore largely predominate. The greater number of my own cases were in the aortic valve, though I found vegetations on both aortic and mitral valves in several cases, and in two lesions of the tricuspid, one of them being associated with vegetations of the mitral also.

In 10% of the 50 cases recorded by Preble, infarcts occurred in different organs. All observers note the frequent association with meningitis. Netter found this association in no less than 45 cases out of 63.

The influence of antecedent endocarditis as a predisposing cause of pneumococcic endocarditis is considerable. Evidence of old endocar-
Endocarditis was found in 12 out of Preble's 50 cases. The occurrence of the endocarditis is often difficult to detect: aortic diastolic murmurs are the most characteristic. Dr. Wells states that the valves may be loaded with vegetations without giving rise to any physical signs. The pyrexia of the pneumonia may pass into that of the endocarditis, but there is often an interval of a few days' apyrexia. In 20 cases this interval varied from 1 to 12 days. The gravity of the prognosis is sufficiently indicated by the fact that recovery took place in 4 only out of 132 cases. In 109 cases the duration of the illness varied from 7 to 180 days, the average being 30 days. Most cases are fatal, and often within a fortnight. Endocarditis may occur without pneumonia. The diagnosis can then only be made by finding the pneumococcus in the blood. In Netter's series of 122 fatal cases of pneumococcal infection, endocarditis is mentioned as the primary localisation in 1.12%. In Dr. Langdon Brown's series of 37 cases, it was the primary manifestation in 3, or 7.5%.

VI. Meningitis and Encephalitis.

Meningitis is a not uncommon, and generally rapidly fatal complication in pneu-
monia. Professor Hewlett believes that fully one-half of the cases of purulent meningitis are pneumococcic in origin. Its frequent association with infective endocarditis has already been noted. In referring to the question of relapse in pneumonia, I alluded to one of my cases in which this complication proved fatal.

In fact, next to the lungs and pleuræ, the cerebro-spinal membranes are probably most frequently attacked by the pneumococcus, not only in association with pneumonia but also as a primary independent condition, as many primary cases have been recorded. The meningitis is usually sero-purulent and widely spread, involving both cerebral and spinal membranes. W. J. Barras records a case of primary pneumococcal meningitis, closely resembling epidemic cerebral spinal meningitis.

Weichselbaum regards the pneumococcus as one of the most frequent exciters of both primary and secondary meningitis. Both he and Netter believe that pneumococcic meningitis may appear in epidemic form. Dr. Councilman of Boston in a report on sporadic meningitis records 10 cases due to the pneumococcus, and in 2 of these the infection was primary, no other lesion due to the organism being discovered. Of 61 cases of sporadic meningitis observed by

91.
him during the past 5 years, 18 were due to the pneumococcus. In addition to the primary ones, 6 were secondary to otitis media and mastoiditis, 2 secondary to ulcerative endocarditis, while the others were secondary to pneumonia and pleurisy.

Foulerton in recording a primary case of pneumococcal meningitis in a man of 30 years of age, states that pneumococcal meningitis may be acute and purulent, or chronic and sero-fibrinous. When the previous form is the only lesion and apparently the primary one, it is possible that infection occurs by way of the nose of middle ear. As regards the latter, association of meningitis with pneumococcal otitis media has been occasionally observed.

Ahfrecht goes so far as to say that even in cases of post-pneumonic meningitis, the infection may occur by direct extension from the thorax along the cellular tissue in the neck to the submucosa of the pharynx, and from thence to the accessory cavities of the nose. He states that he found pneumococci in all of these situations. A continuation of the process from the accessory cavities of the nose and particularly from the ethmoidal labyrinth to the surrounding
lymph channels and from thence to the meninges, produced affections of these membranes. After recounting this circuitous route, Anfrecht admits that the possibility of the virus reaching the meninges by the blood-stream cannot be excluded. To my mind, all evidence goes to prove that the great majority of cases of post-pneumonic meningitis are due to direct blood infection, but that in the case of primary meningitis a certain proportion are secondary to nasal catarrh or otitis media, though in many no such association exists.

Henke records 4 cases of primary pneumococcic meningitis. In Netter's series of 121 fatal cases of pneumococcic infection, meningitis was the primary lesion in as many as 13%. My own cases have mostly been associated with infective endocarditis.

Lazarus Barlow describes two cases of posterior basal meningitis, due to the pneumococcus. Last year I had a case of cerebral abscess, secondary to otitis media, where I found the pneumococcus in the pus, and inoculation from which produced pneumococcal septicaemia in a rabbit.

Bullard and Sims record a case of diffuse pneumococcic encephalitis following acute broncho-pneumonia in a man 50 years of age. They found oedema and numerous punctiform haemorrhages in
the right atrium ovale and elsewhere. Pneumococci were found in abundance in the oedematous areas and also in the other viscera.

**VII. Peritonitis.**

It was Cornil in 1886 who first described pneumococcal peritonitis. In the same year Netter demonstrated the presence of pneumococci in the peritoneal fluid of patients who had died of pneumonia although in these cases there was no evidence of morbid changes in the peritoneum. So numerous, however, have been the cases of pneumococcal peritonitis recorded within the past 2 or 3 years that the condition has come to be regarded as a by no means infrequent manifestation of pneumococcal invasion. Between the years 1900 and 1904, more than eight contributions on the subject with detailed notes of cases have been published in the "Lancet" alone. It is probable that a certain proportion at least of these cases of pneumonia described in the older works, where abdominal pain has been a marked feature simulating acute abdominal disease, have actually been cases where there has been a varying amount of peritoneal inflammation which has subsided or gone on to a fatal peritonitis. I am convinced also that a considerable number of the cases of so-
called idiopathic acute peritonitis with no discoverable cause are in reality cases of primary pneumococcal peritonitis. A case in point, that of a young married lady, came under my observation last February, 1905. There was a history of a chill occurring at her menstrual period: a week later I found all the signs of acute general peritonitis. I called in a surgeon, who had the patient removed to a hospital and at once performed laparotomy. Acute general peritonitis was found, with a quantity of sero-fibrinous exudation. There was no appendicitis or affection in the abdominal viscera, nor was there pyo-mammitt salpinx or other lesion of the pelvic viscera. The fimbriated extremities of the Fallopian tubes were extremely congested: numerous flakes of lymph were visible over the coils of small intestine. The pelvic peritoneum was the most acutely inflamed and extensively involved. No gross lesion being discoverable, the abdominal cavity was simply sponged, a drainage-tube inserted, and the abdominal wound closed up. The patient did extremely well for a few days, when pneumonia of the right lung, followed by patchy consolidation of the left developed, from which she succumbed 10 days after the operation. Unfortunately the peritoneal fluid was not examined.
bacteriologically, but it is interesting to note
that while the patient was in hospital a little
child in the house developed acute pneumonia.

That peritonitis is, however, a com-
paratively rare manifestation is shown by the fact
that out of 162 cases of pneumococcal infection
reported by Netter, the peritoneum was involved
in only two, while Fawcett, from an analysis of
182 fatal cases of lobar pneumonia occurring at
Guy's Hospital, found that there were only 5 instances of peritonitis. It is doubtful, how-
ever, if in all these cases the peritoneum was
sufficiently carefully examined.

Dr. Langdon Brown, in an analysis of 10
fatal cases of pneumococcal peritonitis occurring
at St. Bartholomew's Hospital, found that in two
instances it was primary, there being no other
discoverable lesion: in one it was fol-
lowed by acute nephritis: in 5 cases it followed
empyema, in one pyosalpinx, and in one only
broncho-pneumonia. There was often a multiplicity
of serous inflammation. Thus the peritoneum,
pleura, and pericardium were all involved in
3 cases, the peritoneum and pleura in 3, and the
peritoneum and pericardium in two.

At the meeting of the Clinical Society
held Jan. 8th 1904, Sir Dyce Duckworth and Mr.
Howard Marsh reported at length a case of pneumococcal peritonitis associated with appendicitis. At the discussion which followed, I heard the view expressed that the peritonitis was probably secondary to a pre-existing empyema by way of the blood-stream. Mr. Marsh did not think the appendicitis was the primary focus. The patient made an excellent recovery after laparotomy.

Shaw and Herbert French have actually recorded a case of pneumococcal appendicitis with peritonitis. It was that of a girl of 18, who was seized with violent abdominal pain on April 3rd 1904: there was vomiting on the 4th, the day of admission, and the patient was too collapsed for laparotomy to be attempted, and died a few hours after admission. At the autopsy, acute general peritonitis was found, and about one pint of pale turbid fluid discovered in the peritoneal cavity. The lymph was thickest in the region of the caecum and vermiform appendix. Pus was found in the interior of the appendix: this was examined by Dr. Eyre, the Hospital bacteriologist, and yielded an almost pure culture of pneumococci. This wase appeared therefore to be one of primary pneumococcal appendicitis. Like other pneumococcal serous inflammations, the exudation is either
sero-fibrinous or purulent. In the purulent
form the pus is extremely like that of empyemetic
pus which has already been described and shows the
same tendency to auto-sedimentation. The exudate
is very coagulable and rich in fibrin of greenish
yellow color and not offensive.

Pneumococcal peritonitis is most commonly met
with in children and young people. Only two out
of the 17 cases collected by Dieulafoy having occurred in adults. Amongst children it is more common
in girls than in boys although in adults a greater
number of male cases have been recorded.

Von Brün discusses the general features of
pneumococcal peritonitis in the course of which he
states that the disease may be primary in the peritoneum or may be secondary to the affections of the
lungs, pleura or middle ear.

The prognosis is favorable, recovery being the
rule after operation. Spontaneous recovery on
the other hand, as possible, is extremely rare.
In the primary peritoneal inflammations the explanation of their origin is very unsatisfactory although
in a certain proportion of cases the appendix may be
the primary seat of mischief.

The fact of the large proportion of cases
occurring in girls as compared with boys [Brun; 11
girls to 3 boys, Quehaut 27 girls to 6 boys,
Dieulafoy 17 girls to 2 boys] suggests the possi-
bility of infection by way of the vagina, uterus and Fallopian tubes. The acuteness of the pelvic peritonitis particularly around the end of the Fallopian tubes, suggests that this was the channel of infection in my own case above recorded.

Bryant in recording three cases of pneumococcal peritonitis maintains that the pelvic peritoneum is usually found to be the most extensively involved.

Langdon Brown indeed records an instance of general pneumococcal infection complicated by vulvitis and also mentions the case of a woman of 30 years of age in which a pyo-salpinx was followed by pneumococcal peritonitis, pleurisy and purulent pericarditis.

Aufrecht records experiments where he readily produced by subcutaneous inoculation acute endometritis with abortion in pregnant susceptible animals, the physiological congestion of the parturient uterus rendering it a suitable nidus for the growth of the pneumococcus.

Boulay also has isolated the diplococcus pneumoniae from the uterine cavity while Witte has found the pneumococcus in four out of 39 cases of salpingitis examined.

A certain proportion of the cases of acute peritonitis are no doubt due to direct extension from the lungs and pleura by way of the lymphatics.
of the diaphragm.

Dr. Bryant has found post-mortem in cases with a past history of pneumonia or pleurisy that the upper surface of the liver is often firmly attached to the under surface of the diaphragm by means of fine fibrinous adhesions, while the base of the right lung is similarly fixed to the upper surface of the diaphragm. He is of opinion that a large majority of these cases are examples of cured local pneumococcal peritonitis.

Even allowing for the possibility of recurrence of peritonitis by direct extension from the diaphragm, alimentary canal, (e.g. appendix) and the pelvic organs, there still remain a large percentage of cases where no such origin can be discovered, where the condition is doubtless the result of blood infection; in other words that it is a manifestation of general pneumococcal septicaemia.

VIII Arthritis.

We have already referred to some pyaemic manifestations of pneumococcal infection in the form of suppurative pleurisy, pericarditis, and peritonitis and have also mentioned cerebral abscess. Suppurative arthritis is another very characteristic pyaemic lesion and is preeminently a manifestation which is practically invariably due to blood infection.

It was Leroux in 1899 who first drew attention to arthritis as a complication of pneumonia,
though a case was reported\(^{(67)}\) at a meeting of the Société des Hôpitaux de Paris on November 25th 1898.

In 1901 Dr. Cave\(^{(67)}\) published a series of cases of suppurative arthritis following pneumonia.

During the last few years a large number of cases have been recorded so that it is no longer considered such a rare condition as was formerly supposed.

Raw\(^{(67)}\) has published a series of 7 cases following pneumonia and found in as many as 1 per cent of his pneumonias.

Dudgson and Branson have published a series of 5 cases occurring in infants at the East London Hospital for Children. They state that the pneumococcus is the cause of the great majority of cases of suppurative arthritis in children, and make the further observation that the constitutional symptoms are not nearly so severe as in streptococcic cases. There is often little pain and the child generally eats and sleeps well.

Pathologically the lesion is an acute synovitis although the suppuration may spread occasionally into the periarticular tissues. The effusion may consist of creamy pus or of fairly clear fluid; both varieties contain a pure culture of pneumococci.

The knee is by far the most frequent joint affected and is often the only articulation involved, although the shoulder, ankle and other joints may become affected. More than two joints are seldom involved though a case is recorded by Murray\(^{(6)}\)
the knee, thigh and ankle were all attacked.

Dr. Campbell Howard records 3 cases all of which occurred in the course of a general infection. The sequence of events in 2 of these cases is interesting as showing that arthritis commonly develops during the height of the primary disease.

Case 1. Male 42, lobar pneumonia, pericarditis 7th day, arthritis (right shoulder) 7th day, endocarditis 8th day, meningitis 9th day, arthritis (right ankle) 10th day, death 11th day.

Case 2. Male 79, lobar pneumonia, arthritis (left shoulder) 7th day, arthritis (right knee) 8th day, meningitis 9th day, arthritis (left knee) 9th day, death evening of 9th day.

Litterer however records a case of pneumonia where arthritis of the right knee joint developed on the 16th day, that is ten days after the crisis.

IX. Otitis Media.

Professor Hewlett states in his work on bacteriology that the pneumococcus is the causal agent in one third of all cases of suppurative affection of the middle ear and is therefore responsible for a large number of cases of cerebral abscess with or without thrombosis of the lateral sinus.

Schreiber found the pneumococcus in 6 out of 16 cases of otitis media examined by him, while Green found pneumococci present in 10 out of 73 cases and also found them in 23 out of 144 cases of acute mastoiditis.

In the case of general pneumococcus infection in children Metter found that otitis media was by
far the commonest primary lesion occurring as such in as many as 29 out of 46 cases examined; while in the same series broncho-pneumonia was a primary lesion in but 12 cases and lobar pneumonia in only 1 instance.

In Netter's series of 191 fatal cases in adults on the other hand otitis media was the primary lesion in only 2.44%.

The origin of infection in otitis media is undoubtedly by direct extension from the buccal cavity or naso-pharynx by way of the eustachian tube.

X. Tonsillitis and Pharyngitis.

Throat are by no means an infrequent source of pneumococcal infection. Last year I had a man under my care with acute suppurative tonsillitis and who a few days later contracted acute pneumonia of his right lower lobe.

Dr. Carnal records a case of a woman 34 years of age who on August 3rd, 1904 contracted a septic sore throat of a phlegmonous character followed 5 days later by acute croupous pneumonia which proved fatal.

In both of these cases the tonsillitis led to a general blood infection with pneumonia as a secondary manifestation.
Having thus described in some detail the principal lesions met with in pneumococcal septicaemia I shall now very briefly refer to a few other manifestations which tend to throw light on the possible sources of infection.

**XI. Lesions of the Alimentary System.**

Cases of glossitis and parotitis due to pneumococcus have been described but lesions are also met with in the stomach and intestines.

As a rule the acid juices of the stomach act as a strong prophylactic against pneumococcal invasion of the alimentary canal. This safeguard however is now always sufficient.

A rare but most interesting case is reported by Dr. Foulerton of pneumococcal phlegmonous gastritis which gave rise to a fatal general septicaemia. A similar case in some respects is recorded by Dieulafoy.

Boulay has published a case of pneumococcic enteritis.

Cases of colitis due to the same cause have also been reported while I have already referred to the case of pneumococcic appendicitis with subsequent fatal peritonitis published by Shaw and French.

Three cases of cystitis occurring in the course of pneumonia are mentioned by an observer vide American Medicine, March, 1905 but the pneumococci were not isolated.
XII. Lesions of skin and conjunctivae

Poulerton states that he has found from time to time small acute circumscribed abscesses containing pneumococci on the hands of those who are in the habit of performing post-mortem operations.

He specially relates one case where a medical man cut his finger while making an examination of a dead body in a case of cerebro-spinal meningitis. Within 48 hours there was extensive acute cellulitis of the forearm necessitating treatment by incisions. The effusion was found to contain the pneumococcus in pure culture.

As regards the eye, Arnold Lawson has found the pneumococcus on two occasions in the healthy conjunctiva, thus rendering it like the mouth a direct source of infection.

Gifford has found pneumococci in 39 out of 40 cases of conjunctivitis while Gasperini has described the organism as occurring in 6 cases of kerato-hypopion and in 2 cases of pan-ophthalmitis.

Out of 50 cases of purulent keratitis Uhthoff found the pneumococcus 24 times in pure culture, that is in practically 50% of his cases.

At the meeting of the Société Médicale des Hôpitaux de Paris in April 29th, 1904 Le Gendre and Morax described a case of pneumococcal pan-ophthalmitis associated with ulcerative endocarditis and
also renal and splenic infarcts. In this case
the eye lesion was the primary focus of a general
pneumococcal septicaemia.

XIII Lesions of Female Genital Organs.

In referring to peritonitis I have alluded to
cases of vulvo-vaginitis endometritis and salpingitis.

Cohn has recorded a case of pneumococcal endo-
metritis and general infection in a woman aged 35, who
was admitted into hospital with pyrexia coming
on three months after a miscarriage. After death
there was found suppurative endometritis with re-
tained portions of placenta, ulcerative endocarditis
of the aortic valves, suppurative meningitis and two
softening infarcts in the spleen. The pneumococcus
was present in all the lesions.

Professor A.R. Simpson of Edinburgh mentions
a case of ovarian cystoma from which pneumococci
were isolated.

All these serve to indicate that in females
the genital canal may be an important channel of
pneumococcal infection.
We have considered the various pneumococcal manifestations individually, but in actual cases of septicaemia and pyaemia due to this cause the multiple lesions are often multiple.

I have already referred to the frequent association of endocarditis and meningitis with or without pneumonia, of the common occurrence of inflammation of two or more serous membranes and of the intercurrence of suppurative arthritis with empyema or some other pyaemic manifestation.

We have also seen that in these cases of multiple lesions the blood is usually found to contain pneumococci occasionally in considerable numbers.

We are further shown that all pneumococcal infections including pneumonia itself, tend to assume a septicaemic character. We have seen also that any one of the manifestations may be the primary localisation of the disease thus showing how numerous are the channels of infection.

There is thus no essential distinction to be drawn between the condition met with in the human subject and pneumococcal septicaemia in mice and rabbits, which indeed many of the cases in man closely resemble.
The liability to multiple lesions and more particularly to the pyaemic manifestations is greatest in childhood and early adolescence. Thus the late Dr. Kantack found that in 170 fatal cases of pneumonia no less than 64% of those under 21 years of age died from secondary infection, whereas in the whole series only 35.7% died from this cause. In Langdown Brown's series of 39 cases of multiple infection already alluded to as occurring in St. Bartholomew's Hospital the average age at which death occurred was 15½ years. In view of the frequency of pneumococcal blood infection in children it seems possible that a certain proportion of the obscure pyrexiae observed in children with no discoverable cause may be of this nature.

In adults the clinical features often closely resemble those of streptococcal septicaemia. Indeed the two conditions apart from blood examination cannot may be impossible to be distinguished clinically. There is often high pyrexia commonly of a remittent type while in the later stages a patient may lie in a typically "typhoid" state.

The prognosis in adults is extremely bad. House states that the mortality of complicated cases of pneumonia is nearly four times greater than that of those with no complication.
However a certain proportion of cases do recover even after a succession of multiple lesions particularly when these are of a pyaemic character, as for instance empyema associated with suppurative peritonitis.

Ulcerative endocarditis and meningitis are almost invariably fatal whether occurring singly or in association with pneumonia or some other primary manifestation. Empyema and other purulent inflammations of serous membranes as well as arthritis and local abscesses are as a rule extremely amenable to surgical treatment. In children on the other hand the prognosis in multiple infection is not so grave. We may get a multiplicity of lesions going on for weeks or even months and yet the child may ultimately recover. This probably due to their greater resisting power and more active phagocytosis. That the condition is a less serious one in young people is indicated by the fact that, notwithstanding the greater prevalence of multiple secondary lesions in children pneumonia is a much less fatal disease than in adults.

I shall now proceed to describe a few typical cases selected from a large number that have come under my observation and shall also refer to one or two other cases exemplifying special clinical features.
Case 1. Last year (1904) I had a boy eight years of age under my care. Six days before admission his mother noticed that he had pain and swelling in his right ankle and kept him from school. At night she said that he "wandered in his sleep". The day before admission the boy complained also of slight aching in the region of the left shoulder. There had been no sweating. He was admitted into the the Royal Chest Hospital on February 10th, 1904. There was now no pain or swelling of the ankle joint, but the boy still complained of a slight aching in the left shoulder but there was no tenderness on manipulation. This was now the seventh day of the illness. A distinct systolic murmur was audible at the apex of the heart indicative of acute endocarditis. A few crepitations could be heard at the extreme base of the left lung indicating early pneumonic congestion commencing consolidation. The child looked ill. On the ninth day the physical signs remained unchanged but the boy again complained of pain in his left shoulder and there was slight dyspnoea. On the tenth day there was distinct dyspnoea while a rise of temperature to 102°F. was also noted. The boy complained of some praecordial pain and a to and fro pericardial friction murmur was discovered to the left of the sternum, indicating the onset of acute pericarditis. On the twelfth day the friction was audible all over the praecordia and there was considerable
dyspnoea and praeordial pain the latter being relieved by counter-irritation. On the fourteenth day there was marked dyspnoea, increase of cardiac dulness and also well-marked dulness at the left base with tubular breathing—all the signs in short of lobar pneumonia. There were crepitations also audible at the left apex and there was a loud systolic murmur at the cardiac apex. On the eighteenth day there were patchy areas of consolidation in the left lung and a few crepitations also at the right anterior apex with impairment of the percussion note. The child was now very ill with quick breathing and rapid pulse (170). On the twenty-first day the dulness at the extreme left base became absolute indicating the occurrence of pleurisy with effusion, the fluid obtained on expectoration being sero-fibrinous in character. On the twenty-second day as the child was rapidly getting worse three ounces of blood-stained fluid was removed by aspiration from the left base. The pericardium was also explored both in the fourth and fifth left interspaces but only a very little blood-stained fluid was obtained. On the twenty-third day the patient died. I made a post-mortem examination next day and found pleuro-pneumonia of the left lower lobe which was resolving and also patches of recent consolidation.
in the left upper lobe, and also in the right lung, there was some pleuritic effusion at the left base with tags of lymph on the surface of the pleura. I found also well-marked fibrinous pericarditis with typical masses of shaggy lymph, and a small quantity of sero-fibrinous effusion in the posterior part of the sac, which was obliterated in front by the adherence of the visceral and parietal layers. There was also acute endocarditis, numerous small vegetations being found on both aortic and mitral valves. A blood agar tube was inoculated from the blood from an inter-costal vein and a pure culture of pneumococci obtained (vide Diagram 2). Cultures taken direct from the pleural and pericardial effusions proved sterile. A piece of consolidated lung was excised and next day some of the lung juice was injected into the peritoneal cavity of a rabbit which died from pneumococcal septicaemia. In this case we had a sequence of slight arthritis which recovered without going on to suppuration, endocarditis, pneumonia, pericarditis and pleurisy. I append a temperature chart of the case which shows well the typical remittent pyrexia so often observed in septicaemic cases.

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Case 2. My colleague Dr. Arthur Davies has recently had under his care a case of multiple pneumococcic infection with recovery. The patient was a little girl eight years of age who was taken ill two days before admission and presented all the symptoms of pneumonia (pyrexia, quick breathing and rapid pulse). There were signs of pneumonia consolidation over the anterior aspect of the left lung and at the right base. There was also some rigidity of the abdomen and tenderness and swelling of the right knee-joint. On the fourth day of the illness there were signs of consolidation over the front of the right chest, while the signs were clearing up on the left side. On the seventh day the areas of consolidation were found to be undergoing resolution except at the right base where the dulness persisted. On the thirteenth day there was pneumococcic consolidation of the right apex and exploration revealed an empyema at the right base, the pus containing encapsuled diplococci. At this time there had been well marked leucocytosis (21,000 per cm³). A pint of pus was removed after rib-resection under an anaesthetic, and immediately considerable general improvement resulted. The knee was found to be more swollen and painful and there was now evident distension of the abdomen with tenderness and impaired movement while there were also signs of free fluid effusion into the peritoneal cavity.
peritoneal cavity. On the eighteenth day the right knee was explored under an anaesthetic and _suppurative arthritis_ discovered, four ounces of pus being found in the joint tracking up under the quadriceps extensor muscle. The pus contained encapsulated diplococci. On the twenty-third day there was a tender swelling over the right hip joint but no pus was obtained on exploration.

On the thirtieth day the abdominal symptoms which had been _gradually subsiding_ again became more pronounced. There was now considerable distension which was accompanied by sickness. As the child's general condition had become much worse laparotomy was performed and about three pints of pus evacuated. There was thus _suppurative peritonitis_. The child made an excellent recovery with no ill-effects other than a slight ankylosis of the right knee joint. In this case there was a sequence of pneumonia, empyema, suppurative arthritis and purulent peritonitis.
Case 3. A remarkable case of generalised pneumococcic infection was recorded by Duplocq and Lejonne at a meeting of the Société des Hôpitaux de Paris as long ago as November 25th, 1898. It was a case of migratory pneumonia with an extraordinary multiplicity of lesions.

A robust man of 59 was admitted with pneumonic consolidation in the right axilla and generalised bronchitis. On the ninth day a second focus appeared at the left base and for the first time he expectorated a viscid mucous containing pneumococci. On the thirteenth day a third focus appeared at the right base. On the fourteenth day there was suppurative arthritis of the left shoulder from which half a pint of pus was evacuated. On the sixteenth day there was a fourth focus of consolidation in the left sub-scapular region. On the twentieth day a fifth focus was found in the right supra-spinous fossa. On the twenty-second day a similar focus appeared in the left axilla. On the twenty-third day an oedematous swelling appeared in Scarpa's triangle on the right side. On the twenty-fifth day there was lymphadenitis of the lymphatic glands of the groin. On the twenty-sixth day a seventh focus of consolidation appeared at the left base and on the twenty-eighth day an eighth focus on the supra-spinous fossa. On the
thirty-second day a pre-laryngeal abscess appeared containing pneumococci. On the same day a ninth focus of consolidation appeared at the left base. The patient died on the thirty-third day. The blood also had been found to contain pneumococci. At the necropsy in addition to the pulmonary lesions there were found meningitis, the exudation containing pneumococci. An abscess was also found tracking under the right psoas muscle. The presence of pneumococci was verified by inoculation into mice which produced fatal septicaemia. In this case the successive involvement of the numerous areas in the lung was probably the result of blood infection.

In some cases the patient seems overwhelmed at the outset by the virulence of the infection. Two cases of this fulminating type may be briefly referred to:

Case 1. Dr. Newton Pitt records a case of a youth 17 years of age who died within four days of the acute onset of pneumococcic infection. Dr. Pitt described this case as a typical one of a very acute pneumococcic septicaemia in which the poison overwhelmed the patient before there was time for consolidation of the lung to develop. At the
autopsy there was found acute pleurisy with effusion but no pneumonia. Acute pericarditis, acute endocarditis, acute lymphadenitis of the broncials glands acute membranous colitis, and early peritonitis, Cultivations were made from the peritoneal and pericardial effusion and also from the heart blood and in all instances the pneumococci were found in pure culture.

Case 2. J. Pelmar, also published a similar acute case occurring during the puerperium in a young woman twenty-two years of age. She was suddenly attacked with acute phlegmonous tonsillitis similar to that found in severe cases of scarlatina, followed quickly by septic symptoms and meningitis, to which she rapidly succumbed. Cultures made from the tonsillar and meningeal pus and also from the spleen juice yielded the pneumococcus. There was no pneumonia.

In other cases particularly the pyaemic and post-pneumonic cases, the course of the disease is often much more chronic as in some of the cases already described.

While Medical Registrar at Kings College Hospital I kept under observation a woman thirty-five years of age (a case of pneumonia with relapse and empyema) where the temperature kept at a high level
for a period of two months and yet who made an excellent recovery.

Dr. Parker records a case at length of broncho-pneumonia in a child of 17 months old which lasted three months before proving fatal from general pneumococcic infection.

A certain proportion of cases of pneumococcic septicaemia exhibit the typical symptoms of acute lobar pneumonia with sharp phthisis from the sixth to ninth day and yet show no physical signs whatsoever of lung involvement. Such a case in a child of seven years of age I have at present under my care.

On the other hand we meet with cases which run a long course with but moderate pyrexia and symptoms strongly suggestive very similar to those of enteric fever. Such a case in a little girl of nine years of age I saw in March of the present year.

In concluding these remarks on the clinical features of cases of pneumococcic infection I might point out that even in cases of pneumonia with no evidence other discoverable form of metastasis the severity of the disease often bears no relation whatsoever to the amount of pulmonary consolidation. The severest cases I have met with, many of which have been fatal, have exhibited extremely few pulmonary
physical signs, and where the lung condition was quite inadequate to account for the severity of the symptoms which were explicable only on the hypothesis of an acute pneumococcic septicaemia and toxaemia due to multiplication of the cocci in the circulating blood.

**THERAPEUTICS.**

In conclusion we may ask if there any therapeutic measures specially applicable to cases of pronounced septicaemia with multiple lesions.

1. Treatment by antipneumococci serum.

These are preeminently the type of cases in which we should expect most benefit to accrue from the use of antitoxin. The results however of this method of treatment in pneumonia and complications have been on the whole very disappointing. Washbourne in 1897 reported two cases of pneumonia treated apparently with benefit by the use of antipneumococcic serum, but after further experience he described the results as by no means satisfactory. He recommended that the treatment should be commenced as early as possible and that the injections should be repeated twice a day until the patient was convalescent. The dose he said should be 20 cc. [660 units].
Pane's pneumococcic serum prepared in Italy is the one now usually employed and has been used on several occasions with some apparent benefit, although no decisive results have been obtained. It is advisable to use this serum in large doses 20 cc. in the morning and a similar dose in the evening. The injections may be made either into the subcutaneous tissues of the abdomen or back or else directly into one of the veins at the bend of the elbow.

In Duckworth and Marsh's successful case of pneumococcic peritonitis already referred to anti-pneumococcic serum was employed. On the other hand their colleague Dr. Garrod has recently published a case where apparently no benefit ensued. Several cases however have been recorded from time to time such for instance as the one reported by Guthrie who used it in a case of croupous pneumonia which was steadily getting worse under stimulant treatment and improved directly the use of the serum was commenced. No bad effects have been recorded from the employment of antitoxin and the results though indecisive are sufficiently encouraging to enable one to recommend its use in all severe cases of general blood infection. The treatment should be commenced early in the course of the primary disease before metastases have occurred.
2. **Anti-septic Treatment.**

For some years past creosote and guiacol have been extensively tried for their supposed specific effects in the treatment of pneumonia and often with good results. Large doses as much as 20 minims of creosote or a similar number of grains of guiacol having been given every four hours.

No harm appears to follow their use if the kidneys are healthy. It cannot be claimed for these substances that they have a natural bactericidal effect in the circulating blood but even if they exert only a slight deterrent influence their use may occasionally serve to prevent the occurrence of metastases.

3. The fact that the prognosis is better in children is due no doubt as already mentioned to the more ready reaction of the system to the bacterial invasion and correspondingly more active leucocytoses. In Parker's case quoted where the child lived for three months the vigor with which the system reacted was indicated by a leucocytosis of 73,000. The importance of leucocytosis in prognosis is also to some extent indicated by the frequent successful termination in pyaemic cases which are as a rule accompanied by hyper-leucocytosis. In elderly persons and in persons
debilitated from any cause there is often on the other hand a feeble reaction and the prognosis is correspondingly worse. If then we knew of any therapeutic agent which would encourage the tendency to physiological leucocyte formation its use might conceivably be of value. Dr. Albert Rodin made an interesting and possibly important communication last December [1904] to the Académie de Médécin de Paris on the action of what he calls metallic ferments in pneumohia. He found that subcutaneous injection of solutions containing minute quantities of palladium, platinum gold or silver obtained by passing a small electric arc between metallic electrodes immersed in water not only caused chemical metabolic changes in the system but also affected modifications in the cellular elements of the blood. For some hours after injection there is a true leucocytosis slight in healthy individuals but intense in those infections commonly accompanied by leucocytosis. In the great majority of cases of pneumonia where was this treatment used the crisis occurred before the seventh day and 13 out of 14 cases treated recovered. Rodin asserts that these metallic solutions although exerting no action on the pneumonic lesion itself yet stimulated the reaction of the system against infection and its toxic products.
4. Our chief reliance must however be placed on the energetic treatment of the primary infection. In pneumonia we must maintain the patient's strength at the highest possible level by careful nursing, stimulant drugs and carefully graduated diet.

Surgical measures must be immediately resorted to in empyema, suppurative arthritis, purulent peritonitis, suppurative pericarditis, superficial abscesses and other pyaemic manifestations. Otitis media and tonsillitis must not be overlooked and must be promptly treated. In this way the occurrence of other lesions may be prevented and a considerable proportion of cases will be saved that otherwise would inevitably prove fatal.
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