tensely inflamed and infiltrated; no membrane; not much glandular enlargement. December 4th, temperature 101.5°; diphtheria suspected; 4,000 units antitoxin administered. December 5th, temperature still 101.5°; 3,000 units given. December 6th, seen by Dr. Lloyd also; report on throat swab received, "No diphtheria"; urine nearly solid with albumen; pulse rapid and weak; temperature rose steadily. December 7th, temperature, at 10 p.m., 106°; pulse 152.

December 8th. In the early morning a patch of pleurisy appeared on the right side. Seen by me midday with Drs. Storrs and Lloyd, the patient looked very ill, tongue dry and brown, slight herpetic eruption on the lips, uniform red glazed condition of the whole of the pharynx without either ulceration or membrane; at the right base a patch of dullness with bronchial breathing about 2 or 3 fingerbreadths in extent; no abnormal sounds of the heart; spleen not enlarged. We thought that in all probability it was a case of streptococcus infection from the throat. Ten c.cm. of polyvalent anti-streptococcus serum were administered, and tubes of agar, gelatine, blood serum, and bouillon (ten in number) were inoculated with blood taken from the median basilic vein at 7 p.m. On the morning of December 10th abundant growth of pneumococcus was found in all the tubes; meanwhile 20 c.cm. of the serum had been injected on December 9th, and the patient's condition had improved materially; temperature and pulse falling, tongue becoming moister; taking well, sleeping quietly; 20 c.cm. serum again on December 10th.

The daily administration of serum was continued with evidently good results. The albumen diminished in the urine until only a trace remained. The hypodermic administration of strychnine was pushed until twitching appeared. The temperature fell to 99° on the 15th, and we had great hopes of his recovery. The pulse, however, continued quick, and his exhausted heart began to fail on the 16th. Strophanthin and digitalin had been tried without success. He died on the 17th, with the usual premonitory rise of temperature, 103°. During the last few days of his life there was a haemorrhagic punctiform rash on the thighs. The albuminuria increased again in the end. A sore on the shin from burn during a hot-air bath remained in an unhealthy condition covered with a greyish slough.

Although no cultivation was made from the throat, there seems to me every reason to conclude that the primary source of infection was in the pharynx, and that it was pneumococcal. There was undoubtedly later a patch of bronchopneumonia at the right base, but it interfered in no way with the course of the case. There was neither cough nor expectoration at any time; the respirations were not quickened by it, and with the exception of the pleuritic pain which ushered in its onset its presence could only be ascertained by careful examination. It did not make its appearance until the main features of the case were well advanced.

The exact form which pneumococcal infection of the pharynx may take is still undetermined. Cornil described a case of abscess in the tonsil due to the pneumococcus; Jaccoud a case of pseudo-membranous pharyngitis of similar origin. Rendu and Bouloche¹ in 1891 recorded two cases of acute pharyngitis with sudden onset, accompanied by high fever of short duration, occurring in individuals who were exposed to pneumococcal infection, and slept in the same room. The pneumococcal origin of the infection was proved by inoculation of rabbits. In neither of these cases was there either ulceration or false membrane. In their main features they resemble the cases I have described above, but there was no great glandular enlargement.

In 1901 Monro² described a case of membranous pharyngitis which he considered to be of pneumococcal origin, as also have Bezançon and Griffin.³ The latter observers made use of the agglutinative serum reaction to prove their case.

In the discussion which followed the paper by MM. Rendu and Bouloche (referred to above), Netter summed up the several types of pneumococcal angina as follows:

Suppurative	} proved.
Pseudomembranous	
Follicular	} doubtful.
Inflammatory	
Herpetic	

Recently (December, 1908) Sir Felix Semon⁴ described several cases of ulcerative pharyngitis with perforation of palate, and brought convincing evidence to show that they were pneumococcal in origin.

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Observations

ON

THE THERAPEUTIC VALUE OF THE PNEUMOCOCCUS VACCINE IN THE TREATMENT OF PNEUMONIA

AND SOME OF ITS COMPLICATIONS.

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THE pneumococcus is, perhaps, next to the *coli* bacillus and the staphylococcus, the most constant parasite of the human race. Mackenzie¹ quotes statistics from various authorities, who state that 50 per cent. and upwards of normal individuals harbour this organism. "Hiss says it is more than probable that every individual acts as a host to organisms of true pneumococcus type at some time or other during the winter months, and probably at repeated intervals. The organisms leave the body with the saliva or sputum, and in either moist or dried sputum may remain virulent for a considerable time."²

That the pneumococcus of Fraenkel is the cause of pneumonia has been established since 1889;³ indeed previously, in the year 1886, he showed that a rabbit which had recovered from an attack of pneumonia was subsequently immune to a lethal dose of the organism.⁴ It is, therefore, unnecessary to burden the reader with what is now ancient history.

It may be taken as proved that practically every case of acute pneumonia is a case of pneumococcal septicaemia—that is to say, the infecting organism is not confined to local areas, but may be recovered from the blood.* The crisis in septicaemic conditions, whether it be that of pneumococcus or streptococcus, is determined by the amount of protective material the invaded host is able to elaborate in a given time. When this elaboration is at a sufficient rate to inhibit the reproduction of the infecting organism, it is probable that the clinical manifestation of a crisis will occur. In 1891 the Klemperer brothers explained that the crisis in humans occurs at the moment when the poisonous products manufactured by the bacteria located in the lungs are present in the circulation in amounts sufficient to call forth in the tissues the reactive change that results in the production of the antidotal substance which has the power of rendering the poison inert. To this end they prepared an antiserum, which they used in 6 cases. There was in 4 a temporary improvement, and 2 cases got well.

The Klemperers apparently did not realize that they were dealing with a general infective condition, and failed because their experiment consisted merely in the neutralization of a certain quantity of toxin.

The decade 1890-1900 may be described as the era of serum therapeutics, when antisera were used in many infective processes, but only attained success in that of diphtheria, a local infection producing a general toxæmia. In this connexion the names of Washbourne, Eyre,¹² Pane,¹³ Wilson, Marchaux, Tyler, and Parr should be mentioned. Bokenham, indeed, showed that antipneumococcal serum had no bactericidal effect upon living pneumococci.

In the course of these serum investigations animals were necessarily inoculated with attenuated cultures, increasing in later inoculations in virulence. Foa discovered that animals thus immunized against one strain of pneumococcus were not necessarily protected against others, and Washbourne and Eyre¹² found that Pane's serum protected against four out of five varieties, but not against the fifth. Here, then, arose a second factor, which militated against successful immunization at the bedside.

Wright's work on staphylococcal and tuberculin inoculations from 1902 onwards introduced the present era of vaccine treatment. He himself in his earlier papers argued that inoculation was indefensible in acute infective conditions, because of the probabilities of auto-inoculations. This supposition, based on the results

* Rosenow found pneumococci in 160 out of 175 in 1905; Fraenkel, found pneumococci constantly in the blood; Prochaski found pneumococci in blood of 50 consecutive cases, 1901.

obtained in tuberculous infections, rendered it extremely improbable that bacterial inoculation would be of any value in combating septicaemic conditions; in fact, such a course would increase the disaster.

The analogy, however, between tuberculous infection and an acute septicaemic condition is, happily, not a true one. In the former disease, when fulminating, necrotic foci are continually liberating dead organisms into the tissues, there to act as a bacterial vaccine. In pneumonia the bacteria are of a different type; they have not anatomically the same chance of getting into contact with the tissues, but remain in the lung, and circulate in the blood, until their life-history is done and they are digested. It may be that the spontaneous crisis in pneumonia and acute erysipelas may be due to some such process gradually building itself up.

With some such conception in his mind Macdonald⁵ studied the opsonic index in 8 cases of pneumonia, and found it low during the disease until the crisis was reached, when it suddenly rose as high as 1.6. He laid the foundation of vaccine treatment in pneumonia by producing artificial crises in rabbits infected with the pneumococcus by inoculating them with a vaccine made from the infecting strain. He was able at will to produce an artificial crisis, and recovery if he inoculated the animal with a vaccine made from the same strain with which it had been infected. Control rabbits, not inoculated, died. This research carried out in the bacteriological department of the London Hospital does not appear to have been followed up in hospital treatment.

Preparation of the Autogenous Pneumococcic Vaccine.

It is desirable to prepare the vaccine from cultures of the patient's own pneumococcus. If this is impossible, a stock vaccine made from a particularly virulent strain may be used.

It usually happens that the more virulent the pneumococcus, the more readily does it grow *in vitro*. On several occasions sufficient culture has been obtained after twelve hours' incubation from which to make the vaccine. The statement, therefore, which has been frequently made, that it is impossible to grow enough pneumococci to make a vaccine from in so short a space of time that it may be available, is untrue and misleading.

Pure cultures from chronic infections are difficult, and sometimes impossible, to obtain on account of rapidly growing contaminations. In acute pneumonia, however, if the rusty sputum be washed in sterile saline, and penetrated with a hot wire, a pure culture of the pneumococcus is, more often than not, obtained.

Agar-agar slopes should be used which have previously been smeared with a thin film of blood drawn from the finger. The latter should be washed, dipped in ether, and flamed. The ether flaming should be repeated three times. A narrow tape is wound twice round the end joint, and the skin deeply pricked with a sterilized needle or glass point behind the nail. Squeezing the pulp pumps out sufficient blood, which is then sucked up with a sterile Wright's pipette and nipple, and so conveyed direct to the agar slope. Three drops are sufficient, and if these be mingled with the water of condensation in the tube, a sufficient film can be spread by gravitation over the surface of the slope. For safety, the tube should be incubated for twelve hours before inoculation. It rarely happens, however, if this simple technique is followed, that any contamination with a skin staphylococcus occurs.

It not infrequently happens that sputum is not available. It is usually possible in acute pneumonia to recover the pneumococcus from the blood, if sufficient blood be drawn. This is most simply effected by passing the sterilized needle, attached to a large 20 c.cm. syringe (the "record" is, perhaps, the most suitable), into the median basilic

vein, already distended by compression, and withdrawing 10 to 15 c.cm. of blood; 5 c.cm. of 2 per cent. citrate in normal saline, previously drawn into the syringe, will obviate clotting.

The blood may then be introduced into ten agar sloped tubes. Sufficient growth will be obtained from the surfaces to prepare a vaccine without subculture. Care must be taken in both the above methods to keep the tubes upright and not to refill the slopes with the blood which has settled at the bottom of the tube, otherwise it will be impossible to obtain clean emulsions of the pneumococcus for standardization.

CASE I.⁶

At Christmas, 1905, a lad named A. had a typical left basal lobar pneumonia. His crisis was unsatisfactory, and during January, 1906, he ran a variable temperature, normal or nearly normal in the morning, rising at night to 101° and 102°. There was a small dull patch at his left base, but there was no pleurisy. He was losing ground and weight week by week. His index to tubercle bacilli was normal, and the sputum contained none of these micro-organisms. There were, however, quantities of pneumococci present, and to these his index was low. He was inoculated towards the end of January with a pneumococcic vaccine made from cultures obtained from a case of chronic pneumococcic infection involving the knee-joints. This vaccine, although helpful in the case from which it was derived, had no effect on A.

In February, his condition becoming more serious from continued fever and loss of weight, he was seen in consultation with Dr. H. P. Hawkins. He agreed that probably there was a small consolidated patch at the left base, and that there was no pleuritic effusion. I suggested inoculating the lad with a vaccine made from his own strain of pneumococcus. After some little delay this request was granted. Within thirty-six hours of his inoculation all the usual clinical phenomena of resolution by crisis occurred, and the lad made an uninterrupted recovery. His index before the inoculation was 0.7, and at the crisis shot up to 1.4, whence it gradually declined to normal six days later. It occurred to me that possibly the introduction of the vaccine was coincident with the rupture of a small abscess. The microscopic character of the expectoration, however, negatived this, and later no physical signs were present to support this supposition. At the present time, three years after, the lad is perfectly well and has been in good health since his convalescence.

It would appear that the small dose of vaccine—50 million—was the determining factor in starting the sudden process of self-immunization into action.

CASE II.⁷

On April 30th, 1906, I was asked by Dr. Brooke, of Chingford, to see a case of pneumonia.

The patient, D., aged about 47, was a big man. He was seen on the fifth day of the disease. There was slight consolidation at the left base, definite peritoneal infection, distension of the bowel, effusion into his left ankle-joint, and thrombosis of his left posterior tibial vein. He was in a state of acute delirium alternating with dull apathy. His sputum showed pneumococci which grew rapidly on blood agar. His index was 0.4. A vaccine was prepared, and he was inoculated with 10 million dead pneumococci on May 2nd in the afternoon. Within thirty-six hours his condition began to improve, his peritoneal, stomach, and intestinal conditions were better, and the effusion in his ankle

Chart 1, Case II.—A, Abortive crisis relating only to lung; B, 30 million; C, 50 million; D, 20 million; E, 30 million.

began to subside. His temperature did not, however, drop much until a second inoculation of 30 million was given on May 4th. Observation of his opsonic index taken twenty-four hours after the first inoculation showed that it had risen to 1.2, but by the time the second was given it had fallen again to 0.6. After the second inoculation his temperature fell from 102° to 99° on the morning of May 6th, rising during the day to 102° again. He was accordingly inoculated again with 50 million in the afternoon of May 6th. His temperature fell continuously during the night and the whole of May 7th, rising on the morning of May 8th to 101°. It will be noticed that here the temperature became for the first time inverted, no doubt on account of the wearing out of the immunization. On the afternoon of May 8th he was inoculated for the fourth time with 50 million. On May 11th, 12th, and 13th, his temperature was normal in the morning, rising to 100° at night. During this time his mental condition varied between stupor and acute mania, and, indeed, this condition continued until about May 20th.

The sole remaining focus of infection was apparently in the left posterior tibial vein. On May 14th a fifth inoculation of 50 million was given. On May 15th his temperature never rose

above 98.8°. On the morning of May 17th he was not so well again, and his temperature rose to 99.4°. A sixth inoculation of 50 million on this date was given, and from now onwards it remained practically normal. A seventh and final inoculation of 30 million was given on May 22nd, and from that time he became himself. He made a perfect recovery at the time. At the end of last year (1908) he came to see me with a large ulcer in the lower third of his leg. This had gradually developed during 1903, no doubt due to the original blocking of the posterior tibial vein.

This case was clinically rather one of pneumococcal septicaemia, in which the lung infection was but a small incident. The pneumococcus was recovered not only from his sputum, but from blood drawn from his median basilic vein. The rapidity with which the graver signs of infection yielded to inoculation was remarkable, and I think that the fever was prolonged by the thrombotic condition of his left leg. It appears, too, that the septicaemic condition is not a contraindication for bacterial inoculation. As regards this point, Douglas¹⁴ had successfully inoculated a case of acute septic endocarditis in the previous March (1906) with a streptococcal vaccine derived from the patient's own organism, which had been recovered from the blood. In March, 1908, a case of acute streptococcal septicaemia, with local erysipelas of the head and face under my own care, responded at once to inoculation. The temperature was 105°; there was low muttering delirium with subsultus, picking of the bedclothes; respirations were 40, and pulse 140. An inoculation of 20 million streptococci was given at 10 p.m., and during the night profuse sweating occurred. At 8 a.m. the temperature was 98.8°. No opsonic index was made.

CASE III.

Mr. W. A., aged 43, was seen by my colleague, Mr. G. L. Parsons, who has kindly furnished me with the clinical history.

On December 29th, 1907, he was feverish and slightly jaundiced. On December 31st he developed a cough in addition to the other symptoms, with viscid sputum and increased V. R. at the right apex. On January 1st, 1908, his liver was found to be enlarged, with pain and rigidity in the abdomen. There were definite signs of pneumonia at the right apex, with rusty sputum. On January 2nd the pneumococcus was observed in the sputum, and cultures on blood agar made. On January 3rd the patient sweated profusely; there was general improvement, and signs of resolution at the right apex. On January 4th he became worse; the pain and distension of the abdomen were more marked; there was evidence of infection of the left apex. On January 5th his pulse-respiration ratio was 2 to 1 or less; he appeared very emaciated and suffering from general toxæmia.

On January 6th the left apex and upper half of the left lung were consolidated. Pulse (120) feeble; respirations, 70; mental condition, excitable and delirious. The vaccine having been prepared, a dose of 60 million was given about 11 p.m. January 7th: Little improvement was noticed, and the dose of 60 million was repeated at 8 p.m., twenty-two hours after the first. The temperature fell two degrees that night. January 8th: There was marked improvement. The abdominal pain and distension disappeared, and the consolidation of the left lung began to resolve. The temperature rose one degree, but on January 9th fell to below normal.

Here again the septicaemic condition was arrested within twelve hours of giving the vaccine, though not until the second dose. At the bedside the case appeared to be hopeless, and the vaccine was given as a last resort. The intoxication was very profound, and it was not until January 12th or 13th that he recovered his normal mental state. The mental condition resembled that of Mr. D., periods of apathy alternating with an active fighting delirium.

He made a perfect recovery, and is now (1909) in good health.

CASE IV.

W. F., boy, aged 3½, also under the care of Mr. G. L. Parsons, was seen first on March 13th, 1908. He had been ill already for about ten days. His temperature was 102°. There was pain on the right side of the chest and poor expansion. There were some bronchitic sounds on both sides, and a patch of dullness with crepitations half way down the right side in the mid-axillary line. Complete dullness with loss of breath sounds at the right base. On March 15th there was some improvement in physical signs and symptoms. The temperature fell to 99° for the next two days. On March 18th the temperature rose rapidly to 103°. Pulse and respirations increased in frequency, and fluid in the right pleura extended high up. The urine became dark, and there was increased frequency of micturition. Total quantity passed was small; it contained albumen, pus, and casts.

On March 20th the right pleura was aspirated and found to contain pus. A film showed quantities of pneumococci. Cultures on blood agar were made with a view to the preparation of a vaccine. On March 21st the temperature rose to 104°; a portion of the seventh rib on the right side was resected and free drainage established. On the morning of March 22nd the temperature had fallen to 99°, and there was general improvement. On March 22nd the temperature was 99°. The discharge from the wound had become serous. More urine was passed, which was better in character.

On March 23rd there was constant cough, the temperature rising to 102°. The urine again became scanty and contained albumen; there was incontinence. The drainage tube was removed and the wound, which again had become purulent, was fomented. The temperature fell on the morning of the 24th, but again rose during the day. As the condition was now becoming very serious, 10 million of the vaccine, which had been prepared, was injected. The next morning (March 25th) the child's temperature was normal, but rose to 100° in the evening, and an injection of 10 million was given. There was marked general improvement.

On March 26th a third inoculation of a similar amount was given. The general condition had now improved; the wound discharge became serous again, and the urine, increasing in quantity, was free from albumen, blood, and casts. The pulse and respiration for the next two and a half days was normal.

On April 1st his temperature rose suddenly to 103°, the wound was found to be purulent, and the urine again became thick and contained albumen. Pulse and respiration were feeble and rapid. The right pleura was explored, a small pocket of pus evacuated, and a tube inserted again. An inoculation of 10 million was given. April 2nd. Temperature fell to 99° and under, but the wound still remained purulent. On April 4th the temperature rose to 101°, and another 10 million pneumococci was injected, as the urine was albuminous.

From April 5th onwards the temperature remained normal, the discharge became serous and gradually dried up. The urine gradually lost its albumen. To accelerate matters and prevent further flares of infection a further inoculation was given on the 6th. The child made a perfect recovery.

The influence of the vaccine was very noticeable, both on the discharge and on the urine, and it is remarkable how quickly so severe a pneumococcal nephritis, which was evidenced by the presence of blood casts and albumen, was each time checked and finally cured by inoculation. The rise

of temperature on April 1st and the subsequent fall was no doubt entirely due to the pocketing of a small quantity of pus, and it would be hardly fair to give any credit to the inoculation on that date beyond generally improving the whole resistance of the patient.

As in the other cases, the lung seems to have cleared without much difficulty and the gravity of the complications were the final factors to be reckoned with. No opsonic indices were done. It would probably have been better if they had, as thereby the various rises of temperature might have been prevented by earlier inoculation. Anyhow, this case illustrates very clearly that it is possible to give a child repeated inoculations at short intervals, the sole guide being the temperature. If we remember that

Chart 2, Case III.—A, Abortive crisis; B, 60 million, 11.50 p.m.; C, 60 million, enema; D, too delirious; E, 4.50 p.m.; F, 9 p.m.

Chart 3, Case IV.—A, Aspirated chest, pus; B, operation; C, wound fomented; D, injection of vaccine; E, injection of vaccine.

probably in all these acute conditions the rise of temperature is almost coincident with the fall of resistance, as has been shown by Latham⁷ in the case of pulmonary tuberculosis, the need for indices as a guide to inoculation seems in such circumstances unnecessary.

CASE V.

H. L., aged 36, under the care of Dr. Norman, was taken ill with left basal pneumonia on December 18th, 1908, at 1 a.m. The infection was of a very virulent type, and eventually extended to both lungs. He died on the morning of December 23rd.

I examined his sputum on December 18th, and found it contained many pneumococci and some *M. catarrhalis*. Cultures were made on blood agar, which grew with extraordinary rapidity, showing lanceolate, chain, and diplococcal forms. It was possible on December 19th to make 50 c.cm. of vaccine containing 80 million pneumococci per c.cm.

The first inoculation of 40 million was given on the evening of December 20th. "He was perspiring freely the first two days, and after the first injection it became more profuse, but otherwise there was no improvement in his symptoms, excepting the continual decrease in fever."

He was given a second inoculation on December 21st, and a third on December 22nd. After these two doses there was a

slight rise, the temperature remaining at the higher level. "The abdomen was markedly distended, and, though there was no special vomiting or tenderness, I rather think he had peritonitis. He had a mottled, purplish rash over the abdomen and thighs not unlike that of typhus." There was albumen in the urine. The heart from almost the first became engorged and dilated, and Dr. Norman procured temporary relief by venesection.

A study of the temperature chart indicates that, whilst possibly the first inoculation had some beneficial effect, the remaining two had none.

The remarkable rate of growth of the pneumococcus outside the body is an indication of its virulence.

Chart 4, Case V.—A, 5 c.cm.; B, hypodermic injection of morphine; C, after washing; D, sponged; E, death.

CASE VI.

A. B., aged 60, labourer, was seen on December 27th. He had had a cough for a few days. His temperature was 102.6°, pulse 120, respirations 30. There was crepitation, bronchial breathing, dullness, and increased vocal resonance at the right base. His sputum was crowded with pneumococci. He was given 25 million of L.'s pneumococcal vaccine at 3 p.m. At 9 p.m. temperature was 103°, pulse 114, respirations 30. The consolidation had now extended to the middle lobe of the right lung. On December 28th, 10.30 a.m., temperature 103°, pulse 120, respirations 36, no further extension; 9 p.m., temperature 102.4°, pulse 120, respirations 40. December 29th, 11 a.m., temperature 102.3°, pulse 138, respirations 48; 11 p.m., temperature 102°, pulse 144, respirations 60. He was given 50 million of the same strain of pneumococcal vaccine. On December 30th the patient was moribund, and he died that evening.

In this case the patient was in a feeble state of health to begin with. The vaccine had no effect upon him, and he died of heart failure, the disease not extending during the last two days of his illness. Apparently, the toxic infection of his heart muscle, rather than a rapid extension of the disease, was the cause of death.

CASE VII.

Mrs. S., aged 63, was seen on March 27th. On March 26th she was seized with a severe bout of vomiting, and rapidly became ill. There was general bronchitis over the upper part of both lungs. There was consolidation of lower left lobe, with pain under the heart and failure of that organ. Ordered digitalis and carbonate of ammonia and brandy.

On March 26th the whole of the lower lobe of the left lung was solid. Temperature 100.6°, pulse 120, respirations 42. The pulse, though regular, was very feeble. The sputum was crowded with pneumococci; 25 million of L.'s pneumococcal vaccine was given. The heart did not respond in the least to stimulants nor to digitalis and ammonium carbonate, and she died at 8.30 a.m. the next day (March 27th).

The failure of the heart in this case was the cause of death, and the vaccine failed to produce the least result.

CASE VIII.

Mr. B., aged 58, a well-nourished man in good circumstances, had an influenzal attack of the gastric type lasting from April 4th to 8th, but with no lung symptoms. On April 12th he was

seized with recurring rigors, and when seen had definite consolidation of the base of the left lung. Temperature 102.6° F., pulse 90, respirations 36. An inoculation of 25 million of L.'s vaccine was given at 6 p.m. At 10.30 a.m. next day he was breathing easily. Respirations 24, pulse 80, temperature 97.8° F. He had sweated profusely during the night. The left base was still slightly dull, but marked redux crepitations could be heard.

The crisis in this case occurred during the night, and after the administration of a vaccine obtained from a virulent fatal case (L.). It is reasonable to suppose that the vaccine was a factor in producing a crisis at so early a stage of the disease, between the second and third days at latest.

CASE IX.

W., female, married, aged 45, stated she had had attacks of asthma every winter, and for the last four winters this has been complicated with acute bronchitis. In the winter of 1906-7 *M. catarrhalis* and pneumococci were found in the sputum. Vaccines were made and used.

On February 17th, 1907, an inoculation of the mixed vaccine, 10 million of each, was given. The temperature dropped four hours after inoculation from 99.8° to normal. The cough became looser, and the asthma was relieved.

On February 21st the cough was dry and troublesome, the sputum contained few pneumococci, but many *M. catarrhalis*. An inoculation of the mixed vaccine was given as before. The next day the cough was looser again, but still paroxysmal; the index to pneumococci was 0.93.

February 25th, 26th, cough was more troublesome; the sputum contained chiefly *M. catarrhalis*; a few pneumococci. On February 27th, inoculation with *M.*

catarrhalis vaccine from another strain (Addison), 0.5 c.cm., and on February 28th cough much easier.

March 1st, cough worse; inoculation with Addison's *M. catarrhalis* vaccine 1 c.cm. March 2nd, cough easier. March 3rd, inoculation as before; had a good night. March 7th, improving; more pneumococci in sputum; gave 0.5 c.cm. of her own mixed vaccine. On March 8th the sputum contained less pneumococci and *M. catarrhalis*.

March 9th gave 0.5 c.cm. of her mixed vaccine; no cough. From this time she remained fairly well.

During the following winter, 1907-8, she was under other care, and had no inoculations. There was a long period of several weeks of acute bronchitis with fever, and she did not really improve until the spring.

On November 7th, 1908, she noticed a running from the nose; next day the nasal discharge was examined and found to contain practically a pure culture of *M. catarrhalis*. She had a bad cold in the head. Asthma developed two days later, and on November 12th the temperature rose suddenly to 102°. The sputum contained quantities of pneumococci and a few *M. catarrhalis*. Cultures and plates were made, and eventually a vaccine containing 160 million pneumococci per c.cm. was obtained.

On November 14th, her temperature remaining up over 100°, an inoculation of 80 million was given. The temperature came down to 99.6° during the night; the expectoration was more abundant. On the evening of the 15th the temperature rose to 100.6°, and another 80 million were given. She had a good night, and on the 16th her temperature was 98.6°. The expectoration became rusty and abundant; the breathing deeper and easier. On November 17th, 18th, and 19th the temperature remained down; the sputum contained a few pneumococci and *M. catarrhalis*.

On November 29th there was an increase of catarrh with asthma; no rise of temperature. Sputum showed *M. catarrhalis* with a few pneumococci. Cultures were made. On December 2nd the nasal discharge showed *M. catarrhalis* alone. On December 6th an inoculation of a *M. catarrhalis* vaccine made from the above strain, 30 million, was given. Exacerbations of asthma were treated with the mixed vaccines on December 11th, 14th, 23rd, and 27th. In each case the asthma was relieved and the expectoration became looser and more abundant.

During January, 1909, she was practically free, only a few *M. catarrhalis* appearing in the sputum.

On February 2nd there was a slight return of asthma, and the mixed vaccine was again injected.

This case is interesting by itself. The details of two attacks in 1906-7 and 1908-9 are similar, as regards the infection, the necessity for frequent inoculation, and the results of the inoculations. The prevalence of the micro-organisms in the sputum has proved a very fair guide as to the variety of vaccine; and, indeed, this has been sub-

stantiated in a number of catarrhal infections investigated. In the last attack very important evidence was obtained as to the rôle the *Micrococcus catarrhalis* plays in these mixed infections. In this case the *M. catarrhalis* paved the way for the pneumococcus to become virulently pathogenic. In another case recently the *M. catarrhalis* was the forerunner of a general infection with the Friedländer pneumobacillus, and Allen and Benham both record cases of mixed infection also with *M. catarrhalis* and *B. septus*.

I think, perhaps, in both attacks a stronger vaccine of *M. catarrhalis* might have been used; but in this case it was difficult to grow enough at one time. In the second attack the inoculation of December 16th produced a definite resolution sputum with a fall of temperature to normal—phenomena similar to cases of a definite lobar type.

CASE X.

E. P., aged 58, male. Gave on September 17th, 1908, a history extending over several years. He had been liable he said, to repeated attacks of nasal catarrh, with loss of smell and taste. Latterly these had been more severe; the bronchial tubes had become affected, and he had several times been laid by with jaundice and catarrh of the stomach. Extreme prostration and muscular weakness followed after an attack. Cultures made from the nasal purulent discharge showed *M. catarrhalis*, Friedländer's pneumobacillus, *Bacillus septus*, and a few lanceolated pneumococci in pairs. Vaccines were made of *M. catarrhalis* and Friedländer, and were given during the next three weeks with little result. The indices to Friedländer were normal. On October 14th, 1908, he started a fresh cold. Cultures of the sputum were made on blood agar on the 17th, and showed more pneumococci, but a preponderance of Friedländer. More Friedländer vaccine was given, with the result that this organism was wiped out of the sputum, and on the 28th the sputum apparently contained only pneumococci. Cultures on blood agar were made and a pure strain of the true pneumococcus obtained; a vaccine was made from this, 95 million per c.cm. in strength. On November 4th he had more or less recovered from this cold, and his index to the pneumococcus was 1.7. He was inoculated with 50 million pneumococci.

On November 7th his index for pneumococcus was 2.2; sputum of the 8th contained pneumococcus, *M. catarrhalis* and *B. septus* in the shed squamous epithelial cells, as well as Friedländer. On November 11th he was inoculated with 50 million pneumococci. His index to pneumococcus was 2.0. On November 14th the sputum was less, thin, and clear, but contained all the above micro-organisms. For the first time his general condition was better. He coughed less and was more vigorous. His appetite was returning and his colour improving.

I determined, as my results with *Micrococcus catarrhalis* and Friedländer vaccines had been negative, and as he had obviously improved after two inoculations with the pneumococcus vaccine, to continue the latter, particularly as in this organism alone he had shown an index differing from the normal. Inoculations were given on November 25th, December 3rd, 14th, and 23rd. During this time he remained free from catarrh, and was in excellent health and spirits. He expressed himself as being in much better condition than he had been for several years, although he had been working the whole time at high pressure in the city. During January, 1909, he was so well that inoculations were unnecessary.

On February 2nd, 1909, the sputum was rather thicker and more abundant. It contained *M. catarrhalis*, pneumococcus, *B. septus*, and Friedländer's pneumobacillus. The *M. catarrhalis* was in large amount. As severe colds had been going through his office, and from other sources I was aware that there was an epidemic of *M. catarrhalis* abroad, I gave him 125 million of a *catarrhalis* vaccine.

This case illustrates the feeble toxicity the pneumococcus may assume. Apparently it was doing little in the respiratory tract, but was probably the cause of his malaise, recurrent jaundice, and bilious attacks. I have little doubt (though the evidence is by no means conclusive) that the pneumococcus was the chief offender, because it was a matter of common remark how his colour, energy, and elasticity of spirits returned after the second inoculation with the pneumococcus vaccine. It will, however, require at least a year's careful observation in this case to settle definitely the etiology. Meanwhile it is worth recording this history in the present series of cases of pneumococcal infection.

CASE XI.

Mr. C., aged 50, was sent to Harrogate in the spring of 1908 for intractable gout, to be under the care of Dr. Wesley Smith, who, however, from the history suspected an infective process, and advised a bacteriological investigation.

"May 13th, 1908.—Twelve months ago Mr. C. had pneumonia, and got better, but a chronic cough remained; the lung has cleared up except a small patch at the left base. Before the pneumonia he had a cough with pus, I believe, but was always able to work. Just over a month ago (April 1st, 1908) the left leg began to swell, which looked like an acute attack of gout,

but there was very little redness in the ankle; fluid in the left knee-joint; no temperature. He is anaemic. There is a slight systolic tricuspid murmur. He feels well in his body, gets up every day, and goes out in a chair."

May 17th. His sputum was sent to the Clinical Research Association. A pneumococcus was isolated and subsequently sent to me.

I saw him myself on May 19th. He was lying in bed pale and anxious, breathing quickly, with a rapid pulse. The heart was irritable, with a definite basal murmur. There was an area of slight dullness with vocal resonance over the right middle lobe behind, and definite dullness over the left base. The expectoration was abundant and purulent.

His left leg was oedematous and painful, particularly in the ankle; there was fluid in his left knee. I came to the conclusion that he was in all probability suffering from a prolonged pneumococcal infection widespread in character. His temperature in the afternoon was over 100°. The opsonic indices of specimens of his blood proved instructive.

The blood index for May 19th was 0.71 against the pneumococcus; on May 21st, 0.88; and on May 23rd, 1.0. On this date he was said to be improving; the oedema fluid from the leg gave an index against the pneumococcus of only 0.09.

The use of Bier's passive congestion method by placing a rubber bandage lightly round the upper part of the thigh for twenty minutes daily was advised, and a course of inoculations with a pneumococcus vaccine as soon as it could be prepared. The Bier's treatment was begun at once, and within two days the leg began to go down, the general condition to improve, and the sputum to decrease.

The first inoculations of 30 million pneumococci were given on June 1st and on June 7th. On June 8th, sputum still less, sweating had stopped, but the anaemia was still severe.

On June 17th a third inoculation was given. Dr. Wesley Smith reported: "Mr. C. is a little better. The left leg, which was so swollen, has gone down, and the right leg is now going down. I am keeping him in bed. For a week the sputum has changed in character—instead of being yellow, it is now merely grey mucus, and only one lump every other day. His lung is much better."

The inoculations were continued at intervals of seven days. On July 7th Dr. Wesley Smith writes: "The mucus now contains no pus; the temperature rises to 100° at night, and is 97° in the morning, but sometimes is normal in the morning. The legs are as swollen as much as before."

The inoculations, etc., were continued as before, but with an increased dose of 250 million. On July 28th Dr. Wesley Smith writes: "Mr. C. is getting better. I am sure the vaccine has set him up and done him a great deal of good. The anaemia is getting better. He is gaining flesh, sleeps well all night. The fluid in the knee is gone, and the oedema in the ankles and legs is much better, but the latter are still swollen. The systolic murmur at the base is gone." The larger amount of vaccine was still continued.

On September 12th the doctor reports: "Mr. C. has greatly improved. The sputum is now like grey mucus, and only comes in small quantities. The temperature rises to 99° every night, instead of 100°. He is no longer anaemic. There is only the faintest trace of endocardial murmur. He has got fat. His legs are still swollen. I have just begun the Bier's treatment again. I left it off until now, because he said it upset him, but it does not do so now."

Mr. C. slowly recovered, and returned home early in December.

The points of interest in this case are that he recovered in six months, although he had been infected for a year previously; that, although his joints were probably infected with the pneumococcus, there was no suppuration; that he began to improve generally directly the Bier's treatment was begun, suggesting that this method actually produced auto-inoculation; that his immunizing power gradually returned, wiping out the general infection; and that this was slow, owing to the feeble anaemic state he had got into from the prolonged toxæmia.

Latham^{9 10} in the discussion on pneumonia at the Medical Society of London, March, 1908, stated that he believed that in the near future a great advance might be made by the adoption of vaccine treatment. The lung tissue had some peculiar power of resistance to the pneumococcus, for an abscess of the lung, as the result of pneumonia, was very rare, whilst in other situations the pneumococcus frequently led to abscess formation. This fact encouraged the belief that vaccine treatment might be of great service. The results of vaccine treatment obtained by Boellke, in a few cases of severe pneumonia, and one case of pneumococcal endocarditis were most encouraging. The results of vaccine treatment in case of delayed resolution of the lung, and in pneumococcal infection of other portions of the body were also most encouraging. In 2 cases of pneumonia he (Latham) had recently administered dead pneumococci by the mouth, and in both cases this was followed by a marked fall in the temperature which was progressive, in one case on the third day, and in the other on the second day.

Floyd and Worthington¹¹ record the following cases of pneumococcic empyema treated with a pneumococcic vaccine :

A girl of 2 years entered the Children's Hospital, Boston. February 19th, 1907. For eight days previously there had been pain in the right side. On the day before admission the skin broke on the right front of the chest and considerable pus discharged. On the day of entrance a portion of the eighth rib was resected and a few ounces of pus evacuated. The child was thin and weak and in a precarious condition.

February 22nd. Culture from discharge showed pneumococci. Index to the organism was 0.6. A stock vaccine was used and 50 million organisms given.

February 23rd. Index 0.25.

February 24th. Index 1.17.

February 25th. Index 2.25, child brighter, sinuses discharging freely.

February 26th. Inoculated 50 million organisms.

February 27th. Index 0.69.

February 28th. Index 2.14. Discharge lessening. Eating better. Decidedly stronger.

March 1st. Inoculated 50 million organisms.

March 2nd. Index 1.38. Gaining daily. Inoculations were continued regularly, and the child gained rapidly. After about three weeks she went to the country with no discharge from either sinus and in excellent condition.

A boy of 3½ years entered the Children's Hospital on February 15th, 1907. There was a history of pneumonia, with a crisis of five days previous to entrance. This was followed by a second rise of temperature, and a diagnosis of empyema was made. The portion of the eighth rib in the posterior axillary line was resected and about a quart of pus evacuated. A culture showed a pure growth of the pneumococcus present.

February 18th. Opsonic index 1.1.

February 19th. Patient inoculated with 50 million pneumococci.

February 22nd. Index 1.59.

February 23rd. Index 1.5. Inoculated with 50 million organisms.

February 24th. Index 0.45. The child was restless following the last inoculation, and the temperature rose to 105°.

February 28th. Index 1.2. Temperature still elevated, but general condition improving.

March 1st. Index 0.72. Inoculated with 50 million. Discharge slight, and there has been a steady gain in weight and strength.

March 5th. Temperature normal; general condition good.

March 7th. Index 1.2.

March 13th. Index 2.0. Very slight discharge from sinus. Up about the ward. Fairly well. The general gain continued and the sinus closed rapidly. Child sent to the country for a few weeks.

A girl of 3 years entered the Children's Hospital on February 25th, 1907, with signs of infection on right thigh. The following day an incision was made and about 1 oz. of pus evacuated from the femur. A culture from the wound showed the pneumococcus.

February 28th. Index to pneumococcus 0.71.

March 1st. 50 million pneumococci given.

March 4th. 50 million pneumococci given.

March 8th. Index 1.1. Condition of wound much improved; very slight discharge.

March 10th. Incision closing rapidly; no discharge.

March 19th. Wound healed solidly. Child sent home well.

The criticism which presents itself in the two cases of empyema, is that in both cases sufficient time was not given after operation to see the effect produced by the evacuation of the pus and the consequent autoinoculation which invariably takes place under such conditions. In the first case the index was 0.6 two days after inoculation, probably indicating a negative phase. This interpretation is supported by the fact that a fall to 0.25 was registered the next day, intensifying the general low bacteriotropic pressure. That the index rose rapidly is not surprising, but since the first dose produced so marked a negative phase in this case it should certainly have been reduced in the second inoculation. It was not, with the result that a profound drop from 2.25 to 0.69 was produced. In the second case, on the second inoculation of 50 million, a deep negative phase from 1.4 to 0.45 was produced, involving a rise of temperature, which lasted several days. There is no evidence on paper that this child would not have done perfectly well without special inoculation, and the notes show that there was actually a set-back caused by inoculation of what certainly in this case seemed to be too large a dose. My own experience is that 10 to 20 million of this vaccine is quite sufficient for a child. It is to be regretted that the temperature charts were not given in the reports.

The third case was certainly one for inoculation. These infections of the thigh, so common in young children, and so often associated with the lower epiphysis of the femur, yield quickly to the effects of inoculation if given after the disturbance caused by the operation has passed off.

CONCLUSIONS.

It may be taken as a clinical fact that in pneumonia death usually takes place through failure of the heart. Particularly obvious is this in the cases of virulent pneumonia, where death occurs about the fourth day of the disease. Jürgensen aptly says, "It is the heart, and always the heart, upon which the burden is ultimately thrown. Death results from the insufficiency of the heart."⁹ It is easy to understand, therefore, why in virulent pneumonia

with early heart failure the vaccine treatment in many cases, though it may produce a fall in the temperature, fails. The toxæmia produced is already too profound for just the arrest of the infecting process to be successful. It would seem logical that scientific treatment demands not only the exhibition of the vaccine at as early a stage as possible, before an overwhelming toxæmia has occurred, but also the introduction of a sufficient quantity of an antitoxin at the same time. I am not aware that any work has been hitherto carried out on these lines—the employment of both vaccine and antitoxin—at the same time.

It is not improbable that, in the case of the pneumococcus, the success of a vaccine is not simply due to the fact that it should be autogenous. A good deal of stress is laid upon this feature; but the fact of a vaccine being autogenous narrows down the issue to (1) the right organism being selected, and (2) the vaccine being prepared, if not unduly subcultured, from an organism of requisite virulence.

Fraenkel's pneumococcus is, however, as far as we know, inviolable; it is not like the streptococcus (Gordon), an inclusive term for several varieties. On the other hand, we know from the staphylococcus and *coli* bacillus that these may be so subcultured as to lose their original virulence, and that vaccines so prepared are of little use therapeutically. If, then, a potent and reliable stock pneumococcus vaccine is to be obtained, it should be made from as virulent a strain as possible. There is unhappily no difficulty in the early months of the year in obtaining as much as is wanted. The truth of this argument can only be verified by a great number of observations. My own results, as far as they have gone, certainly tend to support this view.

With regard to the treatment of acute pneumonia by inoculation, the practical conclusions which alone can interest the busy clinician are :

1. That successful inoculation for pneumonia is possible.
2. That inoculation does no harm.
3. That a vaccine from one or a number of virulent strains should be used.
4. That it should be introduced as early as possible.
5. That the estimation of the opsonic index is not necessary.
6. That the observation of the temperature and physical signs is in pneumonia a sufficient guide in gauging the repetition of the dose.

Infections of the lung by the pneumococcus which fail to resolve after an acute pneumonia, as well as pneumococcic infections of other areas, ought certainly to be treated with a pneumococcic vaccine; and these cases appear to afford a reasonable prospect of success.

To place the whole question on a sound scientific basis, needs, however, a vast inquiry by many workers. It was thought, however, that the above observations were worth recording, as helping in some small measure to clear the ground, and so indicate the direction of a research which has already lagged behind all too long.

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- ¹ *Proc. Roy. Soc. Med.*, vol. i, No. 1, p. 3. ² *Ibid.* ³ Sternberg's *Bacteriology*, section v. ⁴ A. Fraenkel, *Bakt. Mikr., Zeit. für klin. Med.*, Berl., 1886, X, 401. ⁵ Macdonald, *Path. Soc. Trans.*, January 17th, 1905, vol. i. ⁶ *Proc. Roy. Soc. Med.*, vol. i, No. 2, p. 45. ⁷ *Ibid.*, p. 46. ⁸ Douglas, *Lancet*, 1906. ⁹ Latham, *Proc. Roy. Soc. Med.* ¹⁰ Latham, *Practitioner*, April, 1908, p. 448. ¹¹ Floyd and Worthington, *Boston Med. and Surgical Journal*, vol. clviii, No. 1, January 2nd, 1908. ¹² Eyre, On the Pyrogenic Activities of the Pneumococcus, *Lancet*, February 22nd, 1908, p. 535. ¹³ Pane, *La Riforma Medica*, 1898, I, 194.

BEQUESTS of £5,000 to St. Bartholomew's Hospital and of sums of £500 each to the Kensington Dispensary and Children's Hospital and the Home for Confirmed Invalids, Highbury, are contained in the will of the late Mrs. Holborn, of Campden Hill, who died on April 28th.

THE French Surgical Association will hold its twenty-second congress in Paris next October, under the presidency of Dr. G. Richelot, surgeon to the Paris hospitals. The opening meeting will take place on Monday, October 4th. The following questions are proposed for discussion : (1) Surgery of the arteries; (2) care of the patient before and after abdominal operations; (3) surgical intervention in injuries of the spine and spinal cord. An exposition of surgical instruments, illuminating apparatus, and dressings will be held during the congress. The General Secretary of the Congress is Dr. Walther, 68, rue de Bellechasse, Paris (7e).