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**REPORTS FOR THE YEARS 1910 AND 1911 FROM THE
EAR AND THROAT DEPARTMENT OF THE ROYAL
INFIRMARY, EDINBURGH.**

Under the charge of A. LOGAN TURNER, M.D., F.R.C.S.E., F.R.S.E.

IV.

**A CONTRIBUTION TO SERUM AND VACCINE THERAPY
IN THE TREATMENT OF INTRA-CRANIAL COMPLI-
CATIONS OF MIDDLE-EAR SUPPURATION.**

BY A. LOGAN TURNER, M.D., F.R.C.S.E.

In a recent discussion upon "The Factors which Conduce to the Successful Treatment of Brain Abscess," at a meeting of the Otological Section of the Royal Society of Medicine, reference was made to the use of serum and vaccines as additional therapeutic measures. It is with the object of recording our own experience in this connection, without reference to the work of others, that the following cases of intra-cranial complication of ear disease are published. The cases have not been detailed in full, our intention being merely to emphasise those points which have a more direct bearing upon the subject under consideration.

SERUM THERAPY.

The following five cases were treated with anti-streptococcic serum subsequent to operation; three recovered and two died. Four were cases of chronic middle-ear suppuration, one of them associated with disease of the labyrinth, while the fifth was a case of acute otitis media with labyrinthine symptoms. The intracranial complications were as follows: Acute lepto-meningitis in three, sigmoid sinus thrombosis in one, and serous meningitis in one. Two of the cases of acute lepto-meningitis and the case of serous meningitis recovered; one case of lepto-meningitis and the case of sinus thrombosis were fatal.

CASE 1.—W. L——, aged sixteen. Chronic middle-ear suppuration (L.) and purulent meningitis; recovery. The patient had been seriously ill for one week before his admission; vomiting, vertigo and headache, with elevation of temperature; no rigors. On admission, November 10, temperature 100° F., pulse 68, respirations 18. Looked ill; frontal headache; neck rigidity; veins of the fundus dilated in both eyes; no Kernig; superficial and deep reflexes normal. Cerebro-spinal fluid under pressure and turbid; a quantity of albumen; polymorphonuclears 40 per cent.; lymphocytes 60 per cent.; no organisms seen in films; no growth obtained in broth. Complete mastoid operation; middle-ear cleft contained *Streptococcus pyogenes*, *Bacillus proteus vulgaris*, a Gram-positive anaërobe. November 11, 12, 13, 14, temperature 99° to 102·8; severe headache; no vomiting. November 12, temperature 102·8°. 10 c.c. anti-streptococcic serum subcutaneously; no definite effect on the temperature. November 14, temperature 101·6°; headache; neck rigidity; double Kernig. Leucocytosis 15,300; polymorphonuclears, 91 per cent. Cerebro-spinal fluid turbid; pus deposit; polymorphonuclears 70 per cent.; lymphocytes 30 per cent.; *Streptococcus pyogenes*, *Bacillus proteus vulgaris*, a Gram-positive anaërobe, obtained. 10 c.c. anti-streptococcic serum subcutaneously. November 15, temperature normal, a small quantity of cerebro-spinal fluid withdrawn, and 10 c.c. of anti-streptococcic serum administered, 5 c.c. into the spinal canal. Temperature in the evening 100·4°. November 16, cerebro-spinal fluid again withdrawn, and 10 c.c. anti-streptococcic serum injected into spinal canal. Examination of this specimen of cerebro-spinal fluid, i. e. the fluid from the fourth puncture after three doses of serum, showed a mere trace of albumen, a few polymorphonuclears and lymphocytes and no organisms on culture. November 17, temperature 100·4°. During the following eight days the temperature ranged from 98·4° and 99° to 101°. Three further doses of anti-streptococcic serum were given subcutaneously during this period. Leucocytosis fell to 8600. The patient's general condition varied a little from day to day. Twenty days after admission his symptoms had disappeared and he commenced to put on weight. He was discharged cured.

CASE 2.—J. R——, aged twenty-nine. Chronic middle-ear suppuration (L.); labyrinthine disease and meningitis; recovery. The patient had had acute symptoms for one week, namely, fever, headache and vomiting. He had also emaciated. He had complained a good deal of vertigo. On admission, June 11 temperature was 99° F., pulse 100; leucocytosis 11,000. He had neck rigidity and pain on moving the head; double Kernig; frontal headache. There was well-marked spontaneous nystagmus on looking to the right or healthy side only.

The radical mastoid operation and a double vestibulotomy were performed, the external semi-circular canal containing a greenish-coloured fluid. The cerebro-spinal fluid removed by lumbar puncture was under slight pressure; turbid; alkaline; contained a considerable quantity of albumen; no reduction of Fehling; many polymorphonuclears and a few lymphocytes; degenerated endothelial cells; no organisms. From the mastoid cells and labyrinth secretion the following organisms were grown: *Streptococcus pyogenes*, a *diphtheroid bacillus* and a *Gram-negative bacillus*. On the following day, June 12, the temperature was normal; pulse 102. A second lumbar puncture was made, and after withdrawal of fluid 10 c.c. of anti-streptococcic serum were injected, 5 c.c. into the spinal canal and 5 c.c. subcutaneously. Examination of the second specimen of cerebro-spinal fluid showed less turbidity, less albumen and fewer cells. Films revealed *Gram-positive cocci*, *Gram-positive* and *Gram-negative bacilli*, but no growth was obtained. Five c.c. of anti-streptococcic serum were again injected into the canal. The patient was feeling better; the temperature was normal and the pulse 92; there was still neck rigidity and double Kernig. June 13, temperature 99°, pulse 98. Cerebro-spinal fluid almost clear and containing a mere trace of albumen and a few cells. A few of the organisms above mentioned were still seen in films, but no growth was obtained. June 14: Temperature 100°. On the following day it fell to normal and remained so. Four days later the neck rigidity and Kernig sign disappeared and the patient was finally discharged.

CASE 3.—H. K—, aged nineteen. Acute middle-ear suppuration (L.), labyrinthitis and symptoms suggesting a serous meningitis. The patient had suffered from pain in the left ear intermittently for eight days. There was slight deafness, redness of the membrane but very little bulging. The temperature remained normal. On the evening of the ninth day there was severe pain, temperature 104° F.; pulse 100. Paracentesis was performed. On the morning of the tenth day temperature 101·8°, discharge from the ear and slight mastoid tenderness. At 11 p.m. the patient vomited. February 18 (eleventh day): Temperature 102·2° F. pulse 96; the patient had felt very sick all night and vomited again in the morning. The sickness was associated with severe vertigo, the bed constantly appearing to him to rise up. There was marked lateral nystagmus on deviating the eyes both to right and left. The patellar jerks were much exaggerated; double ankle clonus; plantar flexion; slight Kernig. Pain on moving the head. A high degree of deafness in the left ear; the medium tuning-fork was lateralised from the vertex to the sound side. The complete mastoid operation was performed; pus was found in the mastoid cells. The *Streptococcus pyogenes* was found in the pus. 10 p.m.: Temperature 100·2°; 10 c.c. of anti-streptococcic serum injected subcutaneously. February 19: a.m. temperature 100° and p.m. temperature 103°. The vertigo and vomiting had ceased, and the nystagmus, now less violent, was only observed on looking to the sound side. The pain in the neck and the Kernig sign were more marked. Lumbar puncture was performed and 10 c.c. of anti-streptococcic serum were injected, 5 c.c. into the spinal canal and 5 c.c. subcutaneously. The cerebro-spinal fluid was under considerable tension but clear. A distinct ring of albumen was obtained and the reduction of Fehling was incomplete; one or two polymorphonuclear cells but no organisms were observed. February 20: a.m. temperature normal; patient felt better; no giddiness, no nystagmus. P.m. temperature 100·2°. February 21: Temperature 101°; 10 c.c. of anti-streptococcic serum were injected subcutaneously. The temperature gradually fell to normal and the nerve symptoms disappeared.

CASE 4.—C. S—, aged seventeen. Chronic middle-ear suppuration (L.), labyrinthine suppuration and purulent meningitis; death. The patient had had

acute symptoms for nearly three weeks—fever, headache, vomiting and pain at the back of the neck. On admission temperature 102.8° F., pulse 121; headache; neck rigidity; paralysis of left external rectus; slight left facial paralysis; double Kernig; well-marked spontaneous nystagmus on looking to the healthy side; low voice heard at one foot from the diseased ear; B.C. > A.C.; T.F. on vertex lateralised to the diseased side. Although the history of the illness was a long one and the patient was obviously ill, operation was carried out. The complete mastoid operation and double vestibulotomy were performed, the external semi-circular canal containing pus and granulations; the facial nerve was found exposed in its canal. Lumbar puncture: The cerebro-spinal fluid was under tension and turbid; distinctly alkaline; a quantity of albumen; no reduction of Fehling; thick deposit on standing; many degenerated polymorphonuclears and occasional lymphocytes. Films made from the pus in the mastoid showed *Gram-positive cocci* and *Gram-positive bacilli*, but no growth was obtained in broth by aerobic methods of cultivation; no apparent growth occurred in broth, nor did agar plates inoculated from the broth show any growth. The cerebro-spinal fluid was found to contain *Gram-positive single cocci*, *Gram-positive bacilli* in large numbers and a few *Gram-negative bacilli*. The Gram-positive bacilli were carefully investigated by Dr. F. H. Reynolds, who regarded them as the *Bacillus aërogenes capsulatus*, while the Gram-negative bacilli found in broth culture were probably dead forms of the same organism; the Gram-positive cocci may have been coccal forms of the same organism. Ten c.c. of antistreptococcal serum were injected into the spinal canal after drawing off the cerebro-spinal fluid. On the following day the temperature fell to normal but the pulse remained rapid. Lumbar puncture was again performed and a second dose of the serum administered in the same way. The patient never rallied, however, the pulse varying from 125 to 144, and she died two days later. *Post-mortem* revealed very extensive purulent cerebro-spinal meningitis extending over the whole base of the brain and down the spinal cord.

CASE 5.—M. W.—, aged fifty. Chronic middle-ear suppuration (R.) with sigmoid sinus and internal jugular vein thrombosis; death. The history revealed the fact that vomiting, rigors and sweating had occurred at intervals for a fortnight. Immediately after admission the temperature rose to 105.6° F.; there was a severe rigor and the temperature fell in a few hours to normal. The radical mastoid operation was performed and a dirty brown, soft sinus wall was exposed. The vessel contained a thin fetid fluid and behind the knee a septic clot which was removed. The internal jugular vein contained pus. It was ligatured just above the sterno-clavicular joint, at which point a healthy-looking clot was exposed. The pus in the mastoid, sigmoid sinus and vein contained an undescribed *Gram-positive diplococcus* and the *Bacillus coli*. Blood taken from the lobule of the ear gave a growth of a similar *Gram-positive diplococcus* and an abundant growth of *Streptococcus pyogenes*.

The temperature remained normal for three days after the operation and though it then rose and was somewhat irregular for the next three days, there was no further rigor until the sixth day after the operation. Anti-streptococcal serum was then administered, and during the following seven days five doses of 10 c.c. were given. During the same period four rigors occurred, two of them being very severe with the temperature reaching 106° F. No improvement took place and the patient died on the seventh day. The post-mortem revealed a septic thrombus in the right innominate vein and some minute abscesses in the lungs.

Remarks.—Of the five cases recorded above, three, with chronic middle-ear suppuration, had meningitis, two evidently of a purulent

character and one of a less severe type; in two of them there was associated labyrinth disease. The fourth case was one of serous meningitis complicating acute middle-ear suppuration and presenting symptoms of acute serous labyrinthitis. The fifth case had septic thrombosis of the sigmoid sinus and internal jugular vein as a complication of chronic middle-ear suppuration. In three of the cases of meningitis and in the case of sinus thrombosis the *Streptococcus pyogenes* was the predominant organism. In the remaining case of meningitis the *Bacillus aerogenes capsulatus* was probably the active organism. In all of them a polyvalent anti-streptococcic serum was used. It was employed in the case of meningitis, in which the *Bacillus aerogenes capsulatus* was eventually recognised because the micro-organisms seen in films might have been streptococci, and it was deemed advisable not to postpone the introduction of the serum until their exact nature was established.

The cases may be divided clinically into two groups, each group in itself possessing certain common features. Thus, in the first, we have three (Cases 1, 2, 3) which terminated in recovery, namely, a purulent meningitis, meningitis of a less severe type, and a serous meningitis. They came under treatment at a comparatively early period in the history of the complication, the first two at the end of a week, the third within twenty-four hours of the onset of the acute symptoms. In two the temperature on admission was 100° F., in one 99° F. In all the pulse was good. The peripheral focus of infection was at once removed, lumbar puncture was performed, and within forty-eight, twenty-four, and twelve hours respectively after the operation anti-streptococcic serum was injected; the injections were repeated at short intervals, sometimes into the spinal canal, sometimes subcutaneously.

In the second group we have two cases (4 and 5), one with purulent meningitis and the other with sigmoid sinus thrombosis and extensive involvement of the internal jugular vein. Both terminated fatally. They came under treatment at some considerable time after the onset of the acute symptoms, the first nearly three weeks, the second after the interval of a fortnight. In the first the temperature on admission was 102° F., the pulse 121. In the second a severe rigor, with the temperature 105·6° F., occurred immediately after admission. Both patients were obviously ill in contra-distinction to those in the first group. Immediate operation was performed in each case, and a careful attempt made to remove all the focal sepsis. In the first case lumbar puncture was carried out and anti-streptococcic serum was used at

once, but in the second the employment of the serum was delayed until the sixth day after the operation. The *post-mortem* in each case revealed the extensive nature of the septic infection.

It is obvious from a study of the two cases (4 and 5) that the disease had progressed too far to admit of a successful result from surgical interference alone. The case of meningitis died on the third day after admission with extensive purulent basal meningitis spreading along the spinal meninges. In the case of sinus thrombosis it was probable, from the *post-mortem* appearances, that the disease had already reached the innominate vein at the time of operation, though the appearance of the clot at the lower end of the internal jugular suggested that an aseptic thrombus had been reached at the site of the ligature. The serum proved ineffectual in counteracting the virulence of the infection. It is possible that if the serum had been commenced immediately after the operation in Case 5, instead of being delayed for six days, a more satisfactory result might have been obtained.

A study of the first group (Cases 1, 2, 3) raises the question as to whether the serum played any part in bringing about the successful results. On the other hand, how far was recovery due to the fact that these cases came under surgical treatment at an early period in the history of the illness and whether operation was not entirely responsible for the cure. It is, of course, difficult when dealing with such a small number of cases to draw reliable deductions. In Case 1 no organisms were found in the specimen of cerebro-spinal fluid withdrawn on the day of admission. Four days after the operation, in spite of a subcutaneous injection of anti-streptococcic serum, the temperature remained practically unaffected, and a second specimen of the fluid contained pus and organisms similar to those already found in the mastoid cells. After a second dose of serum, however, administered subcutaneously, and a third injected into the spinal canal after withdrawal of fluid, the fourth specimen of cerebro-spinal fluid showed a marked improvement and no organisms were grown from it. Four further doses of serum were given, and though the patient's general condition varied from day to day, he slowly recovered. In Case 2 the infection must be regarded as a mild one. The organisms found in the cerebro-spinal fluid were probably dead as they were only seen in films, no growth being obtained. This occurred before any serum had been used. In Case 3 the very early operation with removal of the primary focus probably sufficed in itself to bring about a cure.

We are of the opinion that Case 1 alone furnishes any positive evidence of the efficacy of the serum therapy as an adjunct to operation. In Cases 4 and 5, in which some additional agent was most desired, the serum failed to benefit the patients. In the cases just recorded the anti-streptococcic serum was employed on the supposition that the *Streptococcus pyogenes* was the virulent organism. While undoubtedly this was the predominant organism present in four of the cases, it was not the only one recognised. When using serum care should be taken not to overlook the importance of the part which all the organisms present may play in the propagation of the infection.

VACCINE THERAPY.

The treatment of the following four cases was assisted by the administration of autogenous vaccines. Two were cases of sigmoid sinus thrombosis, and in two there was sinus thrombosis associated with meningitis. Three recovered and one died:

CASE 6.—T. M.—, aged twenty. Chronic middle-ear suppuration (L.), with septic thrombosis of the sigmoid sinus; recovery. Symptoms of acute illness commenced six days before his admission; fever, headache and vomiting. The patient at first denied having had any rigors until again questioned after his operation, when he admitted their occurrence.

September 10.—The radical mastoid operation was performed; a very fetid peri-sinus abscess was opened. Dark coloured, foul-smelling fluid escaped through a small opening in the sinus. The sinus was freely incised and the broken-down clot evacuated. The internal jugular vein was not ligatured, as a healthy-looking clot was exposed at the lower end of the sinus and no history of rigors had been obtained. The *Bacillus proteus vulgaris* and *Staphylococcus aureus* were obtained from the pus in the mastoid and in the sinus. No organisms were found in the blood taken from a vein at the bend of the elbow. Five days later he had a rigor and two days later he had a second and a third rigor. September 18: The sinus was re-investigated: pus was found in the sinus behind the gauze plug; the bulb was exposed and the vein ligatured. The temperature fell to normal. September 20: A *Proteus vaccine* was commenced; dose 200 millions. Five injections were given on five consecutive days. With the exception of a rise of temperature to 102° F. on the evening of the day on which the first vaccine was given the temperature remained normal. A slight rise, however, to 99.8° F. occurred on September 28. The patient felt better. He had a slight cough and a few crepitations could be heard over the left lung. From September 26 to 30 the temperature varied slightly from 97° to 99°. September 30: Temperature rose to 101.8° F. and on October 1 to 103.4° F., but no rigor occurred. A *daily vaccine* of *Bacillus proteus vulgaris* was again started, the temperature during the following eight days varying from 99° to 103°, but always with a downward tendency until October 9, when it reached the normal. The vaccines were then stopped. On October 13 there was again a rise to 101°. Five further injections of the vaccine were made. From this time the patient made an uninterrupted recovery.

CASE 7.—Mrs. D—, aged forty-one. Chronic middle-ear suppuration (L.), with septic thrombosis of the jugular bulb and vein; recovery. The patient had been treated for a fortnight for influenza and during that time she had had more than one rigor. She was admitted on March 11 and operated upon by Dr. J. S. Fraser. The internal jugular vein, which contained pus, was ligatured above the sterno-clavicular joint and dissected out. The radical mastoid operation was performed. The sigmoid sinus was healthy. The pus from the vein contained the *Bacillus coli* and a few short *Gram-positive bacilli*. The temperature on admission was 99° F.; on the following day after operation 100·2. During the next four days there were no rigors; the temperature varied from normal to 99° and 100° and the pulse from 100 to 121. No organisms were grown from the blood taken from a vein about the elbow. The wounds showed a healthy reaction. The patient's general condition, however, was poor. March 17: Temperature rose to 101°, 101·8° and to 102·4° F. On the 18th *Bacillus coli vaccine* (one dose, 40 millions) was administered. Between this date and March 23 the temperature swung from normal and 99° to 102° and 102·6. March 23: A second dose of the vaccine was given. With the exception of a rise of temperature the same evening no further exacerbation took place and the patient rapidly recovered.

CASE 8.—L. M.D.—, aged thirty-one. Chronic middle-ear suppuration (R.), with labyrinth suppuration; sigmoid sinus thrombosis with symptoms and signs of meningitis; recovery. Patient had had severe pain in her right ear for one week and had vomited on the day before admission. She looked ill and suffered from very severe headache. Temperature 101·4° F., pulse 116. There was entire absence of cochlear and vestibular responses in the right ear. Shortly after admission, December 16, she had a rigor. Complete mastoid operation, vestibulotomy and drainage of the meninges through the labyrinth. The sinus wall exposed and found of normal appearance. *Lumbar puncture*: Cerebro-spinal fluid under great tension but not turbid; no deposit; cultures of *Streptococcus pyogenes* and *Staphylococcus aureus* were obtained from the fluid. The pus from the mastoid showed *Streptococcus pyogenes* and *Bacillus proteus vulgaris*. There were no clinical signs of meningitis at this date. During the next three days she had three rigors, consequently on December 19 the sinus was explored. From its lower part a thin, foul secretion was evacuated; the internal jugular vein was ligatured and the bulb washed through. The secretion contained the *Bacillus proteus vulgaris*. The temperature was normal for two days and then commenced to rise. December 22: Temperature 100·2, pulse 120. *Vaccines commenced*: 50 millions of *Streptococcus pyogenes*; 100 millions of *Bacillus proteus vulgaris*. These were given each day for the next nine days. During this period the temperature varied from normal to 100° and 102°. January 1: *Vaccines discontinued*. The patient's general condition much improved; appetite better; in very good spirits and anxious to get up. The temperature still remained irregular, but with the exception of a more marked rise on two occasions was generally lower. January 11: Temperature remained normal; cerebro-spinal fluid ceased to flow through the labyrinth. January 15 and 16: Meningeal symptoms showed themselves; headache; double Kernig: rising temperature; cerebro-spinal fluid turbid and under tension; *Staphylococcus aureus* and *Gram-negative bacilli* obtained in cultures. January 16-26: Temperature varied from 99°-101·6° F. January 26: *Vaccine of the Staphylococcus aureus* commenced and given each day for six days. January 29: Temperature 102·2° F. Another lumbar puncture made; cerebro-spinal fluid still turbid and under increased pressure. February 1: Temperature 98·4° F.; no further rise; the same vaccine continued every other day until February 6. February 9: Lumbar puncture; cerebro-spinal fluid clear; no tension; sterile. Patient later discharged cured.

CASE 9.—J. W.—, adult male. Chronic middle-ear suppuration (L.), with sigmoid sinus thrombosis and meningitis; death. The patient had symptoms of acute illness for twelve days before his admission, fever and sweating and one rigor. February 15: On admission temperature 100° F., pulse 66. Leucocytosis 6300, polymorphonuclears 83 per cent. No meningitic phenomena. Cerebro-spinal fluid under considerable tension, clear; no cells; does not reduce Fehling; sterile. Complete mastoid operation and sinus exposed; no peri-sinus abscess; bone healthy, and sinus wall of normal appearance. Blood from vein in forearm sterile. The temperature continued to be irregular, and though there were no rigors, the patient perspired a good deal. February 22: On account of the sweating the sigmoid sinus was now opened and the internal jugular vein ligatured; a breaking-down clot was found in the sinus. The *Streptococcus pyogenes* was obtained from the sinus, and the same organism was now obtained from a vein in the arm. February 24: *Streptococcal vaccines commenced*, dose 10 millions. Eight vaccine injections made, one every other day. During this period to March 12 temperature varied from 99°–102°. The patient's general condition was very good—he slept and ate well, and put on a little flesh, and his wounds showed healthy reaction. At the same time he occasionally perspired. March 13: Temperature 104° F., headache, vomiting, double Kernig, turbid cerebro-spinal fluid; no organisms. March 16: Delirious. *Streptococcus pyogenes* obtained on culture from the cerebro-spinal fluid. Death on March 20. The *post-mortem* showed an extensive basal meningitis.

Remarks.—Four cases are included in this group (6, 7, 8, 9). All had chronic middle-ear suppuration, and in all there was septic thrombosis of the sigmoid sinus or internal jugular vein, and in two (8 and 9) there was associated meningitis. The first three cases recovered; the fourth proved fatal from meningitis. The organisms found in the infected sinuses were as follows: *Bacillus proteus vulgaris* and *Staphylococcus aureus* (Case 6); *Bacillus coli* (Case 7); *Streptococcus pyogenes*, *Bacillus proteus vulgaris*, and *Staphylococcus aureus* (Case 8); *Streptococcus pyogenes* (Case 9). In Cases 8 and 9, in which meningitis was also present, similar organisms were found in the cerebro-spinal fluid with the exception of the *Bacillus proteus* (Case 8). Operation was performed in every instance, and autogenous vaccines were employed.

If we analyse the fatal case (9) we find that acute symptoms developed twelve days before admission. Owing to the healthy appearance of the wall the sinus was not opened at this date. It was demonstrated on the following day by the negative bacteriological report that there was no infection of the general circulation. On account of irregularity of temperature and sweating, however, the operation on the sinus was performed seven days later, and a streptococcal vaccine was commenced. Eight injections in all were given, one every alternate day. Although the patient's general

condition improved and the wounds showed a healthy reaction, the vaccines failed to prevent the development of a rapidly fatal streptococcal meningitis, which developed seventeen days after the commencement of the vaccines. If the operation upon the sinus had been carried out earlier it is possible that the patient might have responded more satisfactorily to the vaccine therapy.

Cases 6, 7, and 8 came under treatment six, fourteen, and seven days respectively after the onset of acute symptoms. In Case 6 five injections of a vaccine of *Bacillus proteus vulgaris* were given on consecutive days after the second operation on the sinus and vein. The injections were then stopped as the patient felt better, and the temperature did not rise above 99° F. Five days later, however, there was an exacerbation, the temperature going up to 101.8 and 103.4. The vaccines were re-commenced and given daily for nine days, the temperature gradually falling to normal. Four days later a second exacerbation took place, the temperature rising to 101. Five further injections were therefore given, and the patient slowly recovered without another relapse. In this case, I think, we are entitled to assume that the vaccines were of value. After each series of injections distinct improvement took place. In all probability if the first series of injections had been continued over a longer period the relapses would not have occurred.

In Case 7, notwithstanding the delay in the admission of the patient, recovery followed the removal of the infected area. In this case, however, no general blood infection had occurred. Two injections of *Bacillus coli* vaccine were given, but it is difficult to estimate their influence on the progress of the case. The wounds were showing a healthy reaction, and the patient, though feeble, was improving before the first injection was administered; the temperature, however, was distinctly irregular.

In Case 8, operated upon seven days after the onset of symptoms, the illness was very prolonged. In addition to the operation upon the sinus, the cerebro-spinal fluid was constantly draining for a period of three weeks. During this time nine injections of a mixed vaccine of *Streptococcus pyogenes* and *Bacillus proteus vulgaris* were given on successive days. The patient's condition improved in a marked way. Shortly after the cessation of the flow of cerebro-spinal fluid meningeal symptoms showed themselves. The cerebro-spinal fluid no longer contained the *Streptococcus pyogenes*, however, but the *Staphylococcus aureus* and some Gram-negative bacilli were grown from it. A staphylococcal

vaccine was, therefore, commenced, nine injections being given—six on successive days, the remaining three on alternate days. Gradual improvement and recovery took place. It is difficult in this case to apportion the relative therapeutic value of drainage of the meninges and vaccine administration. With the cessation of the drainage and stoppage of the vaccines symptoms again showed themselves. Although recovery supervened upon the second series of injections, lumbar puncture was twice carried out.

Here, also, as in the cases treated with serum, the numbers are so few that it is difficult to estimate the exact effect of vaccine therapy in this class of case. For the same reason it is not possible to draw any deductions as to the relative value of serum and vaccine. While we have laid stress upon the necessity of early operation in meningitis and sinus thrombosis, we can recall more than one case in which prompt interference failed to effect a cure. On the other hand, delayed operation, of which Case 7 is an example, may be followed by recovery. The virulence of the infection is a factor of such supreme importance that the result in any given case must, to a large extent, depend upon this element. Nor, indeed, can the body-cell resistance be overlooked. When we take a comprehensive view of the nine cases which form the text of this paper, and when we note that six of these terminated in recovery, we are, I think, justified in concluding that sera and vaccines have played some part in bringing about these results. In every case of otitic intra-cranial complication there should be no hesitation in employing one or other, as the case may be, in association with the recognised lines of surgical procedure.

I wish, in conclusion, to acknowledge my indebtedness to Dr. F. Esmond Reynolds and to the Staff of the Pathological Department of the Royal Infirmary for their valuable assistance in the bacteriological work and in the preparation of the vaccines.