formation are stressed. The bacteriological findings are summarized. The main features of the acute, recurrent, and chronic forms are described. The largest group is the recurrent one, with some overlap of the other groups into this. The acute cases never pursue as fulminating a course as do some of the *Staph. aureus* ones. In the recurrent group the exacerbations tend to be more acute and more severe than those in the *Strep. viridans* cases, and at times pass unexpectedly on to suppuration within the gland and marked constitutional disturbance.

Suppuration and fistula formation are the only likely complications. In the recurrent cases the parotid saliva is characteristically profuse and tenacious, and contains pus and a large amount of mucus. The sialographic changes are described in the recurrent cases and are usually grosser in type than in the *Strep. viridans* cases. The various lines of treatment are outlined. The main differences between recurrent parotitis due to the pneumococcus and that due to the *Strep. viridans* are summarized.

Prognosis in all cases is good as to life. In the acute group fulminating cases do not occur, and although recovery is the rule the condition may pass into the recurrent phase. In the recurrent group the exacerbations at times tend to be severe, and there is always a considerable element of uncertainty as to the development of suppuration.

On the basis of the evidence presented it is suggested that the natural history of pneumococcal parotitis possesses many characteristics which distinguish it from the other common forms of pyogenic parotitis.

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ANAPHYLAXIS FOLLOWING ADMINISTRATION OF TETANUS TOXOID

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The prophylactic inoculation of man against tetanus was until recent years performed by giving a subcutaneous or intramuscular injection of tetanus antitoxin (3,000 units) during the incubation period of the disease, for preference soon after receipt of a contaminated wound. This procedure aimed at preventing the occurrence of tetanus by neutralizing any toxin formed by the organism, and often necessitated multiple injections at weekly intervals, as the immunity conferred was so short-lived. General reactions, collectively called "serum sickness," followed in about 10 to 15 per cent. of cases injected with sera concentrated by the ammonium sulphate method, and in approximately 2 per cent. of those given the modern refined and concentrated sera prepared by selective treatment with proteolytic enzymes. These reactions were usually of the delayed type, characterized by the occurrence of rashes, malaise, joint pains, and some pyrexia seven to twelve days after the serum had been injected; occasionally, however, when a small desensitizing dose of serum was not given as a preliminary measure, immediate anaphylactic reactions were seen, especially among individuals who had been inoculated with similar heterologous serum at least a week previous, and so had time to develop

hypersensitivity to the serum. Briefly, the main drawbacks to this type of prophylaxis were that the immunity given was only passive, partial, and temporary, lasting merely a few weeks, and that serum sickness was a common occurrence.

Advantages of Tetanus Toxoid

To overcome these defects tetanus toxoid was first adopted on a large scale for the protection of man in 1936, for the compulsory inoculation of the personnel of the fighting services in France. In 1938, following the researches of Major J. S. K. Boyd, R.A.M.C., this form of prophylactic inoculation was adopted in both the British Army and the Royal Air Force on a voluntary basis. Boyd's work confirmed the result of similar researches in many countries, notably in France, Germany, and the United States of America—namely, that inoculation with tetanus toxoid had the power to produce an active and relatively permanent type of immunity to tetanus.

To attain this degree of protection two doses of 1 c.cm. of tetanus toxoid are given subcutaneously at an interval of not less than six weeks. This dosage, as Boyd has shown, is as effective as the three-dose method used in France, and produced from 0.1 to 2 units of antitoxin per c.cm. of blood serum within a month of the second inoculation. The amount of antitoxin adequate to protect man against tetanus is, according to Sneath, Kerslake, and Scruby (1937), 0.01 unit per c.cm. of blood serum: this minimum protective quantity of antitoxin has been confirmed by various observers to be present in the blood of man in the majority of instances for a period of two years after immunization. Ramon and Zoeller (1933) found that even up to a period of five years after immunization the blood of man contained enough antiserum to protect against infection with tetanus. This work still requires confirmation; but it can be accepted as proved that for two years after immunization with tetanus toxoid the antitoxin content of the blood can be relied upon either to prevent the occurrence of tetanus or so to modify the infection as to guarantee cure with modern anti-tetanus therapy. Thus it is now possible to protect man against tetanus before exposure to the danger of contaminated wounds, whether in peace or war, instead of after wounding as hitherto.

As regards the danger of reaction following injection with tetanus toxoid, Boyd (1938) stated that the toxoid produces no general or local reaction. This statement was made as the result of limited experience and is correct in the majority of instances, but, from observations made on a large number of Royal Air Force personnel so inoculated, it has been found that general reactions, even to the extent of severe peptone shock or anaphylaxis, may sometimes occur. Thus, in the follow-up of 61,042 individuals immunized by the two-dose method of giving tetanus toxoid, fourteen cases, or 0.023 per cent., showed definite constitutional symptoms, and two of these—that is, 0.0033 per cent., or 1 in 30,521, of those inoculated—had immediate anaphylactic crises, as shown in the accompanying table and detailed below. All these general reactions resulted from the second injection, which was given about six weeks after the first, and came on shortly after inoculation, usually within a half to one hour; it is thought that these reactions were due probably to peptone shock, as individuals subsequently tested by the scratch method showed hypersensitivity to Witte peptone, which was a constituent of the tetanus toxoid administered. The toxoid used in every case recorded here was the standard preparation supplied by Messrs. Burroughs

Wellcome and Co., who inform me that it consists of beef extract containing 1 per cent. Witte peptone, together with the toxin of *Clostridium tetani* rendered atoxic by formalin. Dr. H. J. Parish of the Wellcome Physiological Research Laboratories kindly supplied me with various dilutions of the Witte peptone and beef extract used in the preparation of tetanus toxoid, and of difco proteose. In the three cases tested significant positive skin reactions were obtained with the Witte peptone, but not with the beef extract or difco proteose. Further research is being done at the Wellcome laboratories to determine the exact role of Witte peptone and other ingredients of tetanus toxoid in causing allergic phenomena, as there is some doubt regarding the diagnostic value of the scratch test.

Table showing Incidence of General and Local Reactions following Subcutaneous Inoculation of 61,042 Healthy Individuals with Tetanus Toxoid, using Two 1 c.cm. Doses at a Six-weeks Interval.

Total Number of Persons Inoculated	Acute Anaphylactic Reaction (a)	Definite Constitutional Symptoms (b)	Local Reactions Only (c)
61,042	2 cases (0.003%)	12 cases (0.02%)	651 cases (1.06%)

(a) Anaphylactic shock as described in text.

(b) Constitutional symptoms were mainly frontal headache and pains in body and limbs as in influenza, coming on one-half to one hour after inoculation and lasting about six to eight hours. There was slight pyrexia (99° to 100° F.), shivering, and some complaint of dizziness. Seven of these cases had urticaria of limbs and body.

(c) Local reactions consisted of stinging of the inoculated area for a few minutes, followed by brawny swelling and pain for twelve to twenty-four hours; twenty-two cases had urticarial swelling and itching around site of inoculation for a few hours.

Anaphylactoid reaction the result of peptone inoculation was first described by De Waele in 1907, and appears to be due to some toxic principle peculiar to Witte peptone: Dale (1929) states that this acts as an endothelial poison. Though peptone anaphylaxis is not often encountered in medical practice it is odd that more cases have not been recorded in view of the widespread use of various toxoid preparations of recent years. In fact, the record given above of 61,042 persons inoculated with tetanus toxoid suggests that the incidence of acute (non-fatal) anaphylaxis following toxoid is about 1 in 30,000, which approximates to that following horse-serum inoculations given subcutaneously. It is desirable, therefore, that all those who use tetanus toxoid should realize that the occasional case may suffer from peptone shock, and should be prepared to treat it. For this purpose 1 in 1,000 adrenaline hydrochloride should always be at hand, and, to lessen the risk of anaphylaxis occurring when the individual is alone, injections of tetanus toxoid should be given during working hours, when other people are likely to be about and could summon medical aid should untoward symptoms appear. Moreover, great care should be taken to avoid injecting into a small vein, as this greatly increases the risk of severe reaction. A refinement before giving toxoid would be the application, by means of a skin test, of various dilutions of the brand of peptone contained in the particular make of toxoid, but this is not practicable in most instances.

The following case histories are illustrative of anaphylaxis after the injection of tetanus toxoid.

Case I

A healthy, well-built man aged 52, a swimming-bath instructor, received two subcutaneous injections of anti-tetanus serum (1,000 units) eleven years ago and did not suffer from serum sickness. On November 22, 1938, he was given a second injection of 1 c.cm. of tetanus toxoid forty-four days after the

first. The official record made by Dr. W. G. Forde, who attended him, was as follows: "He was admitted to sick quarters at about 5 p.m. (that is, an hour after inoculation with tetanus toxoid). He was then in a state of collapse, suffering from dyspnoea, restlessness, shivering, and intense general pruritus, with frequent bouts of vomiting. The skin was erythematous, the fingers and hands showing patches of a dead white colour, giving a curious marble-like appearance. The man stated later that within a quarter of an hour of the injection he felt his eyes getting hot. He looked in the mirror and saw that his eyes were bloodshot. He then noticed that his lips were becoming very swollen, and had the feeling that his teeth were going to fall out. These symptoms were immediately followed by vomiting, diarrhoea, and loss of consciousness. He does not know how long this lasted, as he lay unnoticed in a lavatory. On recovering consciousness he went out of the lavatory, but soon collapsed again; whereupon he was taken to the sick quarters, where he was detained for an hour; he remembers nothing of his stay there. An injection of 0.75 c.cm. of adrenaline hydrochloride (1 in 1,000) quickly relieved the itching, and within twenty minutes there was a remarkable general improvement."

Subsequently I tested this man for response to a scratch test with various dilutions of Witte peptone and beef extract as used in the preparation of this tetanus toxoid. He gave a distinct reaction to a 1 in 10,000 dilution of Witte peptone, a wheal the size of a sixpence appearing in twenty minutes; a larger wheal occurred in seven minutes with a 1 in 1,000 dilution and did not disappear by the end of an hour. This reaction indicated a high degree of sensitivity to Witte peptone. Tests with beef extract and difco proteose gave negative responses.

Case II

This patient, a healthy airman aged 24, had no history of allergy or of inoculation with other sera or toxoids except with 1 c.cm. of tetanus toxoid forty-six days previously. Inoculated by me in the left deltoid region with 1 c.cm. of tetanus toxoid (second injection) on March 31, 1939, at 10.10 a.m., he returned ten minutes later complaining of dizziness and flushing. There was general swelling of lips, gums, and cheeks; but the inoculated area appeared normal. Beads of sweat appeared on the forehead; the temperature was 99.6° F. and the pulse 90. He quickly became dyspnoeic and vomited twice. He was given 0.5 c.cm. of 1 in 1,000 adrenaline hydrochloride, and during the next fifteen minutes returned to normal, except for erythema and urticaria, which gradually developed over the body and limbs. Mainly the urticaria persisted for eight hours, though a few wheals were present the next day; general itching accompanied the urticaria.

Skin tests in this case gave a positive reaction to a 1 in 1,000 dilution of Witte peptone, a wheal appearing in half an hour.

Summary

Two cases of anaphylactic shock following administration of a second dose of tetanus toxoid are described.

The incidence of general and local reaction following the subcutaneous inoculation of 61,042 healthy individuals with tetanus toxoid, using two 1 c.cm. doses at a six-weeks interval, is reviewed. Anaphylactic reactions occurred in 0.003 per cent. of cases, less severe constitutional symptoms in 0.02 per cent., and local reactions in 1.06 per cent.

Though the incidence of general reaction after tetanus toxoid is rare it is advisable to be prepared to treat it expeditiously with adrenaline hydrochloride when it does occur.

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