ANAPHYLAXIS AFTER INJECTION OF TETANUS TOXOID

REPORT OF A CASE

BY

H. J. PARISH, M.D., M.R.C.P.Ed.

AND

C. L. OAKLEY, M.D., B.Sc.

*Wellcome Physiological Research Laboratories,
Beckenham, Kent*

The following case of anaphylaxis is of special interest in view of the large number of injections of tetanus toxoid that are now being given in this country and abroad. Although allergic symptoms following the administration of this prophylactic are rare, the possibility of their occurrence must not be overlooked, and adrenaline should always be available when injections are given. Over 300 members of our staff received two injections each of 1 c.cm. of tetanus toxoid last summer, the usual interval between injections being six weeks. Reactions both local and general were negligible, the one exception being a case of anaphylaxis after the second injection. Details are as follows:

History of Case

A healthy woman with no known allergic diathesis had received during recent years injections of staphylococcus toxoid, diphtheria prophylactic, and T.A.B. vaccine without showing any allergic reactions. On July 20, 1939, she was given 1 c.cm. of tetanus toxoid deep subcutaneously over the left triceps, the only after-effects being slight stinging and pain down the arm within a few minutes of injection. In our experience these symptoms frequently occur after tetanus toxoid. A second injection of 1 c.cm. was made into the same site seven and a half weeks later—namely, at 3.10 p.m. on September 11, when the patient again had slight stinging and pain down the arm. Within ten minutes she had a pricking sensation round the margin of the anterior half of the tongue and inside the nose. She felt she was "getting hotter and hotter," and soon there was marked flushing of the face and hands. At this stage there were no wheals and no rash. Approximately twelve minutes after injection extremely severe abdominal pain came on suddenly, and rapidly increased until the patient "rolled about in agony." She had an intense desire to micturate and passed very small amounts of urine. Backache was severe, and there was swelling of the lower lip, which passed off quickly. Cold clammy sweat was observed over the face and arms, and speech was incoherent.

When the patient was first seen by us twenty-five minutes after the injection she complained of intense abdominal pain of a cramping character and backache which resembled menstrual pain but was more severe. The injection area was slightly swollen. The pulse was 52, regular, small, and soft. Neither then nor previously was there any respiratory embarrassment, nor were the accessory respiratory muscles in action. Adrenaline 1 in 1,000, 0.4 c.cm., was given within a few minutes. The abdominal pain was much less three minutes later, had practically disappeared in ten minutes, and had gone completely in half an hour, when the patient was mildly excited and wanted to get up. There was no vomiting or diarrhoea. A second examination of the injection area made one hour after the inoculation revealed brawny swelling, but there was no swelling or tenderness of the local lymphatic glands. Ten minutes later flat pinkish wheals (some circular, some pseudopodial, 5 to 20 mm. in diameter) appeared over the inside of both thighs and in the flexure of the elbows, and there was a tendency to wheal formation round the waist. There was fairly marked itching over the wheals, over the

scalp, and between the toes. Two hours after the injection of toxoid a scarlatiniform rash with diffuse flushing was observed over the face and hands. A second injection of adrenaline 1 in 1,000, 0.6 c.cm., was given. Later in the evening and during the night the patient had very slight abdominal pain. Six hours after the injection of toxoid the wheals had disappeared, but the diffuse flush remained over the arms and thighs, with blanching at the site of the injections of adrenaline. The itching between the toes persisted longer, and the patient had a general "washed-out" feeling, as after influenza. Next morning all symptoms had disappeared, except the feeling of debility and a sense of constriction round the head. On the second morning after injection the patient was apparently quite well.

Eleven days after the second injection of tetanus toxoid the antitoxin content of the blood was 4 international units per c.cm. This was the highest value in a series of approximately one hundred blood samples taken from members of our staff at intervals ranging from eleven days to seven weeks after the second inoculation.

Discussion

It is customary when considering cases of anaphylaxis to perform scratch or intradermal tests with the antigen and its components in the hope of incriminating some substance as the anaphylactogen. In preparing the tetanus toxoid the medium used for growing the bacilli was an extract of beef to which 1 per cent. of Witte peptone had been added (Dr. F. Witte kindly informed us that the ordinary Witte peptone is made from beef and pork fibrin). Scratch tests were made on the patient's forearms with (a) the batch of tetanus toxoid which gave rise to the allergic reaction; (b) beef extract and (c) Witte peptone, which are constituents of the broth used for the growth of tetanus bacilli; and also (d) another peptone—namely, difco proteose. Minute drops of dilutions of these materials were placed on the skin, and superficial abrasions of the areas were made with Hagedorn needles, care being taken not to draw blood and to keep the scratches so far as possible of uniform depth. Additional droplets of the test solutions were then rubbed into the abraded areas with the flat surface of the needles. Dilutions of the four materials, 1 in 10,000, 1 in 1,000, 1 in 100, and 1 in 10, were prepared in borate buffer solution (B.B.S.), and were used in sequence, beginning with the weaker dilutions and continuing with the next stronger dilutions, usually after an interval of some hours. A very small and transient urticarial wheal was observed in the area of the 1 in 1,000 Witte peptone inoculation after approximately eight hours. A slight but definite urticaria developed in the area of the 1 in 100 Witte peptone inoculation within one hour, lasted about one hour, and faded gradually. Larger wheals with more surrounding erythema were observed after 1 in 10 dilutions of Witte peptone and of the tetanus toxoid itself. These reactions appeared within ten minutes, and lasted somewhat longer than the wheal produced by the 1 in 100 dilution of Witte peptone. After 1 in 10 difco proteose a raised erythematous area without urticaria developed within two or three hours and had faded considerably five hours later. The other scratch tests were negative.

At a later date further scratch and also intradermal tests were done on this patient and on a number of persons who had received two injections of tetanus toxoid without showing any anaphylactic symptoms. The reagents included beef, pork, and horse muscle extracts and peptic digests of beef, pork, and horse fibrins, and of other products kindly prepared for us by our colleague Dr. C. G. Pope. It was noted that various dilutions of the digests caused more wheal formation and surrounding

erythema than similar dilutions of the extracts, and that within a few minutes of injection many persons developed reactions to these test products and to Witte peptone at least as severe as those shown by our anaphylactic case. Further investigations are in progress which it is hoped will be the subject of another paper. Our observations throw considerable doubt on the value of scratch and intradermal tests as usually interpreted on the basis of early readings. Nevertheless, our patient was the only subject who developed mild anaphylactic symptoms—itching of the nose and tongue, slight swelling of the lower lip, smarting of the eyes, and flushing of the face—soon after 1 in 1,000 dilutions of Witte peptone and two other beef fibrin digests had been injected intradermally; and she alone showed areas of redness, 50 to 60 mm. in diameter, swelling, and induration ("like those occurring after staphylococcus toxoid") about two hours later at the sites of injection of these products. These "late" reactions were at their maximum about this time and faded completely during the next three hours.

We feel, therefore, that Witte peptone may be the substance in tetanus toxoid to which the patient had become sensitive. Some degree of sensitivity to Witte peptone may be more common than is generally supposed: Parish (1936) and Bousfield (1936) reported cases in this country and referred to others in America in which allergic reactions had followed the use of Schick test fluids, which at that time were stabilized by Witte peptone.

The patient in the present inquiry had received two courses of staphylococcus toxoid—in May, 1937, and January, 1938. In view of the high content of Witte peptone in the medium in which the staphylococcus toxin was prepared it was thought that sensitization to the peptone might have been acquired by the repeated injections of staphylococcus toxoid. The patient, however, had tolerated the first injection of tetanus toxoid in July, 1939, which led to the suggestion that it was this injection that had caused the sensitization. We have heard of other allergic reactions after second injections of tetanus toxoid. These manifestations appear to be rare and readily controlled by the injection of adrenaline. It would seem advisable to keep all persons injected with tetanus toxoid under observation for at least half an hour.

Summary

A case of anaphylaxis after the injection of tetanus toxoid is described.

Allergic phenomena, though alarming, appear to be rare, and are due to some constituent of the medium in which tetanus toxoid is prepared, possibly the Witte peptone.

Adrenaline 1 in 1,000 should always be readily available as a precautionary measure when tetanus toxoid is injected.

REFERENCES

- Bousfield, G. (1936). *Med. Off.*, **56**, 193.
Parish, H. J. (1936). *Lancet*, **2**, 310.

Male Vagrants in Sweden.—An examination of eighty-one tramps showed that over half were to some degree mentally defective, one-fifth certifiably so. One-tenth suffered from schizophrenia, two-thirds showed constitutional psychological abnormalities. The incidence of insanity in their near relatives was also very high.—Psychiatric Examinations of Certain Male Vagrants and Alcoholists in Sweden in the Year 1938 (Eng.). G. Adell.—*Acta psychiat. Kbh.*, 1938, **13**, Fasc. 4, 447.

MARCH FRACTURE—PIED FORCE

BY

F. A. R. STAMMERS, Ch.M., F.R.C.S.

Major R.A.M.C., Surgical Specialist

Army medical officers everywhere have been asked to see all sorts of foot troubles precipitated by military training. More often than not these are due to pre-existing conditions such as hallux rigidus, hallux valgus, hammer-toe, or pes planus, which, though formerly symptomless, break down under the strain of route-marching, physical training, and the general extra footwork the soldier is called upon to do in heavy army boots. Even a seemingly normal foot may develop trouble under such circumstances, and none is more dramatic in onset or crippling in effect than the so-called march fracture. This short paper records three cases admitted within the first two months of the war to what was probably the first Territorial general hospital to function. So little is said of the condition in the textbooks, and so puzzling may it prove at the beginning, that no apology is necessary for reporting these cases.

Case I

A medical officer, aged 41, while walking along a corridor at about 10 a.m. one day, felt discomfort in the outer part of the forefoot. Within half an hour this amounted to frank pain, and by lunch time he was forced to walk with a marked limp; yet he is satisfied that there was no trauma, sudden strain, or unaccustomed activity, at any rate within several hours previously. On examination there was tenderness on deep pressure on the dorsum of the fourth interosseous space just behind the heads of the metatarsal bones, and weight-bearing, especially on the outer border of the foot, was very painful, though all discomfort ceased with rest. Next day the situation was much the same, but a slight puffiness appeared in the fourth interosseous space at the site of the tender point, and the enforced gait of walking on the inner border of the externally rotated foot produced the added discomfort of peroneal strain. By the third day oedema of the dorsum was sufficient to hide the extensor tendons of the toes, and weight-bearing was so painful that had he not been able to do his work at his own pace he would have been forced to "go sick." The diagnosis of march-foot was considered, even though there had been no question of long marching and in spite of the fact that the only sign mentioned by textbooks as characteristic—namely, pain on pulling on the toe of the affected metatarsal—was absent; moreover, an x-ray picture failed to reveal any bony abnormality. Two other signs, however, developed—pain on pushing the third toe axially backwards on to the metatarsus, and tenderness on pressing the plantar surface of the head of the third metatarsal; the dorsal tenderness in the fourth interosseous space was still present. The condition remained much the same until a fortnight after the onset, and then walking became less painful provided it did not exceed fifty yards. By the end of a month about a mile could be covered without pain, after which severe aching in the fourth interosseous space ensued and an occasional click was sensed in this region. A second x-ray picture, taken at this stage, showed callus round a transverse crack in the neck of the third metatarsal bone. About a week later the oedema in the dorsum began to subside, and a more localized swelling, corresponding to the callus, remained. It was seven weeks before full activity was completely painless, and ten before the extensor tendons were unmasked by residual thickening of the soft tissues.

The second and third cases were admitted on the same day, about a month after the first, and each had developed symptoms a few days before admission.