ACCIDENTAL ACQUIRED HYPERSENSITIVITY TO TETANUS ANTITOXIN

BY

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Reactions to tetanus antitoxin are a familiar problem to casualty officers, but it must be very unusual for a casualty officer to develop symptoms merely from handling this serum. It has not been possible to discover any account of such reaction in the literature, but in the following case it does seem to have occurred.

In an attempt to confirm the diagnosis, the trial dose of tetanus antitoxin recommended for allergic subjects (Laurent and Parish, 1952; Parish, 1958) was injected subcutaneously and produced a severe and prolonged allergic reaction.

Case Report

A 23-years-old woman casualty officer noticed that after giving a patient an injection of tetanus antitoxin she had slight swelling of the eyelids with some conjunctival injection. Two days later she gave three injections of tetanus antitoxin in the early hours of the morning. By 5.45 a.m. she had quite severe oedema of the eyelids and was sent off duty. Apart from the swelling of the eyelids, she felt well.

I saw her the next afternoon, and from her history a possible exogenous cause for the urticarial swelling of the eyelids, which was still present, was thought to be the contact with tetanus antitoxin. She admitted that she held the syringe up at eye level and expressed antitoxin through the needle to get the correct dose. It was therefore possible for the serum to have reached her conjunctiva by air-borne droplets. She gave no personal or family history of allergic disease.

Some years previously she had been immunized with tetanus toxoid. This is a mild prophylactic which does not contain horse protein or anything else likely to cause sensitization. She had never had serum, nor had she been immunized against diphtheria. The possibility of injections of diphtheria prophylactic, T.A.F., which contains a small amount of horse serum, was excluded.

On examination there was urticarial swelling of her eyelids with no scaling to suggest epidermal damage. In order to confirm the presumptive diagnosis, she was given 0.2 ml. of a 1 in 10 dilution of tetanus antitoxin intradermally into the right forearm at 3.30 p.m. on October 16, 1959. A weal and flare 4 by 1 in. (10 by 2.5 cm.) developed in 10 minutes, and five minutes later her nose began to run and she started to cough. Five minutes later she became very distressed and developed acute bronchospasm. Her colour remained good and there was no evidence of vasomotor collapse. She was given 0.3 ml. of 1 in 1,000 adrenaline subcutaneously and admitted to the ward for observation, though her asthma was subsiding.

On admission at 4 p.m. she was given 8 mg. of chlorpheniramine maleate orally. At 4.45 p.m. an acute generalized urticarial eruption appeared, and in half an hour she complained of epigastric pain and vomited repeatedly. Another 0.3 ml. of 1 in 1,000 adrenaline was given, but she continued to vomit, and later the same evening she became more wheezy and complained of a feeling of constriction in the retrosternal region. By 11.50 p.m. she was collapsed and dyspnoeic; the urticaria was intense, and by this time had involved her lips and throat. The most distressing symptom was the repeated vomiting. Hydrocortisone succinate, 100 mg. given intravenously, brought some improvement in 30 minutes. By

2.15 a.m. on October 17 she was again worse, and another 100 mg. of hydrocortisone was given intravenously. At 5 a.m. 100 mg. of hydrocortisone and 10 mg. of chlorpheniramine maleate were given intramuscularly.

During the morning she appeared better, and treatment was changed to intramuscular prednisolone and chlorpheniramine maleate 10 mg. every three hours. By this time it was hoped that the worst was over.

At 4 p.m., however, she developed another and more severe attack of urticaria, vomiting, and asthma. Her blood-pressure fell to 75/50. She had not passed urine for 20 hours, and the possibility that she had developed anuria was considered; but she was encouraged to try to pass urine, and did pass 13 oz. (840 ml.), which contained no abnormal constituents. Blood taken at this time showed a urea content of 54 mg./100 ml. and normal electrolytes.

The patient was naturally very alarmed, and treatment was changed again to hydrocortisone, 100 mg. three-hourly, chlorpheniramine maleate, 10 mg. six-hourly, together with intramuscular sodium phenobarbitone, 3 gr. (0.2 g.) every eight hours.

She slept fairly well, but at 11.30 a.m. on October 18 her condition again gave anxiety with a recurrence of vomiting, urticaria, and asthma. This passed off after an additional dose of 100 mg. of hydrocortisone intramuscularly had been given. The regime of hydrocortisone, 100 mg. three-hourly, chlorpheniramine maleate, 10 mg. six-hourly, and sodium phenobarbitone, 3 gr. (0.2 g.) eight-hourly, was continued.

On October 19 she was much improved—only a residual urticarial patch on the site of the injection to her forearm remained. Treatment was changed to cortisone, 50 mg. t.d.s., and chlorpheniramine maleate, 8 mg. t.d.s.; the cortisone was lowered steadily until October 22, when it was discontinued. By this time she was so far recovered that she was discharged home. (The total dose of steroids amounted to 60 mg. of prednisolone and 1,900 mg. of hydrocortisone in 56 hours.) She did not develop serum sickness, and recommenced duty as a casualty officer on October 26 with strict instructions to avoid any contact with A.T.S. She has remained well. It was afterwards discovered that her father suffered from urticaria due to quinine, but no other family history of allergy was elicited. In view of the possibility that the reaction might have been due to the formation of immune A iso-antibodies (Crawford *et al.*, 1952), the patient's blood was examined. Her blood group was B, Rh positive. It contained ordinary anti-A but no alpha-haemolysins or incomplete anti-A.

Discussion

In view of the intense systemic reaction to the very small dose of tetanus antitoxin, there is little doubt that the initial urticarial swelling of the eyelids was a manifestation of allergy to horse serum. Whether the conjunctiva was the route by which she became sensitized it is impossible to prove; she had given injections of tetanus antitoxin some three years previously when a medical student, and it may have been at this time that she became sensitized. It is well known that the conjunctiva will show evidence of hypersensitivity, as at one time it was used as a site for a sensitivity test for tetanus antitoxin or other horse serum.

Though reactions to tetanus antitoxin are common, severe reactions are rare. Moynihan (1955) found some reaction after 5.29% of 7,580 injections; only two of these were so-called anaphylactic shock, and these were not severe.

The incidence of fatal reactions has been estimated at between 1 per 50,000 and 1 per 200,000 (Laurent and Parish, 1952). The reaction which did develop in the present case was in itself unusual, as there was no vasomotor collapse at the onset but a combination of rhinitis, asthma, and urticaria. Vomiting was a

prominent and distressing feature. The attack resembles closely that described by Baybutt (1959) in an infant who had received a first injection of gamma-globulin, but in that instance both parents had suffered from severe allergic disease.

Though the patient survived, the response to treatment was disappointing. Adrenaline, which was used perhaps in too small doses, had a very temporary effect on the asthma, and even large doses of antihistamine and steroids did not control the urticaria and vomiting for 48 hours.

My impression was that large doses of sodium phenobarbitone were more valuable than all the other measures, and, given the same situation again, I would use sedatives earlier.

Again in retrospect, the trial dose of tetanus antitoxin was too large, though it may be noted that the patient did not give a personal or family history of allergic disease. Parish, Laurent, and Moynihan (1957) suggest 0.2 ml. of a 1 in 10 dilution for subjects with a history of allergy, but a 1 in 100 dilution (with tenfold increments at intervals of half an hour) would be safer, though somewhat more tedious. The invalidism caused by serum sickness, the difficult decisions on whether to give tetanus antitoxin or not which face the casualty surgeon, and the occasional frightening reaction such as the present one, should give a stimulus to a bigger campaign of active immunization.

The considerable hazards of injecting tetanus antitoxin and the even greater risks of tetanus can both be eradicated by an all-out drive to increase active immunization. Personal records of all preventive inoculations—and of allergy, etc.—are very important.

Summary

A woman casualty officer developed urticarial swelling of the eyelids after giving tetanus antitoxin. Despite the absence of an allergic history, a test dose of 0.2 ml. of a 1 in 10 dilution of tetanus antitoxin precipitated a severe and prolonged allergic reaction. The asthma, urticaria, vomiting, and collapse lasted 48 hours, but subsided after adrenaline, antihistamines, and 1,900 mg. of hydrocortisone.

It is presumed that the patient was sensitized by tetanus antitoxin entering the conjunctival sacs. The intense reaction to a test dose of tetanus antitoxin confirmed the high degree of sensitivity which had developed. Such cases can be avoided only if a more vigorous active immunization campaign succeeds in making passive immunization unnecessary.

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Plans are being made to build a new leprosarium in the Karonga district of Nyasaland's Northern Province, where 33 people out of every 1,000 living on the lake shore are lepers.

EFFECT OF OXYGEN THERAPY ON OEDEMA IN PATIENTS WITH COR PULMONALE

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Peripheral oedema attending cardiac decompensation in patients with pulmonary insufficiency is often more resistant to ordinary treatment with digitalis, low-salt diet, and diuretics than oedema in primary heart disease.

The cases reported below are examples of how oxygen therapy, in some instances combined with artificial ventilation, may eliminate oedema in such patients under circumstances where other causes of the elimination can be left out of account.

Case 1

A man aged 40 submitted to thoracoplasty years ago for pulmonary tuberculosis. He was admitted to hospital on August 29, 1956, with diffuse pulmonary fibrosis, pronounced pulmonary insufficiency, and cor pulmonale, but with no signs of bronchitis or active tuberculosis. Before admission he had had increasing dyspnoea and moderate oedema, which had been treated with aminophylline, digitalis, oxygen, and mercaptomerin, with no effect.

On admission the patient was cyanotic and severely dyspnoeic. The liver was palpable one handbreadth below the curvature, and there was moderate oedema. The temperature was 37–37.6° C., B.P. 125/80, pulse rate 100–120/min.; weight 89.2 kg. Administration of digitalis was continued, and 1–2 litres of oxygen per minute were given through a nasopharyngeal catheter most of the time. On September 3 the patient was confused, and analysis of the arterial blood showed: oxygen saturation, 92%; $p\text{CO}_2$, about 120 mm. Hg; pH, 7.21. The patient was therefore placed in a tank respirator with an intratank pressure of $-20/+7$ cm. of water at a rate of 20 per minute, and 1 litre of oxygen per minute was admitted through the catheter. During the oxygen-and-tank treatment the arterial blood showed: oxygen saturation, 93%; $p\text{CO}_2$, 90–80 mm. Hg; pH, 7.28. The treatment was discontinued on September 6 owing to melaena. The urine volume trebled (Fig. 1) during the first 24 hours of oxygen-plus-tank treatment (September

FIG. 1.—Case 1. Effect of oxygen therapy and tank ventilation on diuresis and body weight.