FATAL TETANUS IN A BOY AFTER PROPHYLACTIC TETANUS ANTITOXIN

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The use of antitoxic serum as a specific prophylactic for the prevention of tetanus after injury is now so general that any occasion of failure merits careful consideration. A case of tetanus is here recorded in which, in spite of the accepted prophylactic dose of antitoxin within two hours of the accident, the patient contracted and died from tetanus. In this instance, as is discussed below, the failure appears to be attributable to a state of hypersensitivity to the foreign serum proteins that had been induced by a similar prophylactic injection given six months before.

Case Report

A schoolboy aged 14 was admitted to hospital on June 25, 1953, having injured his left hand when experimenting with an explosive mixture of sulphur, phosphorus, and potassium chlorate. An explosion of this mixture caused lacerations of the fingers, with some full-thickness skin loss. He was given 1,500 international units of antitetanus serum on admission and his injuries were treated by cleansing, debridement, suture, and the application of free skin grafts. He received a ten-days course of penicillin, 200,000 units six-hourly (8 million units in all).

On December 29, just six months later, he was readmitted with lacerations of the left hand, abdomen, and thigh due to the explosion of a similar mixture packed into a metal tube. He was given a prophylactic dose of 1,500 I.U. of A.T.S. after he had failed to produce any reaction to a subcutaneous test dose of 0.1 ml. He was treated as before by cleaning, debridement, and suture of the lacerations with the application of split-thickness skin grafts to areas of full-thickness loss on the fingers. He again received a course of penicillin, 500,000 units of soluble penicillin initially followed by 300,000 units of procaine penicillin daily (6,200,000 units in all).

On January 10, 1954, twelve days after the injury, a diagnosis of tetanus was made when the patient complained of difficulty in swallowing and showed trismus and stiffness of the erector spinae muscles.

Arrangements were made to give a treatment dose of A.T.S., and, in view of the recent previous administration of horse serum, a test dose was given which produced a mild urticarial reaction. Accordingly, he was desensitized by the administration of 0.025 ml. subcutaneously, the dose being doubled every 15 minutes until 1 ml. had been given. Then 1 ml. was given intravenously, and on the injection of the first 0.1 ml. a considerable reaction was produced; the skin of the face and neck became bright red, and the pulse rate rose from 80 to 180 a minute and the respirations from 20 to 40 a minute. When the reaction had subsided, the rest of the injection and a further 86,000 units of A.T.S. were given intravenously without further reaction (100,000 units in all). The septic wound on the hand and the wound of the abdomen were then excised to prevent the further absorption of toxin.

Tetanic spasms began on the following day and were at first of a few minutes' duration, but later lasted from ten to twenty minutes. They occurred about once or twice an hour and increased in severity. Their effects were mitigated by the subcutaneous administration of a saline drip containing hyalase and succinylcholine chloride ("scoline"), 1:1,000.

On January 12 tracheotomy was performed, the more easily to aspirate the bronchial secretions and swallowed sputum which embarrassed respiration. The patient showed no signs of improvement and died on January 15, five days after the first appearance of symptoms and seventeen days after receiving his injury.

Necropsy Report

A necropsy was carried out seven hours after death. The deceased was well nourished and of normal development for his age. The following injuries were present: (1) Extensive lacerations of the skin of the left palm and of the palmar surfaces of the left thumb and first and middle fingers. These lacerations had been recently reopened and the deep tissues widely exposed. There was no gross sepsis present. The pattern of these fresh injuries was similar to that of the injuries received on June 25, 1953, but from the remnants of the old skin-grafts remaining they appeared to be slightly less extensive. (2) A wound had been excised in the right iliac fossa, and an oval area of skin and subcutaneous tissue 6–7 cm. across had been removed. (3) A superficial wound, 1–2 cm. in diameter, over the left anterior-superior iliac spine involving cuticle only. (4) A wound which externally appeared identical with No. 3 above was present on the anterior surface of the left upper thigh. Dissection, however, revealed that this was in fact a penetrating wound, and some cloth fibres were found in its depth lying on the deep fascia.

Internal examination revealed an acute suppurative bronchopneumonia of the hypostatic type, some acute fatty degeneration of the myocardium and liver, and granulocytosis of the spleen. The rectus abdominis muscles were intact.

Tissues were excised from the wounds, and these together with the cloth fibres were examined for *Cl. tetani* without success.

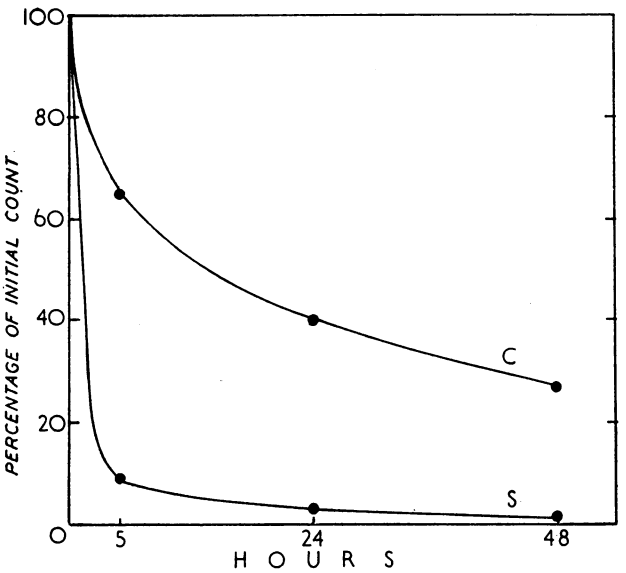
Discussion

The general question of the influence of hypersensitivity to horse serum on the duration of passive antitoxic immunity in man has been reviewed by Robertson (1916) and by Schmidt (1934). Among a number of equivocal records, two studies are notable for their careful execution and informative results. The first was made by Park and Zingher (1916), who found by comparative Schick tests that the period of passive immunity that followed a second inoculation with diphtheria antitoxin lasted only about half as long as that which followed the first. In the second, Hooker and Follensby (1931) determined the duration of the passive immunity to the Dick erythrogenic toxin that followed an intradermal inoculation of the specific antitoxin in the following three groups of persons: normal controls and "immediate reactors" and "delayed reactors" to tests with horse serum. They found that the controls and the "delayed reactors" usually retained an effective portion of the test dose of antitoxin at the local site for more than 24 hours, whereas in the "immediate reactors" the antitoxin lost its potency in less than four hours.

In experiments upon specifically sensitized animals, Glenny and Hopkins (1923–4) clearly demonstrated that foreign proteins such as those of serum are removed from the circulating blood much more rapidly than from the blood of control animals, and their findings have since received support from studies made with antigens labelled with radioactive isotopes. Talmage *et al.* (1951) observed that rabbits which had had previous parenteral exposure to bovine gamma-globulin, but in whose blood no specific circulating antibody could be detected at the time of the second injection, eliminated the gamma-globulin at a rate similar to that of the control

animals for two days and *then at a sharply accelerated rate.* On the other hand, rabbits with some demonstrable specific circulating antibody at the time of reinjection showed a precipitate fall in the concentration of the antigen in the blood *which began at the moment* of the injection. Laws and Payling Wright (1952) also observed a striking difference in the rates of disappearance of bovine serum albumin from the circulating blood of control and specifically immunized rabbits (see Chart), and found that within a few minutes of its injection into the latter animals much of the antigen had been removed by the liver.

From studies on both human beings and animals there thus seems to be concordant evidence that previous experience of a soluble antigen—and among these diphtheria and tetanus horse-serum antitoxin must be included—leads to a much accelerated removal from the circulating blood



Radioactivity of blood of control (C) and sensitized (S) rabbits at various intervals after the intravenous injections of radioiodinated bovine serum albumin (from Laws and Payling Wright, 1952).

on a second or subsequent injection, and consequently to a curtailment of any effectiveness that it may possess as a passive prophylactic agent.

One important practical conclusion emerges from the present discussion. Once a person has received an injection of any horse-serum antitoxin, irrespective of the disease for which it may have been given, that person should be promptly immunized against diphtheria and tetanus with the appropriate toxoid. By thus creating the state of active immunity, which can be effected without any unpleasant side-effects, any future need for passive protection against these diseases with horse-serum antitoxin is rendered unnecessary. Furthermore, before any surgical measures are undertaken in tissues which have been previously traumatized and may in consequence harbour contaminating tetanus spores, active immunization should always be undertaken shortly beforehand as a precautionary measure.

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MEPHENESIN AND GALLAMINE TRIETHIODIDE IN TETANUS

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The majority of deaths from tetanus result either from tetanic spasm and exhaustion or from pulmonary complications. In many cases the symptoms will be so mild that simple sedation with barbiturates or paraldehyde is all that is required, but these cases will get better whatever the treatment and are not discussed here. In severe cases, however, it is imperative to prevent, or at least relieve, the tetanic spasms, and to this end we have used a continuous intravenous infusion of normal saline into which the appropriate drug can be injected.

The choice of relaxant depends upon the severity of the case and development of tolerance to the relaxant. Thus, Smith and Thorne (1952) showed that steadily increasing doses of gallamine triethiodide were required, and we have noted a similar tolerance to mephenesin. Curare has been found unsatisfactory in tetanus because of the narrow borderline between relaxing and paralysing doses. (In seven cases reported by Godman and Adriani (1949) treatment was regarded as unsatisfactory for this reason in all cases.) Like curare, gallamine triethiodide is thought to act by blocking transmission across the myoneural junction of voluntary muscle, but the margin of safety between relaxation and respiratory paralysis is greater and the occurrence of histamine-like reactions to gallamine is rare. The mode of action of mephenesin is not fully understood, but is believed to be the result of selectively depressing reflex hyperexcitability in the spinal cord without greatly affecting neuromuscular transmission. Thus respiratory depression is minimal. On the other hand, mephenesin produces haemolysis (Wilson and Gordon, 1948), and this may prevent sufficient being given to control the spasms.

Case Report

A well-built man aged 22 had for some weeks been engaged in operating an excavator in the digging of a 50-ft. (15-metre) sump in cultivated land. On the evening of March 17, 1953, he noticed that his jaw was a little stiff. This became progressively worse, and when admitted to the Kettering General Hospital on March 19 he had only ¼ in. (6 mm.) separation of the jaws; there was increased tone in all voluntary muscles, and board-like rigidity of the abdomen. A thorough examination revealed no signs of skin abrasion or injury.

He was given 100,000 units of tetanus antitoxin intravenously (this was repeated one week later), soluble penicillin, 500,000 units four-hourly, and 4 dr. (14 ml.) of paraldehyde in 100 ml. of saline rectally. In spite of this, within a few hours of admission painful muscle spasms began, increasing in frequency and severity during the next four days. On March 20 an intravenous infusion of normal saline was set up and run in at the rate of 1 pint (570 ml.) in eight hours, 5,000 units of heparin being added to each pint of saline. In this way the drip was kept going for nine days with only one change of vein. In order to control the spasms a 10% solution of mephenesin ("myanesin") was injected into the drip tubing in doses of 5–10 ml. This was followed by immediate relief of the spasm accompanied by a feeling of tiredness and transient "drunkenness." In an attempt to reduce the general muscular rigidity between spasms the patient was also given mephenesin by