MEPROBAMATE IN TETANUS

BY

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The value of oral meprobamate (syn. Equanil, Miltown, Mepavlon) has been for some months investigated in this hospital group, as a component of the premedication for children. An interesting publication has appeared recently on the use of this drug in tetanus (Perlstein, 1959).

CASE HISTORY

The patient was a boy aged two years. Three weeks before admission to hospital he had severe pharyngitis and tonsillitis accompanied by trismus. This was treated successfully by injections of penicillin. Eleven days before admission he stuffed some paper into his right nostril and six days before admission he fell indoors but no injury was noticed. The following day he had a swelling under his right eye and was generally unwell. Two days later there was thick yellowish-green pus discharging from the right nostril, he had difficulty in swallowing and would not eat. The following day he could or would not open his mouth, and he was taken to the family doctor, who diagnosed a recurrence of the pharyngitis and prescribed a nasal spray. That night the child had a series of "fits", apparently provoked by attempts to swallow saliva, and the following night, which preceded his admission to hospital, he is described as having "fits", every five to fifteen minutes throughout the night, lasting about three minutes each, during which he coughed, choked, and became rigid.

On admission he was conscious, alert, with good colour and not obviously anaemic. There was slight swelling under the right eye, and small lymph nodes were palpable in the neck but not elsewhere. There was marked trismus, the sterno-mastoids were very tense, and the back was rigid so that he could be raised almost to the vertical position by lifting his head. Kernig's sign was negative. Tone was normal in the legs, but it was difficult to assess in the arms as he resisted attempts to estimate it. There were no abnormal findings in the cardiovascular and respiratory systems. His temperature was 100°F, pulse rate 120/minute, and respiration rate 38/minute. He had been immunized against diphtheria, whooping cough, and poliomyelitis, and had been vaccinated. He had not received tetanus toxoid, nor A.T.S. There was no history of convulsions.

Tetanus was diagnosed, and after an intramuscular injection of 4 ml paraldehyde the child fell into a deep sleep. An intravenous infusion of normal saline was set up and, after a subcutaneous test dose, 100,000 units of A.T.S. were given intravenously. Penicillin, 500,000 units intramuscularly twelve-hourly was also prescribed, and he was nursed in a quiet, darkened room. He slept all night, having received additional 3 ml of paraldehyde intramuscularly.

1st day after admission.

In the morning his breathing was rather laboured and mucus collected in his throat. Later he managed to swallow this and his breathing improved. He was given paraldehyde 1.5 ml intravenously twice during the morning to control spasms. It was decided to try to obtain an injectable preparation of meprobamate meanwhile and to continue with the existing regime. He was having moderate extensor spasms of trunk, arms, and legs, whenever he was disturbed, and intravenous promethazine 20 mg, and mephenesin 300 mg, produced no significant effect during an attempt to secure greater control of the spasms to enable a lumbar puncture to be performed. In fact promethazine seemed to increase the frequency and severity of the spasms. The c.s.f. showed raised protein at 55 mg/100 ml and 8 lymphocytes/c.mm.

2nd day.

The child's condition continued to be controlled by paraldehyde and the spasms were less frequent than the day before. He remained awake nearly all morning and talked with difficulty to his parents. His neck and back were still board-like and he reacted to stimuli, mainly tactile, with extensor spasms. The risus sardonicus was very marked. He intensely disliked having his bedclothes changed and he was unable to take anything by mouth. An attempt to give him water by spoon was abandoned after much coughing and spluttering. During the day he was given 1.5 litres of 5 per cent dextrose with 1.5 g. sodium chloride and 0.5 g. potassium chloride, and 0.5 litre of "Aminosol" by intravenous drip, and three doses of 3 ml paraldehyde. A further 300,000 units of A.T.S. were also given intravenously.

3rd day.

He was reasonably well controlled by paraldehyde during the night and in the morning there was no clinical difference from the previous day. The meprobamate solution was received early in the morning, and an intramuscular injection of 1 ml (80 mg) was given at 9.50 a.m. After half an hour there was slight lessening of muscle rigidity and the dose was repeated. At about 11 a.m. the child asked for a drink and took 2 fl. oz. of water, followed by 2 fl. oz. of milk from a spoon without coughing. The ward sister reported complete relaxation developing at this time and considerable general improvement, especially of mood. He talked cheerfully to his parents, and played with his toys. By 1 p.m. he was again becoming restless and the effect of the meprobamate appeared to be wearing off, so it was decided to give 2 ml (160 mg) intramuscular 3 hourly during the day, and 3 ml paraldehyde at 6 p.m. to promote sleep. He continued to drink well during the day, so the intravenous drip was taken down before he settled for the night; it was still running well, with no tender-
ness along the course of the vein, but there was some swelling around the cannula. The skin over the site of the intramuscular injections was sprayed with ethyl chloride before introducing the needle and he did not complain of the injections.

4th day.
He slept well, needing 3 ml paraldehyde during the night. He was given his first injection of meprobamate at 8 a.m. and was well relaxed an hour later. It was decided to repeat the injections 2 hourly during this day, to maintain relaxation as fully as possible. He was drinking very well.

5th day.
The injections were making his muscles rather “knobbly”, although he did not complain at any time, so the meprobamate was reduced to 4 hourly and controlled him quite adequately. In the evening he had one spasm lasting about a minute, accompanied by cyanosis which passed off spontaneously. He was taking thicker milk food now, with vitamin supplements.

6th and 7th days.
Meprobamate was continued as previously, but paraldehyde was replaced by chloral 5 grains (300 mg) at 6 p.m. on the 7th day. He slept well.

8th day.
He received no drugs at all. Muscle tone was rather increased, with occasional slight twitches but no real spasms. Nembutal elixir was given at night, and he slept well.

9th day.
He received no drugs all day, and sat up in bed and played.

10th day.
He ate soft foods and required no sedation. The jaws were still a little stiff. He was moved into the general ward.

11th day.
He stood up and walked with support. He was eating and drinking very well.

12th day.
He was walking by himself, but stiffly, and if he lost his balance he could not regain it and prevent himself from falling. He was eating a normal diet for his age, but had become rather spoilt and disliked being in the ward with other children. Although he was still rather stiff, his parents were anxious to have him home, so he was discharged the following day. He had lost only 1 lb. in weight while in hospital.

Subsequent progress was reported by the parents.
He continued to fall over on losing his balance for the next four or five days and his back remained stiff for three weeks or so. He ate and swallowed well, but tried to avoid chewing for about a fortnight and he was unable to yawn comfortably for three weeks. When seen at the outpatient clinic six weeks after discharge he was fit and well and all the intramuscular “knobs” had been absorbed.

He and the rest of the family are now being immunized against tetanus.

DISCUSSION
Current methods of treatment are purely symptomatic, and aim at keeping the patient alive “until the disease process has worn itself out” (Ablett, 1956). The drugs used to control the muscular spasms fall into three groups: the older hypnotics, especially paraldehyde; the newer phenothiazine derivatives; and the neuromuscular blocking agents. These last are used to convert the tetanus patient into a “polio-equivalent”, who is then managed by tracheostomy and intermittent positive pressure respiration.*

The disadvantages of these methods is that the patient is placed under certain disabilities with each. Ideally, and accepting that tetanus is a self-limiting disease confined to the central nervous system (a view not now universally accepted), symptomatic treatment should aim at controlling muscle spasms and restoring normal muscle tone without undesirable side effects. Perlstein (1959) reported on some forty patients treated with meprobamate. Although the results were complicated by the fact that some of his patients were drug addicts there was a significant decrease in the mortality of the non-addicted.

The case reported here was of moderate severity only and it is not pretended that the administration of meprobamate prevented the child from dying of tetanus. It is felt, however, that the drug, by allowing him to be fed normally and by making his management generally easier, did remove the possibility of his dying from the treatment that he might otherwise have received. Meprobamate does not appear to affect the autonomic nervous system and herein lies its great advantage over the phenothiazine compounds. The heart rate, respiration and temperature regulation are not affected by meprobamate. The drug is almost insoluble in water and is dissolved in a solution containing polyethylene glycol, which accounts for the knobbiness of the muscles.

* This treatment has a longer history than may be thought. The use of curare in tetanus was first suggested by Sewell, head of the London Veterinary College, and a friend of Charles Waterton, before the latter’s South American expedition of 1812 (Aldington, 1949). The first recorded use of the drug appears to have been in Turin in 1859, when a patient was successfully treated by local application with absorption from the site of injury (Stetson, 1959).
It is possible to provide a rationale for the use of meprobamate in tetanus. It has recently been shown that tetanus toxin resembles strychnine in that it selectively suppresses inhibitory action, while leaving synaptic excitatory action unaffected (Brooks, Curtis and Eccles, 1955, 1957). Davies and her colleagues (1954) have shown that tetanus toxin has little or no effect upon monosynaptic proprioceptive impulses and that it appears to depress inhibitory action on the interneurones of polysynaptic pathways. This finding was confirmed by Brooks and his colleagues (1955). The toxin appears to exert its effect near the synaptic junctions of the inhibitory pathway and the motor neurones, thus depriving the latter of the inhibitory influences that are necessary for the normal co-ordination of spinal reflexes (Wright, 1959).

Meprobamate has been shown to have a marked inhibitory action at the interneurones of polysynaptic pathways (Berger, 1956). It was found to be more effective in reducing muscle spasm than in lowering normal proprioceptive muscle tension and in small doses it relieved spasm experimentally produced by tetanus toxin or strychnine (Berger, 1954). However, this effect was not connected with the site of action of the drug at the time. There is also a selective depression of the thalamus which, as will be shown, may be of significance in the management of tetanus.

Auditory and visual stimuli, originating, travelling, and being assessed for "significance" (Walter, 1954, 1958) above spinal cord levels, with resulting inhibition or facilitation, do not normally produce muscle spasms. That these sensory stimuli may produce spasms in tetanus appears to indicate that the inhibitory mechanisms concerned with these senses also are to some extent affected by the toxin. If this is so, the toxin presumably travels through the medulla to reach the higher levels of the reticular formation and beyond without causing death. If the toxin is acting at and around the level of the midbrain, the value of the phenothiazine drugs, as of meprobamate, becomes obvious. In particular, chlorpromazine has been found experimentally to block arousal to auditory stimuli (Schneider, 1958).

**Discussion of possible mechanisms involved.**

Brooks and his colleagues (1955) have suggested the following two explanations of the mode of action of tetanus toxin. It is proposed that, like strychnine, it becomes attached to the subsynaptic inhibitory areas on the motoneuronal membrane, thus preventing the action there of the inhibitory transmitter, or alternatively it may be that, like botulinus toxin, it prevents the release of the inhibitory transmitter substance.

In the light of these suggestions it seems desirable to look again at the natural course of the disease and to examine such terms as commonly found in this association as "until the disease process has worn itself out" or "burnt itself out". In regard to the first suggestion, it may be wondered whether the toxin is gradually displaced from these subsynaptic inhibitory areas, or whether fresh receptor substance has gradually to be synthetized to replace that which is irreversibly blocked; and whether some means could be found of accelerating these processes. On the second, an analogy may be drawn with the blocking of an enzyme system by the "irreversible" anticholinesterases, characterized by diisopropyl fluorophosphate (DFP) where recovery, if it occurs at all, takes some weeks during which the enzymes are regenerated. These changes became rapidly reversible by pyridine-aldoxime-methiodide (PAM) when the chemical action of D.F.P. was understood and an antidote could be sought (Nachmansohn, 1959). Possibly in tetanus too there is the inactivation of an enzyme system and that which involves pyridoxal in the decarboxylation of glutamic acid to the neural inhibitory substance y-amino butyric acid (G.A.B.A.) (Elliott and Jasper, 1959) seems worthy of investigation from this point of view. Convulsions have been reported associated with pyridoxine (vitamin B6) deficiency in infants and this condition has been reproduced experimentally in animals. Glutamic acid decarboxylase activity is decreased by pyridoxine deficiency and the brain level of G.A.B.A. is reduced; when the brain level falls to 50 per cent to 30 per cent of normal, convulsions occur.

There is also evidence that convulsions following inhibition of the synthesis of G.A.B.A. do not occur spontaneously but are triggered by normal impulses that otherwise do not produce this effect (Killam, 1958). Unfortunately
G.A.B.A. is ineffective when given intravenously, but a derivative able to cross the blood-brain barrier might be of value in tetanus. It would also be interesting to assess the effect of pyridoxine and related compounds. Unfortunately or otherwise, by the time this train of thought was sparked off its clinical destination had already been quenched, but in the light of present knowledge the fact that meprobamate and the phenothiazine drugs continue to act in tetanus seems in favour of Brooks's second suggestion.

SUMMARY
The course is described of moderate tetanus in a child of two. He was treated with A.T.S. and penicillin, and sedated initially with paraldehyde. He was unable to swallow, so an intravenous infusion was necessary at first. A preparation of meprobamate suitable for intramuscular injection was obtained, and this was successful in reducing spasm, enabling the child to remain conscious all day, and to be fed by mouth.

Present knowledge of the mode of action of tetanus toxin is reviewed, and the rationale for the use of meprobamate and the phenothiazine drugs is indicated.

The possible role of the inhibitory substance \( \gamma \)-amino butyric acid in tetanus is discussed.

ACKNOWLEDGMENTS
I am indebted to Dr. B. W. Cromie and Mr. R. L. Stephens of Messrs. John Wyeth Ltd. for their speedy response to my request for the specially prepared solution, and to my colleague Dr. C. A. Birch and the medical and nursing members of his unit, to which the child was admitted.

REFERENCES