ANNOTATION

Curarine and Myanesin in Tetanus

In discussing the value of new remedies in the treatment of tetanus it is wise first to recall certain general points about its prognosis and treatment. Tetanus is a disease in which prognosis can be assessed with a considerable degree of accuracy during the early stages. This depends chiefly on the length of the incubation period and the rapidity with which reflex convulsions develop. The longer the onset of the latter is postponed, the more likely is the patient to recover. If reflex convulsions occur within 48 hours of the first appearance of trismus the prognosis is bad. Previous active immunization or prophylactic anti-toxin, the presence of local tetanus, a slight relatively clean wound, and an otherwise healthy patient in good physical condition are additional favourable factors. A severe or septic wound, infancy, old age or a predisposition to chest disease are unfavourable.

By carefully considering all these factors, cases of tetanus may be divided into three prognostic groups: those who will almost certainly recover, those who will almost certainly die and an intermediate group in which the issue is in doubt. It is also important to remember that in most cases reflex convulsions wax and wane in a definite sequence and so allowance must be made for the particular phase at which the treatment is begun. In attempting to sum up the results of any new form of treatment in tetanus, it is essential to apply the prognostic yard-stick.

Treatment of tetanus may be considered under five headings: (1) The prevention of further absorption of toxin from the wound and the neutralization of all toxin still circulating in the blood and lymph by giving a large dose of antitoxin, preferably intravenously; (2) Local treatment of the wound; (3) General supporting measures—nursing, feeding and sleep; (4) Prophylactic measures to prevent secondary infections, particularly pneumonia, by the administration of penicillin and sulphonamide drugs; (5) Control of reflex convulsions. The tonic rigidity of tetanus, apart from the discomfort and inconvenience it causes, is relatively harmless and by itself need not cause anxiety.

Curarine is thought to act by blocking the efferent nerve impulse at the myoneural junction, and so paralysing skeletal muscle. The intercostal muscles and the diaphragm are those last to be affected. Curarine has been used in an attempt to control reflex convulsions which, when severe, may be dangerous, and to lessen tonic rigidity so that feeding and nursing are made easier. Such treatment is symptomatic only, but is often of value in preventing exhaustion, and so weighting the scales on the side of recovery. Its use would be justified if it could be shown that it would do this more effectively and with no more risk than sedatives, such as paraldehyde or barbiturates.

The ideal drug for this purpose would be one which was easy to administer, which had a prolonged and certain action in preventing reflex convulsions and in relaxing the jaw, and which had no untoward effects in depressing respiration or causing respiratory spasm. Further, it should have no other toxic effects. An aqueous solution of gourd curare was found to control the reflex convulsions in an inevitably fatal case of tetanus, but there was no evidence that it prolonged the patient's life, for hyperpyrexia and death occurred at the expected time (Cole, 1934). After further trial this preparation was abandoned because it appeared to cause respiratory difficulty, and was considered dangerous.

When curarine was isolated, West (1936) gave it by intravenous drip to patients with severe tetanus, but this method was found to be impracticable and it was subsequently given by intramuscular injection; d-tubocurarine chloride is now used in anaesthesia as a routine for the production of muscular relaxation. For this purpose it is safe and reliable in the hands of an experienced anaesthetist. There is, however, one great difference between the patient anaesthetized for a surgical operation and a patient with tetanus. In the former, respiration is under the complete control of the anaesthetist during the hour or so the operation lasts, whereas in the latter there is no such control and the drug is needed for at least several days and possibly a week or more.

The great disadvantage of an aqueous solution of d-tubocurarine in tetanus is that its effect is too fleeting (Adriani, 1947; Ellis, 1948), only lasting for a maximum of an hour, and if the drug is pushed it is liable to cause respiratory difficulty or paralysis—a most undesirable effect in tetanus. No reliance should be placed on antidotes such as prostigmin. In order to obtain a more prolonged effect, Weed (1948) used a preparation of d-tubocurarine in wax and oil which produced muscular relaxation for 18-24 hours in three cases of tetanus. This appeared satisfactory but for one episode of respiratory difficulty, salivation and cyanosis. The cardiovascular system was carefully studied during treatment and no untoward effects were noticed. Godman and Adriani (1949) also used a preparation of d-tubocurarine chloride in wax and oil in two patients, but they found that the results were not satisfactory because the degree of paralysis was unpredictable. In one patient complete res-
piratory paralysis was inadvertently produced so that the patient had to be placed in a respirator for two hours before she recovered. At present there is no preparation of curare which is reliable and safe, chiefly because the margin between the dose needed to produce muscular relaxation and control of convulsions and that which will cause a dangerous paralysis of respiratory muscles is too small. If all other measures fail, and curare is given a trial, the initial dose of the aqueous preparation should be small, say 5 milligrams intramuscularly to an adult, and it should only be increased carefully and gradually according to the response in the individual patient. The optimum dose of curare in oil wax suspension is at present uncertain. In order to maintain complete control of respiration and ensure a clear air-way, Godman and Adriani (1949) have advocated early tracheotomy in all but the mildest cases of tetanus—a suggestion which at least emphasizes the importance of complete respiratory control. It should be remembered that respiratory spasm is common in severe cases of tetanus and may be the result of the disease rather than the therapy.

Of the various chemical substances suggested as alternatives to curarine, myanesin should be mentioned, as it has undergone extensive experimental and clinical trials. Berger and Bradley (1947) have shown that this drug produces muscular relaxation without causing respiratory arrest or influencing the blood pressure. It has, further, a wide margin of safety, is of low toxicity and is quickly destroyed in the body. Myanesin antagonizes the convulsions produced by strychnine, probably by depressing reflex activity in the spinal cord, and so might be expected to control the reflex convulsions of tetanus. Myanesin has been used in the treatment of tetanus and favourably reported on by various observers (Belfrage, 1947; Torrens, 1948; Godman and Adriani, 1949) and the risks of causing respiratory embarrassment, although not negligible, are considerably less than with curarine. Haemoglobinuria and thrombosis are complications which rarely occur. It may be given either intramuscularly or orally in doses of 0.5 to 1 gm. for an adult, repeated every few hours according to the effect produced. It is wise to start with the smaller dose and increase this carefully until a satisfactory response is obtained. During treatment the effect of respiration should be carefully watched. If myanesin is given in conjunction with barbiturates, the dose should be reduced.

Theoretically myanesin should be a safer and more effective drug and limited tests suggest that this is so. Further trial is merited in appropriate cases of tetanus, preferably severe ones, in which well-tried measures are unsatisfactory.

Summary
The treatment of tetanus with curarine and myanesin is symptomatic only. At present curarine is unsatisfactory and is still on trial. The optimum dose is uncertain, the benefits doubtful and the risks, particularly of respiratory depression, considerable. For ordinary purposes well-tried sedatives, such as paraldehyde or barbiturates, are preferable and curarine should be reserved for cases in which these have failed, and it should then only be given under carefully controlled conditions. The same reservations apply to myanesin, but with this drug the risks appear to be less and the results more promising. In assessing the value of these new drugs in tetanus it is most important that due regard should be paid to the prognostic criteria in each case.

Leslie Cole, M.D.(Camb.), F.R.C.P.
Senior Physician, Addenbrooke's Hospital, Cambridge

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Leslie Cole

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