extent of the elevation can be correlated with the occurrence of skin xanthomas (Ahrens *et al.*, 1950). Testosterone lowers the total serum cholesterol level in primary biliary cirrhosis (Ahrens *et al.*, 1950; Parkinson, 1952), and we have confirmed this finding. This further action of testosterone in obstructive jaundice may therefore prevent or ameliorate the xanthomatous skin lesions.

Absence of bile from the intestines leads to steatorrhoea with imperfect absorption of calcium and the fat-soluble vitamins. Patients with prolonged obstructive jaundice develop secondary changes in the bones with kyphosis, spontaneous fractures, and radicular pain. Androgen administrations result in a diminished urinary loss of calcium and phosphate and a conspicuous fall in urinary nitrogen (Reifenstein and Albright, 1947). Testosterone may therefore have an additional beneficial effect on the bone lesions of obstructive jaundice.

We have confirmed the rise in the serum bilirubin level in jaundiced patients given testosterone. Methyltestosterone has even been implicated as the cause of an obstructive type of jaundice in seven non-jaundiced patients receiving the drug for its androgenic action (Werner *et al.*, 1950). The mechanism of the jaundice is not known. The increase in the depth of jaundice should not be a contraindication to giving testosterone for its antipruritic action.

Masculinization in female patients is an unfortunate complication of testosterone therapy. Most patients are, however, willing to suffer this disability if the intolerable itching can be alleviated. The exact amount of testosterone needed to prevent itching is still unknown. In some subjects it may be possible to give just enough to relieve the pruritus and yet not induce masculinization. It is suggested that in female patients treatment should be started with 25 mg. of sublingual methyltestosterone daily for three weeks. This dose can then be given three times a week. In some patients it may be possible to reduce the dosage still further and still prevent itching. Male patients with chronic obstructive jaundice show signs of androgen deficiency, and benefit by the full daily dosage of 25 mg. of methyltestosterone sublingually.

Subcutaneous implants of testosterone propionate would seem to be an ideal method of exerting a continuous antipruritic effect. This is true if absorption is adequate (Case 2). However, in some patients absorption is very slow (Cases 1 and 4) and pruritus continues unrelieved. Subcutaneous testosterone propionate implants have therefore proved unreliable, and sublingual methyltestosterone administration is recommended for routine use.

Summary

Methyltestosterone (25 mg. daily sublingually) relieved pruritus within seven days in seven patients suffering from chronic obstructive jaundice. The rationale of this therapy is not known. Testosterone propionate by subcutaneous implant was not so effective, perhaps owing to inadequate absorption.

Other effects of prolonged testosterone therapy were an increase in the depth of jaundice, a fall in the serum cholesterol level, and masculinization in three of the six female patients treated.

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TETANUS SUCCESSFULLY TREATED WITH GALLAMINE TRIETHIODIDE

BY

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The treatment of tetanus falls into two parts—an attack on the infecting organism and control of the muscular spasms. The infecting organism is dealt with by giving toxoid and antitoxin in amounts and by routes which vary widely, but all authorities agree in advising heavy dosage, some recommending intrathecal injection in addition to the intravenous and intramuscular routes; wound toilet is performed.

In the past, control of spasms has been attempted by heavy sedation, and since the introduction of the muscle-relaxing group of drugs D-tubocurarine and mephenesin have both been used in the treatment of tetanus. In this country, Spencer Wells (1858–61) was the first to describe the treatment of tetanus with woorara, which contains an active principle, curarine, isolated by Boussangault in 1828; of three cases treated, one recovered. Only two years previously Claude Bernard (1856) had given his original description of curare and discussed its mode of action.

Difficulties in Treatment

During subsequent years the use of curare in the treatment of tetanus has been reported on many occasions, but Cole (1934) and other authors have noted the difficulties for long encountered owing to the lack of a standard preparation. Ory and Grossman (1948) reported two recoveries after the use of curare; they found that the drug caused too much relaxation, the tongue often falling back and causing respiratory obstruction. They also advised the use of atropine to counteract increased bronchial secretion, another troublesome feature in cases receiving curare. Adriani and Ochsner (1947), commenting on five cases treated with curare, stated that one patient died an hour after the administration of a single dose of curare which had been followed by respiratory and circulatory failure; the cause of death was not determined but was probably in part due to curare. They found that the action of curare was extremely abrupt in onset and that the effective response lasted for an average of 20 to 30 minutes. As the dose needed to relieve spasm was too close to that causing complete curarization, they had great difficulty in avoiding respiratory depression and obstruction.

Godman and Adriani (1949), reviewing the management of cases of tetanus, felt that true evaluation was difficult owing to the wide variations between individual cases. They thought that, while the control of rigidity and spasm was essential, no relaxant was entirely satisfactory. For mild cases they preferred a combination of phenobarbitone and "tolserol" (mephenesin), but admitted that though barbiturates were good as sedatives they were of little use as relaxants unless given in doses which would produce anaesthesia. Except in mild cases they recommended early tracheotomy in order to prevent downward spread of upper respiratory infection. Their experience with curare and with curare in oil was unsatisfactory.

Weed *et al.* (1948) used D-tubocurarine in wax and oil successfully in three cases. They found that a prolonged relaxant effect was produced without many of the unpleasant side-effects of curare, and that, while injections often did not need repeating until 18 to 24 hours had elapsed, the daily requirement of the drug increased progressively. Their findings were confirmed by Binger and Devnich (1950), who treated two cases with a similar preparation. Their aim was to produce relaxation without causing apnoea ; they reserved sedatives and hypnotics for use at night.

Trial of Gallamine

It will be seen that success has been hampered by the difficulty of maintaining the degree of relaxation required on a steady level owing to the comparatively short period over which all these drugs, with the exception of curare in wax and oil, produce sufficient effect. There is also the difficulty of giving adequate dosage without embarrassing respiration. Doughty and Wylie (1951) and Thompson and Norton (1951) report that respiratory depression is less marked with gallamine triethiodide than with D-tubocurarine, especially in the conscious subject. For this reason it was decided to try the effect of administering gallamine ("flaxedil") for the control of tetanic spasms.

Case Report

A married woman, a typist aged 35, was admitted to hospital at 1 a.m. on May 12. Four days previously she had first noticed difficulty in swallowing, trismus, and breathlessness on exertion. These symptoms continued, and on the day before admission stiffness of the muscles of the back of the neck and shoulders developed. At times she noticed a feeling of tightness in her abdominal muscles, but there was no definite history of spasms. For some months she had suffered from cracks in the finger-tips, and a fortnight previously a septic thumb had developed, which healed slowly. She had never been immunized against tetanus or received tetanus antitoxin.

Examination showed an alert and co-operative woman of average build. Her temperature was 99° F. (37.2° C.), pulse 100, and respirations 16. Mucous membranes were pale. Definite trismus and stiffness of the neck muscles were present. Two upper molars were carious. Hypertonus of the abdominal muscles was pronounced. On one thumb there was a small scar. No other abnormal physical signs were present.

Tetanus was diagnosed, and at 2 a.m. 100,000 units of tetanus antitoxin was administered intravenously. At 6 p.m. 200,000 units was given ; which dose was repeated daily until May 16, followed by 100,000 units daily until May 19. In addition, tetanus toxoid, 1 ml., was given on May 12. The patient was nursed in a single-bedded room and a special nurse was provided.

Trismus and dysphagia increased after admission, and on May 13 feeding was started by means of a Ryle's tube passed intranasally ; this was maintained until May 28. On May 13 her breathing was becoming laboured and bronchial secretions were expelled with difficulty. Her temperature rose to 101.4° F. (38.5° C.), and her pulse to 120. Scattered rhonchi were present on auscultation, so crystalline penicillin, 500,000 units eight-hourly, was begun. On May 15 she had well-marked risus sardonicus and was unable to protrude her tongue, as her front teeth could be separated only ¼ in. (0.6 cm.). Muscle hypertonus was pronounced and tetanic spasms were occurring with increasing frequency and severity.

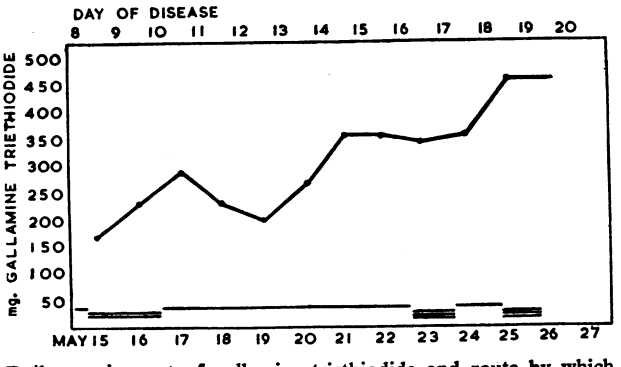
At this stage it was decided to try the effect of gallamine in reducing the severity of the spasms. An initial dose of 40 mg. was given intravenously ; within one minute there was relaxation of the abdominal muscles and diplopia. Diaphragmatic respiration became exaggerated, but for six minutes there was considerable weakness of the intercostal muscles. One hour later the patient was comfortable and able to open her mouth a little. Three hours after the injection trismus had returned and further frequent tetanic spasms were occurring.

The effect of gallamine intramuscularly was next tried: an injection of 80 mg. was followed by abolition of all but slight transitory spasms, swallowing became possible, but coughing remained difficult. Four hours later a further 40 mg. intramuscularly and ¼ gr. (16 mg.) of morphine sulphate subcutaneously allowed the patient to obtain several hours' light sleep. For the next 16 hours 30 mg. of gallamine was given four-hourly by intramuscular injection, but during the afternoon of May 16 the dose was increased to 40 mg. three-hourly, as spasms, although no longer painful, were still occurring.

On May 17 the patient's general condition was unchanged, but as the spasms were not completely controlled by intramuscular injections and as frequently repeated injections by this route were thought undesirable, a slow intravenous saline drip was begun, and gallamine was injected into the rubber tubing of the drip at a dose of 10 mg. each hour. Morphine sulphate, ¼ gr. (16 mg.), and amylobarbitone sodium, 3 gr. (0.2 g.), were given nightly. Next day she was cheerful and felt better after a moderately good night's sleep, no further muscle spasms having occurred since shortly after the drip was started. Pyrexia—99° F. (37.2° C.)—continued and was associated with a low-grade respiratory infection, crepitations being present, especially at the base of the left lung. The haemoglobin was 47% (6.9 g.%) and the white cells numbered 14,500 (polymorphs 84%, lymphocytes 14%). Penicillin was discontinued, and sulphamerazine, 1 g. eight-hourly, was given in the form of "cremomerazine" through the Ryle's tube.

On May 19, as no further spasms had occurred, the frequency of gallamine injections into the drip was reduced to 10 mg. every 90 minutes ; but next day, as slight spasms had occurred during the night, the dose was increased to 10 mg. hourly, being further increased to 15 mg. hourly in the evening.

On May 21 the patient's general condition remained unchanged. Her temperature was 99° F. (37.2° C.). She was free from spasms, except for one short period when the drip became blocked. As the anaemia was not responding to colloidal iron by the Ryle's tube, a transfusion of 1 pint (570 ml.) of blood was given on May 22 and repeated on May 24. Sulphamerazine was discontinued, and gallamine was continued at the rate of 15 mg. hourly until the afternoon of May 23, when, in view of the depletion of available veins, it was decided to change to a subcutaneous infusion, to which was added hyaluronidase, 1,000 units, six-hourly. It required 14 mg. of gallamine hourly by this route to keep the patient free of spasms. While the second blood transfusion was being given the gallamine was again administered intravenously. Slight facial spasms occurred on May 25, so the dose was increased to 20 mg. hourly.



Daily requirement of gallamine triethiodide and route by which administered. (Intravenous, —— ; intramuscular, = ; subcutaneous, ≡ .)

By the morning of May 26 the patient was able to open her mouth a little wider. At 11 p.m. she was found to be perspiring freely, the respiration was gasping in character, and her muscles were extremely relaxed, so the drip was stopped, and by 1 a.m. she was quite comfortable. The next morning she was breathing without difficulty and no sign of muscle spasm remained : she was alert after a very restful night. No further gallamine was required. On May 28 she was able to eat solid food. Although muscle tone remained increased, no further spasms occurred. Respiratory infection resolved rapidly, the low-grade pyrexia ended on May 30, and her general condition steadily improved. The anaemia did not respond to oral iron, and an iron-absorption test showed no absorption. A course of "ferrivenin" totalling 1.47 g. was given, raising the haemoglobin to 82% (12.1 g.).

Over the 11½ days of continuous administration 3,710 mg. of gallamine triethiodide was administered (see Chart). At no time was an oxygen tent or artificial respirator required.

Summary

A case of tetanus is described which began about two weeks after a minor injury to a thumb that had become septic. At the time of admission trismus and hypertonus were present. By the eighth day of the disease it was obvious that the increased frequency and severity of the tetanic spasms would not respond to normal sedation with barbiturates and morphine, and it was decided to try the effect of gallamine. At first this was administered intramuscularly, but three-hourly injections proved insufficient to control spasms. Hourly injections into the rubber tubing of a saline intravenous drip were found to be satisfactory, as was administration hourly into a subcutaneous hyaluronidase infusion.

As the days passed it became noticeable that steadily increasing amounts of gallamine were required to prevent spasms ; in view of this, the sudden termination of the tetanic spasms was quite unexpected. Morphine sulphate, ¼ gr. (16 mg.), and amylobarbitone sodium, 3 gr. (0.2 g.), were administered each evening and at other times as required.

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At the anniversary meeting of the Royal Society on December 1 Dr. E. D. Adrian, in his presidential address, paid a special tribute to Sir Charles Sherrington, who died last March at the age of 94. He had been president of the Royal Society from 1920 to 1925. In Dr. Adrian's words, "few scientists of our time have been so well qualified to judge the advance of human understanding of the natural world, for he lived long enough to have witnessed most of the great achievements of the present era, and he had made an intimate study of the science of the Middle Ages, when the schoolmen and alchemists were as satisfied with their theories as we are with ours."

PROLONGED WOUND ANALGESIA AFTER SURGICAL OPERATIONS

CLINICAL TRIAL OF EFOCAINE

BY

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Post-operative pain is an almost universal sequel to every type of surgical procedure and, apart from causing distress to the individual patient, contributes to a number of secondary complications such as inhibition of the cough reflex and consequent pulmonary collapse, retention of urine, delayed mobilization leading to venous stasis and thrombosis, loss of sleep, and delayed convalescence.

The aqueous solutions of local analgesics hitherto in use have suffered from the disadvantage of rapid diffusion and elimination from the area of infiltration, so that even with the addition of adrenaline the effect is unlikely to last for more than four hours. Oily solutions such as "proctocaine" and benzocaine compound injection *N.F.* (A.B.A.) have been inconsistent in their action, and have caused trouble from abscess formation and local necrosis.

American workers (Iason and Shaftel, 1952a, 1952b ; Puderbach and Shaftel, 1952 ; Raicus, 1952 ; Weinberg, 1952) have recently described a new product marketed under the name of "efocaine," composed of procaine base 1%, with procaine hydrochloride 0.25%, and butyl *p*-aminobenzoate 5% in propylene glycol 78% and polyethylene glycol 300 2%. This clear solution is non-oily, though somewhat .viscous, and is freely miscible with body fluids ; none of the constituents appear to have any toxic effects. The solution is saturated, but on contact with the body fluids the local analgesic is immediately precipitated in a relatively insoluble form which exerts an effect for from 8 to 20 days.

Clinical Trial

In order to obtain experience of the use of this product and to assess its therapeutic possibilities, a series of patients were selected who were undergoing the commoner operations in which post-operative pain usually necessitates the administration of analgesic drugs. The first two cases were elective appendicectomies performed through McBurney incisions. At the conclusion of the operation, before peritoneal closure, the solution was introduced into the intermuscular plane above and lateral to the incision, 5–6 ml. being used. The wounds were insensitive for the whole of the patient's stay in hospital (eight days), but both patients complained of intestinal discomfort for the usual 36 hours.

Having established that prolonged analgesia of a small wound could be obtained, a regional block of T 11 and 12 and L 1 (2 ml. each nerve) was then attempted in a nephroureterectomy for renal tuberculosis, with a right paramedian as well as a lumbar incision. Here there was a good deal of pelvic dissection, which resulted in abdominal discomfort. Complete analgesia was not achieved, but the lumbar incision remained partly anaesthetic for 20 days. A similar lumbar block of T. 11 and 12 and L. 1 was performed on a patient after left lumbar ganglionectomy by the anterolateral route. There was no post-operative pain and the scar was only slightly sensitive on the twelfth day.

Three inguinal hernia patients were given 10–12 ml. of the solution, partly into the intermuscular plane near the iliac