CURARE IN OIL IN THE TREATMENT OF SPASTIC CONDITIONS

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The therapeutic possibilities of curare in diseases of the central nervous system have been considered for nearly a century, but because of the dangers of the drug it was originally used only in desperate cases of tetanus and hydrophobia. Progress towards a more specific use was made when Hartridge and West (1931) and others, between 1927 and 1931, demonstrated conclusively that, in doses which did not produce general paralysis, curare had a selective action, abolishing decerebrate rigidity in cats and tetany in dogs. The mode of action was not clear, but Bremer (1927, 1928, 1931) suggested from animal experiments that weak solutions of the drug blocked nerve-endings which were continuously in action more than those which were at rest; because of this it was possible to reduce muscle tone without greatly affecting voluntary power.

In 1932 West described 17 cases of severe pyramidal or extrapyramidal rigidity in man, due to various causes, treated with crude curare obtained 30 years earlier from South America. He found that, given hypodermically in doses of 2 to 20 mg., the drug produced a definite measurable reduction in spasticity, the effect being produced in from 10 to 40 minutes and lasting 2 to 48 hours. Clinical improvement coincided with the registrable changes, and he found that massage and physical exercises were facilitated under the influence of the drug. Most of the patients complained of giddiness, headaches, and a feeling of drunkenness (but no diplopia) 10 to 30 minutes after the injection, but there was a tendency for all these symptoms to diminish as treatment continued. Objectively, a temporary nystagmus and a fall in blood pressure were noted, the latter being corrected by subcutaneous adrenaline, which also relieved the headache. West concluded that the drug was of some use in reducing the spasticity of pyramidal disease, but was not so good as hyoscine in Parkinsonian rigidity.

Interest in the drug from a neurological point of view was revived with increasing experience of its effect in anaesthesia and psychiatry. Harvey and Masland (1941) used it intravenously (in doses of 1 to 2 mg. per kg. of body weight) in the treatment of a variety of spastic conditions (23 cases), but they concluded that it was of no real use because of the inconvenience of the side-effects and the shortness of its action. They suggested that a drug which lasted longer might be of some value. While their conclusions were negative they were unable to explain the cause of the lasting relief which a few of their patients reported.

Bennett (1941) arrived at different conclusions, using similar doses of the drug, also intravenously, in 12 spastic children. The majority of his patients were improved over a period of months, mainly because the muscle relaxation effected made it easier to carry out more extensive physiotherapy. Side-effects were not very troublesome, but Bennett admits that the disadvantage of the treatment is that the action of the drug is not sustained. Denhoff and Bradley (1942) reported even more favourably, also on spastic children. They used an extract of curare ("intocostin"—Squibb), and the drug was given intramuscularly in doses

of from 0.9 to 3.3 mg. of curare per kg. of body weight. The relaxation produced lasted approximately four days, and they were very much impressed with the way in which the educational programme could be accelerated by the drug.

Schlesinger (1946) described the use of a 3% suspension of *d*-tubocurarine chloride in a peanut-oil-white-wax, mixture in 11 cases of extreme spasticity secondary to injuries of the spinal cord. He gave it intramuscularly in doses of 30–45 mg. of the alkaloid (1–1.5 ml. of the suspension) every four days, and claimed that the action of the drug given in this form was prolonged often up to three days. The undesirable effects of aqueous curare were absent except that during the adjustment of the dosage slight blurring of vision was noted. In his series of cases (details of four being given) he found that flexor spasms were relieved, spasticity was decreased, and during the period of relaxation physical exercises could be given.

Present Investigation

It seemed possible that a great advance had been made, and the present investigation was conducted with a view to confirming Schlesinger's conclusions in general neurological cases. Seventeen patients were selected for treatment, the only criteria being that their spasticity should be of the pyramidal type and that it should be their chief disability. The series comprised one case of traumatic quadriplegia, one of spinal cord compression, one of motor neurone disease, one of subacute combined degeneration, and 13 of disseminated sclerosis. Six of the patients were definitely bedridden, four could walk only a few steps with the greatest difficulty, and the remainder had varying degrees of locomotive disability. No special apparatus was used to test the degree of spasticity, and response to treatment was assessed so far as was possible on unequivocal clinical findings—for example, did the injections enable a bedridden patient to walk or allow an ambulatory one to discard a stick?

The curare employed was "tubarine" (oily) (Burroughs Wellcome and Co.), and the usual maintenance dose was 20–40 mg. given intramuscularly (1 ml. = 30 mg. of *d*-tubocurarine chloride).

Case Reports

Traumatic Quadriplegia

Case 1.—A man aged 56 suffered damage to his cervical cord on Dec. 7, 1946, following a blow. The resultant spastic quadriplegia was thought to be due to a haematomyelia. As this cleared up a partial Brown-Séquard lesion was found, there being gross spasticity of the right arm and leg, with sensory loss in the left arm and leg. Four months after injury flexion-spasms appeared which were associated with severe pain in the right leg. A dose of 15 mg. of curare in oil produced diplopia, a feeling of drunkenness, vomiting, and slight diminution of spasticity for a few hours in both the arm and the leg. The next dose of 30 mg. produced, after 10 minutes, diplopia which lasted approximately one day, necessitating the use of an eye-shield. After five minutes tone in the limbs was considerably reduced, but 30 minutes later it had started to increase again and the limbs went back to their original stiffness after a few hours. Flexor spasms were not reduced, several taking place during the two hours after the injection of the curare. Several further administrations of curare in oil in 30-mg. doses did not produce any appreciable change in muscle tone, but tolerance from side-effects developed. Some six weeks later the flexor spasms became much worse and were extremely painful. It was therefore decided to try the effect of curare in oil together with quinine sulphate, 10 gr. t.i.d., Harvey (1939) having shown the latter drug to possess curare-like qualities. The effect of the combination was remarkable in that the spasms disappeared within a few days and morphine could be discontinued. The treatment was stopped after a month and the flexion spasms did not reappear.

Paget's Disease of the Spine

Case 2.—A man aged 62 had had pains in the legs and increasing difficulty in walking for the past three years. On admission to hospital in April, 1946, he showed evidence of a spastic paraplegia thought to be due to a spinal tumour. Laminectomy performed on May 14 showed extreme sclerosis of the vertebrae, with ossification of the dura due to Paget's disease, for which nothing could be done. For seven months after operation the story was one of increasing stiffness of the legs, so that on readmission in December, 1946, he was unable to stand and the picture was one of a severe spastic paraplegia, with pain and flexor spasms beginning to be a prominent feature. It was decided to try the effect of curare with a view to lessening the spasticity. The drug was at first given as aqueous tubocurarine intramuscularly in doses of 20 mg., later increasing to 30 mg. every third day. It was found that the drug produced definite lessening of the spasticity and voluntary power became better for a few hours, but at no time was the patient able to stand. The side-effects of the drug were diplopia, nausea, and a feeling of drunkenness. Injections of tubocurarine in oil intramuscularly were then substituted, beginning with a dosage of 20 mg. and increasing up to 40 mg. on alternate days. These injections produced minimal improvement; his pain and flexor spasms were not improved, and, although side-effects were slightly less noticeable than with ordinary curarine (probably because of increased tolerance), yet relief from the spasticity was also less and did not materially help the patient's condition. With neither type of curare was he able to walk. The spasticity became so extreme that adductor tenotomy was performed and the patient was put in a plaster-of-Paris spica. Unfortunately decubitus ulcers developed and he died suddenly from heart failure three months after operation. He had been under treatment with curare intermittently for five months. Post-mortem examination confirmed the diagnosis of Paget's disease of the spine.

Motor Neurone Disease

Case 3.—A woman aged 45 suffered from typical motor neurone disease. She showed a bulbar palsy of mixed pseudo and true types, an exaggerated jaw-jerk, a spastic tongue, wasting of the intrinsic muscles of the hands, increased tendon reflexes in the arms, and gross spasticity in the legs, rendering her bedridden. The administration of 30 mg. of curare in oil every third day produced a slight reduction in spasticity, but the patient remained bedridden and her speech was unaltered. She insisted, however, on keeping up the injections, as she was sure the drug was doing her good—in particular her legs felt warmer. No disagreeable side-effects occurred.

Subacute Combined Degeneration of the Cord

Case 4.—This patient, a woman aged 58, was admitted with very spastic legs, bilateral extensor plantar responses, and pronounced diminution in joint sense due to subacute combined degeneration. She had suffered from pernicious anaemia for many years and had been on liver therapy; her blood picture at the time of admission was normal. The administration of curare in oil up to 45-mg. doses produced no effect whatsoever.

Disseminated Sclerosis

Case 5.—A woman aged 56 had had a spastic paraplegia, nystagmus, dysarthria, and euphoria due to disseminated sclerosis for over 10 years. She had one month's history of flexion spasms, which were very painful, and on admission she was found to be bedridden and to have 20% of flexion contracture in both knees. Doses of curare in oil daily, increasing from 10 to 30 mg., produced marked diplopia and a feeling of drunkenness. There was slight diminution in tone in the legs but no relief of flexion spasms, and no diminution in the flexion contracture despite additional active physiotherapy.

Case 6.—A woman aged 29 was admitted with a spastic paraplegia and nystagmus, having been bedridden for three months. She volunteered the statement that her stiffness was worse in cold weather. Doses of curare in oil up to 30 mg. and exercises produced some subjective improvement, and she managed to get out of bed. Her condition three months later was much the same as on discharge from hospital, although she had had no further curare.

Case 7.—A woman aged 51 had had difficulty in walking for 10 years and on examination was found to have spastic legs, R > L, very brisk arm reflexes, exaggerated knee-jerks, left ankle clonus, and extensor plantar responses. The C.S.F. Lange curve was 4321000000 and the W.R. was negative. Curare in oil in doses ranging from 15 to 40 mg. produced a definite decrease in spasticity, and for the first three-quarters of an hour after injection reversal of the plantar responses was noted. There were no side-effects, and the patient could walk reasonably well—certainly better than on admission.

Case 8.—A woman aged 67 was admitted with diplopia and spastic paraplegia with bilateral ankle clonus and extensor plantar responses. She had been almost bedridden for six months. The Lange curve was 5543321000 and the W.R. was negative. Repeated injections of 30 mg. of curare in oil produced some diminution in muscle tone but no alteration in reflexes. The change was not enough to aid the patient's walking materially.

Case 9.—A woman aged 34 complained of dragging of the left leg for the past five weeks. She was found to be euphoric and to have a spastic paraparesis with bilateral extensor plantar responses. Curare in oil in doses up to 20 mg. produced considerable improvement in the gait, both subjectively and objectively. There were no side-effects. This case was the least severe of the series.

Case 10.—A man aged 36 had dragged his left leg for four years and now had great difficulty in walking after a few minutes. He was found to have very brisk tendon reflexes, bilateral ankle clonus, and bilateral extensor plantar responses. Tubarine in oil in doses of 22.5 mg. produced no change; doses of 30 mg. caused blurring of vision in half an hour, and rather less foot drag; doses of 45 mg. produced diplopia ++, drunken feeling +, and reeling gait. His gait was definitely no better 30 hours later.

Case 11.—A woman aged 36 had had spastic ataxic gait, brisk reflexes, and extensor plantar responses for four years. Tubarine in doses of 45 mg. produced slight improvement in gait and no side-effects. Objectively there was little improvement.

Case 12.—A woman aged 39 had had difficulty in walking for four years. Her legs were ataxic and spastic, R > L, reflexes brisk, plantars extensor. Tubarine in doses of 22.5 mg. and 30 mg. produced mistiness of vision, but no objective signs or side-effects. Doses of 45 mg. produced misty vision, sensation of drunkenness, and great ataxia. Twenty-four hours later there was no subjective improvement, but she was possibly walking a little better.

Case 13.—A woman aged 36 had been ill for 10 years, but when admitted she was undergoing a spontaneous remission. Her legs were slightly spastic, tendon reflexes brisk, plantar responses extensor; she was walking quite well. After 22.5 mg. of tubarine she felt a bit dithery, and had a feeling of warmth in her hands and feet. After 30-mg. doses she had ptosis, a feeling of detachment, and was walking worse. Her hands went warm and then cold within an hour. After 45-mg. doses she felt drunk and muzzy, her legs were cold, and she was more ataxic. Next day walking was better.

Case 14.—A woman aged 63 had been ill for five years. She managed to take a few steps round her room by holding on to the furniture. She had very spastic legs and bilateral extensor plantar responses, but no anaemia or sensory changes. Tubarine in 22.5-mg. doses had no effect of any kind. Doses of 30 mg. produced blurring of vision in 50 minutes; after one hour her legs became more spastic than before the injection; there were no side-effects. Two hours after 40-mg. doses she was still very spastic, and the plantars were extensor. No objective improvement was seen and there were no troublesome side-effects.

Case 15.—A woman aged 26 had had for two years diplopia, spastic legs, very brisk reflexes, flexor plantar responses, and gross ataxia on heel-to-knee tests, but her gait was fairly good. Tubarine in doses of 22.5 mg. produced drunkenness, "wobbly when walking." Doses of 30 mg. produced diplopia ++ and nystagmoid jerks; jerks still brisk. She was walking very badly indeed, and was more ataxic than ever. The drug was discontinued because of the side-effects.

Case 16.—A man aged 42 had had a dragging left leg and slightly ataxic gait for six years. He was found to have left ankle clonus, brisk reflexes, and bilateral extensor responses. Tubarine in doses of 20 mg. and 30 mg. produced severe side-effects, blurring of vision, and drunkenness, great ataxia, but no objective improvement in gait. The drug was discontinued at patient's own request.

Case 17.—A woman aged 44 had had disseminated sclerosis for 10 years. Brisk tendon reflexes, bilateral extensor plantar responses, and spastic paraplegia were present. She was able to walk a few steps, but had not been out of her house for three years. Tubarine in 30-mg. doses did not give any relief but made the patient giddy and more ataxic.

Discussion

While we are in agreement with previous authors that curare temporarily diminishes the tone in spastic muscle without producing general paralysis, we have not been able to substantiate Schlesinger's claim that curare in oil has overcome the disadvantages of the drug in aqueous solution, nor have we been impressed with it as a therapeutic agent in our series of patients.

Side-effects.—Troublesome symptoms occurred in 10 of our 17 cases (so severe in two that the drug had to be discontinued), but we found, as West did with aqueous curare, that a tolerance usually developed on continued administration.

Length of Action.—In general the relaxation of muscle tone was apparent in 10 minutes, maximal in 20–30 minutes, began to wear off in an hour, and was completely absent in 24 hours. This action is no longer than that of aqueous curare, although, as with that drug (West, 1932; Harvey and Masland, 1941), some of our patients thought that relief lasted several days.

We have no satisfactory explanation to offer for the temporary reversal of plantar responses noted in Case 7 and merely record it as a matter of interest.

Therapeutic Value.—Reviewing our 17 cases, we find that in 11 the treatment either produced no improvement (7) or the patients were actually worse (4). The reason for definite deterioration appears to be that curare by lessening spasticity sometimes unmasks previously concealed posterior column loss. Turning to the cases in which improvement was noted, the only remarkable success was in Case 1. Here curare in oil was of no use until it was reinforced with quinine, but the combination of the drugs resulted in cessation of the flexion spasms, which did not return when the drugs were stopped a month later. (It may be worthy of note that all cases in which favourable results were reported by Schlesinger were traumatic in origin.) In the remainder of our cases which were thought to be improved the benefit was slight and usually only apparent to the patient. It was very difficult to assess minor fluctuations in muscular power, and interrogation of patients showed that there was considerable natural variability: thus hot weather and previous exercise both resulted in temporary improvement. Another factor which had to be borne in mind, particularly in dealing with disseminated sclerosis, was natural remission (Case 13). Even more important was the psychological aspect of the treatment. Most of our patients had been chronically ill for long periods, and when fresh hope was engendered by the new drug, intensive physiotherapy, and the encouragement of being a centre of interest once more, there was a natural tendency to think the treatment was doing good.

Bearing all these factors in mind, we do not feel that the improvement noted in six of our cases can with any certainty be attributed to tubarine, particularly as 11 showed no benefit whatever. In our opinion, therefore, curare in oil is not the hoped-for advance in reducing spasticity in

neurological disease, and we do not feel that our results justify the expense of the treatment, at any rate so far as adults are concerned. We have not used the drug in children, but it seems likely that the same disadvantages would obtain, and a recent communication (Collis, 1947) on the subject of reablement in Little's disease makes no mention of its use. Further investigation is necessary to see whether a combination of drugs is any more successful.

Summary

The value of curare in oil in reducing spasticity of pyramidal type in 17 cases of neurological disease has been investigated.

In our opinion the drug has not proved superior to aqueous curare, and has been of little use in the rehabilitation of our patients.

Our thanks are due to Dr. H. S. Pemberton and Dr. Leslie Cunningham for help in providing some of the cases, and to Messrs. Burroughs Wellcome and Co. for the initial supply of tubarine.

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LOUSE-BORNE RELAPSING FEVER IN PERSIA

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An epidemic of a recurrent fever occurred in Abadan between November, 1945, and June, 1946—1,087 cases being admitted to the isolation hospital. We intend to show that this was in fact an epidemic of louse-borne relapsing fever, and to give an account of its symptomatology and the results of treatment with arsenicals.

In reviewing the available literature no report has been found of louse-borne relapsing fever in Persia. Current textbooks do not mention the disease as occurring there, although Rogers and Megaw (1944) say it is common in most parts of India. The present epidemic was undoubtedly part of the widespread epidemics described in the Mediterranean and North Africa during 1943–5—e.g., Algeria (Grenoillau, 1946), Morocco (Sicault, 1944), Cairo (Wolman, Omar, and Abu-Taleb, 1945), and Abyssinia (Charters, 1945); and reviewed by Stuart (1945), who also mentions Tunisia, France, Greece, Rumania, and Turkey.

The tick-borne disease is found all over the Middle East and Central Asia—namely, Cyprus (Wood and Dixon, 1945), Palestine (Adler, Theodor, and Schieber, 1937), Azerbaijan (Popow and Achundow, 1936), Persia (Delpy and Rafyi, 1939), Caucasus (Maruashvili, 1945), Afghanistan (Avanessov, 1938), Kazakhstan (Andreev, 1944), and Tashkent (Kassirsky, 1933)—but it has, of course, different characteristics from louse-borne relapsing fever.