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INTRAVENOUS ACETYLCHOLINE IN TREATMENT OF THE NEUROSES

BY

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A great deal is known about the actions of acetylcholine, but little has been written about its value as a therapeutic agent. It is known that cholinesterase rapidly destroys acetylcholine *in vivo*. Hence in using the drug intravenously the chief difficulty lay in choosing the optimum dose which would avoid the lesser danger of too rapid destruction and the greater danger of arresting the heart's action (Carmichael and Fraser, 1933). In spite of the handicaps a number of uses have been found for the drug, given as an intravenous injection. It has been considered an effective method of treating paroxysmal tachycardia (Martindale, 1952), and Williams (1941) found it helpful in the diagnosis of epilepsy, since it could provoke epileptic discharges in the E.E.G. records of certain epileptic patients. It was used first in the treatment of psychiatric patients by Fiamberti (1940, 1950), who gave intravenous doses of 600 mg., by which he produced syncope, unconsciousness, and often a convulsion. This approach was considered to be of value in treating the early stages of schizophrenia, and a recovery rate of 80% was reported. The basis for this form of treatment was the apparent similarity to the convulsive shock produced by leptazol or E.C.T. Poort and Stigaard (1944) found that doses of up to 1,000 mg. could be injected safely. However, it did not gain wide repute, and unsatisfactory results were obtained by several workers, notably Harris and Pacella (1943).

A more modified form of treatment, using an intravenous dose of up to 200 mg. of acetylcholine chloride, was introduced in Spain by Lopez Ibor (1950, 1952), who found this approach useful in the treatment of certain neuroses and particularly of patients suffering from recurrent attacks of tension. Following a visit to Spain, Sargent (1952) introduced the treatment at St. Thomas's Hospital and reported on the initial findings.

The present paper describes a series of 211 patients who have been treated over a period of two and a half years at the same hospital.

Method

The Roche preparation of crystalline acetylcholine chloride was found to be the most reliable form of the drug. It was freshly prepared as a 10% solution in dis-

tilled water, usually as 200 mg. in 2 ml. The patients were given the injection intravenously, at least one hour after a meal, and initially a dose of 50 mg. was injected very slowly to test the sensitivity of the patient. This initial dose was then generally increased during subsequent treatments by 50 mg. to the total amount of 200 mg. A reaction usually occurred after the rapid injection of 50 mg. of acetylcholine chloride, but the remainder of the 200 mg. could then be given more slowly to prolong the reaction. Extra care has to be taken in those very sensitive to doses as small as 25 mg. The response took two forms: one showed coughing, flushing, salivation, lacrimation, sweating, etc., and was accompanied by momentary slowing of the heart; the other was primarily syncopal in form and was associated with prolonged cardiac arrest, unconsciousness, and convulsive movements. Physiological observations on these effects, including a description of a syncopal attack of 28 seconds, have been reported elsewhere (Phillips *et al.*, 1952). Barlow and Howarth (1953) have shown that the second, more severe reaction is similar to a Stokes-Adams attack. However, the aim of the treatment was to produce the first, milder reaction, and this could be achieved by gauging the rate of injection to suit the individual patient. There was little in the way of after-effects, and most patients were able to leave hospital five minutes after the injection, although the more elderly benefited from resting for 20 to 30 minutes afterwards.

Before a course of injections was begun the cardiovascular system was examined particularly, and in middle-aged patients a routine E.C.G. was done. It was also found possible to control attacks of spontaneous auricular fibrillation, which occurred in four patients, by giving a prophylactic dose of quinidine sulphate, 5 gr. (0.32 g.), half an hour before injections, and treatment could be continued. No fatalities occurred in over 6,000 injections when care was taken to gauge the dose correctly by gradually increasing speed and amount, especially in the sensitive patient.

The usual course of treatment consisted of 30 injections given over a period of six to ten weeks, depending on how often the patient was able to attend for treatment. Daily clinics have been held at St. Thomas's, and most patients found it possible to continue at work at the same time.

Results

The 211 patients consisted of 125 men and 86 women. The majority of patients who had this treatment, and incidentally the group which was helped most, suffered from symptoms which we have chosen to call "obsessive" (Sargent, 1952) or obsessional. These may result from exposure to stress, either psychological or physical, such as an acute debilitating illness, may start abruptly, and can often become self-perpetuating. The obsessional aspect of the condition commonly takes the form of a recurrent thought of an unpleasant nature or a particular phobia which is associated with a great deal of tension. This tension is experienced inwardly, and there is little or no overt evidence of its existence except the complaints of the patient. The reason why care has been taken to define this condition is because the drug proved to be of little value in the treatment of the classical obsessional neurosis, often dating from early childhood or accompanied by compulsive ritualistic behaviour.

Until it became clear that this particular obsessional group reacted best to this treatment, a wide selection of patients with anxiety symptoms were treated, including some in all of the following diagnostic categories: obsessional states as defined above, conversion hysteria, varied types of depression, schizophrenia, anxiety hysteria, classical obsessional neuroses, psychopathy, and chronic eczema.

Obsessional or Obsessive Tension States.—This category comprised 104 patients (Table I), of whom the surprisingly large number of 73 (70.2%) were improved by the treatment (Table II). Many were people who experienced the inner sense of tension already described, and they often

TABLE I

	O.S.	A.H.(M.)	A.H.(Po)	S.	O.N.	P.
Male { No. of patients	71	19	16	6	2	8
Average No. of injections ..	34.8	25.9	8.25	20	30.5	20
Female { No. of patients	33	15	30	2	3	2
Average No. of injections ..	28	29.6	6.16	88	71	23

O.S. = Obsessional state. A.H.(M.) = Conversion hysteria (monosymptomatic). S. = Schizophrenia. A.H.(Po) = Anxiety hysteria (polysymptomatic). O.N. = Obsessional neurosis. P. = Psychopathy.

Note:—Four skin cases are not included in Tables I and II: none derived any benefit from acetylcholine injections.

TABLE II

	O.S.	A.H.(M.)	A.H.(Po)	S.	O.N.	P.
Improved ..	M F 52 21	M F 7 7	M F 2 1	M F 1 2	M F — —	M F — —
	70%	41%	6.5%	37.5%	—	—
	18 12	9 6	9 10	4 —	2 3	6 2
Unchanged ..	29%	45%	41.3%	50%	100%	80%
	1 —	3 2	5 19	1 —	— —	2 —
Worse ..	1%	15%	52.2%	12.5%	—	20%

had fears of insanity or of dying. One such patient, who had fought through the Burma campaign without significant upset, was debilitated by dysentery, helminthic infection, and orchitis complicating mumps. He suddenly developed an irrational fear of insanity, became tense and anxious about travelling, and had had panic attacks of fluctuating intensity over a subsequent period of six years. However, he carried on with his work so far as was possible. These patients often gave a history of previous attacks or a periodic course in which attacks might partially lift, and then got worse again. Others showed phobic states which were monosymptomatic in nature—for example, a woman with a single obsessive fear of killing her child. The phobia could be replaced by rumination over a single thought—for example, a word such as syphilis. These conditions must be distinguished, however, from those in which, for instance, fear of syphilis might be only part of a chronic generalized anxious and hypochondriacal state.

Anxiety Hysteria.—The classical symptoms of this condition did not respond to the treatment—most patients were made worse. This point is referred to below. Sometimes, however, a conversion symptom presented itself as a single fixed persistent pain, and then some improvement occurred, probably because of an obsessive component to the total picture. Of such patients 34 were treated; 14 (41%) were helped, while 5 (15%) complained that they felt worse. An example of this was a patient who developed a pain in his leg after the diagnosis of disseminated sclerosis had been made in his brother, and this symptom had persisted for 15 years. Others helped were a group of patients complaining of bitemporal headache. Gross hysterical states were certainly never helped, although these patients are a group normally improved by treatments with a high degree of suggestive value.

Depressive States.—In general, acetylcholine injections seemed to increase the depth of an endogenous depressive illness. It was a matter of clinical observation that this was an effect it shared with modified insulin therapy. Therefore it was contraindicated in the treatment of depressions showing retardation, etc. However, there was a place for it in the treatment of patients suffering from mixed states of depression and obsessional tension. Such depressions were generally reactive in nature, but a few were in the involutional group. These patients usually had one E.C.T. each week, and acetylcholine injections were given throughout the week. This combination of treat-

ments appeared to be efficacious in resolving the illness more rapidly than E.C.T. would have done alone, and can be combined on an out-patient basis. Six patients responded to this combined treatment, and these have been included in the obsessional group described above.

Schizophrenia.—Eight patients were treated, of whom three recovered from their particular attack under treatment. All three were, however, subject to recurrent illnesses of schizophrenic type, and showed obsessive traits in their pre-morbid personalities. They had previously had courses of insulin coma or E.C.T., and two of them had had modified leucotomies. The acetylcholine, however, seemed to help only the tension component to the total picture. These patients had full courses of acetylcholine injections and seemed to derive more benefit from syncopal reactions produced by the rapid injection of 200 mg. intravenously, which were less easily tolerated by the other groups of patients.

Other Conditions.—It will be realized that the term "anxiety state" is not used in this series. The reason is that it became apparent that a distinction had to be made between anxious patients of obsessive personality, who were able to contain their tension, and those with more hysterical trends, who tended to project their anxiety. The former are included in the obsessional group and the latter in the category of anxiety hysteria. Five patients, however, who showed numerous obsessional compulsive phenomena received courses of treatment, and no change for the better occurred. Some cases of psychopathy and eczema were also treated; for, as is usual in all fresh therapeutic ventures, many patients in these difficult categories tend to get referred for treatment. On the whole they were not helped by acetylcholine injections.

Use in In-patients

In addition to the above examples of its use in out-patients, acetylcholine was found to be of value as an adjunct to the standard in-patient treatments. It could be used as a further sedative measure to reinforce the action of modified insulin and, if necessary, could be given twice daily. Its use with E.C.T. was confined to the mixed states of obsessional anxiety and depression, and here its action lay in taking the edge off the tension experienced by such patients after E.C.T. had removed the depressive component. It was of use, too, in clarifying the diagnosis of mixed states of depression and anxiety. Often only a few injections tended to increase depression if this was the most important factor, and E.C.T. could then be substituted. In states of acute tension that can follow abreactive treatments in wrongly selected patients, repeated acetylcholine injections were often found better than the barbiturates in damping these down again, because they achieved rapid sedation without producing an added mental confusion. It was also found useful in the follow-up treatment of alcoholics who had had emetine aversion treatment, were now off alcohol, and still had symptoms of residual tension.

Discussion

Early in the investigation some difficulty was experienced in finding the type of patient who might benefit most from the treatment. At first, most of the patients treated were chronic hospital attenders suffering from anxiety hysteria, and the injections served only to increase their fears. At this stage the investigation was nearly given up, but it was continued because of the response of one woman who had been referred for consideration of leucotomy. She was suffering from a monosymptomatic obsession that she might harm her child; this was accompanied by great tension and had lasted for over two years. The (28) injections gradually relieved her symptoms, and the operation of leucotomy was thus avoided; she has remained well for over two years. Another early patient who showed a good response was also noted to be suffering from a recurrent tension state with obsessional features. Then other patients were selected for treatment because mostly

they had single fixed symptoms, the illness showing a fluctuating intensity, and because there was evidence of a good basic personality, as shown by their ability to carry on with their work despite their illness.

With the final analysis of the results it has been possible to distinguish further prognostic criteria. Those helped most were frequently between 30 and 50 years of age. Body-build seemed particularly important. By far the best results were obtained in those of athletic build. These tolerated the treatment well, while the asthenic and the pyknic, especially the young obese patient, were not helped. They proved particularly sensitive to the injections and became easily frightened.

The treatment was certainly contraindicated in patients whose anxiety was overt in nature. Such people complained of palpitations, breathlessness, diarrhoea, vomiting, and frequency of micturition. Many of them showed a marked emotional immaturity, and a tendency to project their symptoms typical of so many of those suffering from anxiety hysteria. Table II shows the poor results obtained in this group.

The chief response noted when treatment was successful was a gradual lessening of tension—the emotional component of the phobia or obsessive thought decreased, and it became less troublesome. Schizoid patients showed an improvement in rapport and sometimes reported an increased clarity of thought.

The benefit alcoholic patients derived from the treatment was in keeping with the fact that they often have an obsessive personality; indeed, their drinking is often of a compulsive nature. They are usually tense individuals experiencing a great deal of subjective anxiety.

It might be argued that the typical patient who has shown a good response to treatment is basically the person of good personality and body build who does well with any form of non-specific therapy. Such patients have good driving personalities; they have mastered various stresses successfully, and they are able to contain their anxiety. But many of them present notoriously difficult problems from the point of view of treatment, and their illnesses may last a long time. It has been our experience that these patients are usually untouched by psychotherapy, E.C.T. makes them worse, and the use of sedatives may result in a build-up to undesirably high and prolonged dosages. A small number of such patients were given injections of normal saline in the same way as other patients were given acetylcholine. No response occurred until acetylcholine was substituted for normal saline. It seemed, in fact, that acetylcholine was often able either to shorten the attack or to produce a more complete remission of symptoms. Our results in this respect were therefore found to confirm those reported by Lopez Ibor (1952).

Summary and Conclusions

An investigation has been described in which intravenous acetylcholine was used in the treatment of varied forms of neurosis. The patients who were helped most fell within a specialized group of obsessive or obsessional tension states, which have been defined. Of 104 patients in this group, 70.2% were improved by the treatment.

It has also been found useful in certain patients as a treatment complementary to E.C.T., modified insulin, and the emetine aversion treatment for alcoholism.

Over 6,000 intravenous injections of acetylcholine have so far been given. The treatment, with the precautions described above, has been found to be a safe one, and is relatively simple to use on an out-patient basis.

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THE PREVENTION OF CONGENITAL SYPHILIS

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The incidence of early acquired syphilis reached its peak in England and Wales in 1947. This was followed by a rise in the incidence of congenital syphilis in the years 1948 and 1949, since when there has been a fall in the number of reported cases. The Ministry of Health report for 1951 revealed, however, that during that year 1,127 cases of congenital syphilis were seen for the first time at venereal disease clinics in England and Wales. The figure for 1952 was 946. Since congenital syphilis is now regarded as an almost 100% preventable disease (Aron *et al.*, 1947; Cole *et al.*, 1950; MacFarlane, 1950; Marinkovitch, 1951), these figures are alarmingly high. The more especially is this so when they are compared with 699 (1951) and 375 (1952) notifications for diphtheria, a comparably controllable infection.

No data are available to allow an estimate to be made of the number of congenital syphilitics born in the years 1951 and 1952 in whom the disease is as yet undetected, nor are there figures to show the number of abortions and miscarriages in which syphilis played a primary or contributory part.

Early infectious syphilis is now comparatively rare in adults, but many untreated or inadequately treated infections acquired during and after the late war are at present in the latent stage. Many of the females in this category are of child-bearing age, and while their syphilis is not contagious it is transmissible to the foetus. Kampmeier (1946) estimated that, irrespective of the stage of syphilis, 70% of foetuses born of syphilitic mothers are infected. The best hope, therefore, of prevention and ultimate eradication of congenital syphilis depends on detection and treatment of such women during the antenatal period.

Latent syphilitic infections can be adequately diagnosed only by the Wassermann or similar serological test.

MacFarlane found 515 (0.7%) of 71,645 antenatal Wassermann tests to be positive during the years 1944–9. Even with the apparent decline in early syphilis he was still able to detect 45 (0.28%) cases among 15,812 antenatal Wassermann tests made during 1952 (personal communication).

While antenatal Wassermann testing (and, where omitted, post-natal Wassermann testing) has become the established routine in almost every hospital and local authority obstetric practice, the Report of the Venereologists Group of the British Medical Association