TREATMENT OF PROGRESSIVE MYOCLONIC EPILEPSY WITH MEPHENESIN*

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During an investigation of the effect of mephenesin on certain cerebral dysrhythmias it was found that the drug abolished myoclonus in two cases of progressive myoclonic epilepsy, and it has since proved possible to control this hitherto intractable symptom of the disease by using very heavy dosage of mephenesin.

The disease was first clearly described by Unverricht (1891). The patients have occasional attacks of grand mal, but their major disability is myoclonus, in the production of which there is a strong reflex element (Dawson, 1947). The disease progresses until they exist in "status myoclonicus" and die of exhaustion and inanition within four to five years of the onset. Often there are signs of a cerebellar disturbance (Ramsay-Hunt, 1921), and cerebellar changes are found at necropsy (Hodskins and Yakovlev, 1929).

Early in the course of the disease the myoclonus may respond to the usual anticonvulsants, but it soon becomes resistant to and uncontrollable by drugs without producing incapacitating cerebral depression. Bradshaw (1954) reported that myoclonus may be partially suppressed by phenacemide ("phenurone"), but this is the only drug that has appeared to offer any relief, and the relief afforded was apparently not striking.

Case 1

A girl aged 16 was admitted to St. Thomas's Hospital in March, 1952. She had previously been a patient at the National Hospital, Queen Square, under the care of Dr. S. P. Meadows. She had suffered from grand mal for eight years and myoclonus for seven years. She had been helpless for four years, could not feed herself or leave her bed, and her speech was slow and jerky. Many days were passed in status myoclonicus. Phenobarbitone, phemitone, phenytoin sodium, bromides, troxidone, and phenylmethylbarbituric acid ("rutonal") had been tried and a combination of phenobarbitone and phenytoin found to be the most helpful in preventing grand mal and perhaps slightly reducing the myoclonus.

The patient, during a period when severe facial and general myoclonus was constant, was placed on a couch and an electroencephalographic record was taken for 30 minutes (see Fig.). This showed many cortical spikes and high-voltage slow waves; there was also a moderate amount of muscle artifact in the frontal leads. An intravenous infusion of 1% mephenesin in normal saline was begun, and within 50 seconds the cortical spikes and muscle artifact had disappeared and the record had become dominated by high-

voltage slow waves. Myoclonus ceased. In 35 minutes 1.75 g. mephenesin had been given. The patient felt a little sleepy during the latter part of the infusion. The E.E.G. began to revert and myoclonus began to return 20 minutes after the infusion ended. The experiment was repeated seven days later, when the patient had been deprived of anticonvulsants for three days. The results were similar except that epileptic activity in the E.E.G. was not totally abolished.

Oral treatment with mephenesin was started and the myoclonus was well controlled. She was deprived of mephenesin on four occasions, and each time she relapsed dramatically but was readily controlled again, first by an elixir containing 2 g. of mephenesin per oz. (30 ml.) in about 30% alcohol, and later by a suspension of mephenesin carbamate.

The patient left hospital in May, 1952, taking 1 gr. (65 mg.) of phenobarbitone thrice daily and 1 oz. (30 ml.) of mephenesin elixir four times a day. She was now well enough to dress herself partially, to feed herself, write, knit, and walk with assistance. Reflex myoclonus still occurred but was

Case 1. Top: typical section of E.E.G. before treatment. Bottom: E.E.G. three minutes after start of infusion of 1% mephenesin intravenously.

infrequent, whereas previously it had prevented every voluntary act. During the following 18 months she had five minor and two major grand mal seizures.

In November, 1953, she developed an acute attack of vomiting, and, probably correctly attributing this to the mephenesin, she stopped taking it and within 24 hours relapsed completely and became speechless and helpless. She was readmitted to hospital five days later in status myoclonicus and having had a grand mal attack on each day of relapse. She had six major fits during her first 12 hours in hospital. She had been vomiting her phenobarbitone also. Paraldehyde, 5 ml. intramuscularly, failed to control the myoclonus, so she was given 2 g. of mephenesin intravenously as a 1% solution in normal saline in 20 minutes. Within five minutes of the start of the infusion the myoclonus ceased. She relapsed an hour later and the mephenesin was repeated with the same result. Four hours later she relapsed yet again and was given 8 ml. of paraldehyde intramuscularly and 0.75 g. of mephenesin carbamate by mouth; she then slept. She went home 16 days later, taking 1.25 g. of mephenesin carbamate four times a day and 1 gr. (65 mg.) of phenobarbitone three times a day. She was then better than she had ever been. She has since been liable to attacks of "gastritis," which are attributed to the mephenesin carbamate. She is now taking about 15 g. of mephenesin carbamate a day either as 20% suspension or as tablets.

Case 2

A woman aged 29 was admitted to St. Thomas's Hospital in January, 1954. Facial myoclonus had begun five months previously and had spread, so that for three months she had been confined to bed and unable to feed herself. Occasional grand mal attacks occurred from this time. She had two

*A summary of this paper was read and a film demonstrating the first two patients shown at a joint meeting of the Swiss Neurological Association and the Association of British Neurologists at Interlaken in June, 1954.

periods of remission; the first, lasting one week, occurred when she was given 1 gr. (65 mg.) of phenobarbitone and 1½ gr. (98 mg.) of phenytoin thrice daily; the second, of 10 days, followed an attack of grand mal. Grand mal attacks were always followed by remissions, which became shorter and shorter until there was only a few minutes' quiescence before the myoclonus recommenced and gradually increased in violence until another major fit occurred hours later.

An electroencephalographic record in January, 1954, when she had had no anticonvulsant drugs for three days, showed random spikes in association with slow wave activity. A second record when taking phenobarbitone showed much low-voltage fast activity with random spikes. The spike activity was greatly reduced after an intravenous infusion of 1.5 g. of mephenesin.

Oral treatment was begun, and 15 minutes after 3 g. of mephenesin as elixir both the spontaneous and the reflex myoclonus ceased. She became practically normal, but relapsed in three hours and was readily controlled again by 3 g. of mephenesin. This sequence of events was repeated many times. A control elixir containing no mephenesin was substituted and proved ineffective. She was then allowed to take 3 g. of mephenesin as elixir whenever she felt the myoclonus returning, and in a few days she was taking 27 g. a day. She was mildly drunk on this dose, as the elixir contains about 30% alcohol. It was therefore decided to try mephenesin carbamate in the hope that a lower dose could be used, since it is more potent than mephenesin when tested on animals (Berger, 1952). This was given as a suspension and contained only 1% alcohol.

On the first day she took 9 g. of mephenesin and 12 g. of carbamate, on the second day 24 g. of carbamate; on the third day she relapsed, returned to taking the elixir on demand, and became drunk again. The myoclonus of the throat was the first to return after each dose and so she had to swallow the elixir in sips. This resulted in anaesthetization of the throat (mephenesin is a local anaesthetic), and inhalation of the drug and of food. The resulting lung infection was treated with penicillin, and a stomach tube was passed for medication and feeding. When she recovered mephenesin was given partly as the elixir, for rapid action, and partly as crushed tablets, so that her alcohol consumption was reduced, although the tablets seemed rather less effective. A few days after this regime began she had increased her daily total to 48.5 g. of mephenesin, but it soon fell to an average of 30 g. a day, 10 g. as the elixir and 20 g. as tablets.

She left hospital in February, 1954, on a regime of mephenesin, phenobarbitone (33 mg. t.d.s.), and primidone (250 mg. b.d.). The latter drug alone had not prevented relapses of myoclonus. She could walk, dress, and feed herself, but had a slight irregular tremor of both hands which made her writing illegible. A month later she reported that she had had no grand mal since leaving hospital. She had been doing her shopping and housework, but was still unable to write clearly and feared to carry saucepans lest she should drop them. She had been taking 2 g. of mephenesin as elixir on waking, when the myoclonus was fairly severe. The elixir controlled the myoclonus sufficiently to enable her to swallow 3.5 g. in tablets 30 minutes later. She had been taking 3.5 g. in tablets once or twice between meals with 2 g. as elixir at meal times. Her daily requirements had varied, being about 30 g. total—8–10 g. as elixir and 20–22 g. as tablets. During April and May she reported that she had had no myoclonus and that she was reducing her mephenesin dosage.

The common side-effects of mephenesin—dizziness, drowsiness, and vomiting—are less severe if the drug is taken after food, and in this case are not troublesome.

Other Cases

After it had become clear that the drug was effective in these two cases Dr. E. Arnold Carmichael, of the National Hospital, very kindly allowed us to give intravenous infusions to three of his cases.

Case 3.—This patient, a young woman aged 21, had never been normal. From the age of 4 irregular jerking movements of all four limbs had been noted. The condition progressed until myoclonus was constantly present, and for the past eight years she had been confined to her bed totally incapacitated by the myoclonus. Mephenesin, 1.5 g., was given intravenously in 15 minutes. There was a complete abolition of the myoclonus as in the previous cases and of a similar duration. She has since been treated with oral mephenesin, which appears to be effective, but the correct dose has not yet been determined, as she has great difficulty in tolerating the drug, although it was clear that it was enabling her to get on to her legs.

Case 4.—A woman aged 41 had suffered from myoclonus for three years. She had been confined to her bed for one year and had been for the most part totally disabled, but there was a marked periodicity in her condition. Mephenesin, 2 g., was given intravenously in 20 minutes, and this had a less dramatic effect than in the other cases. The myoclonus did not disappear completely, but the movements were sufficiently reduced to enable her to sit up and get off the bed on to her legs. This had previously been impossible. Oral mephenesin has since produced enough relief to allow her to walk and to sit up in an armchair. The duration of its effect is short and, unfortunately, when the effect wears off the myoclonus is more violent than it was before treatment was begun.

Case 5.—A youth aged 19 had suffered from attacks of grand mal and myoclonus, causing ataxia for six years. Although never able to work, he was much less incapacitated than the previous patients and was able to care for himself and to walk, although unsteadily. As the myoclonus was mild the effect of intravenous mephenesin was not marked. He has, however, started to take the drug orally and he appears to be slightly improved.

Cases 3, 4, and 5 have been treated for a few weeks only, and it is too early to assess their response.

Mephenesin

Mephenesin was introduced by Berger and Bradley in 1946, when they showed that its principal action is depression of the spinal cord. It was later shown by Berger (1947), Henneman *et al.* (1949), and Kaada (1950) that the site of action is probably on the spinal cord internuncial neurones. Polysynaptic neural circuits are easily depressed and monosynaptic circuits withstand large doses. Henneman *et al.* (1949) also found that mephenesin decreases or abolishes facilitation and inhibition, reaching anterior horn cells from all levels of the central nervous system, and that the electrical activity of the bulbar reticular substance is reduced. Reversible paralysis sparing respiration can easily be produced in animals by large doses, and it is not due to a peripheral effect. A neuromuscular blocking action can be demonstrated only by toxic doses (Berger, 1947), and there is no record of this effect having been achieved in man.

That the drug has actions high in the central nervous system of man may be inferred from the slight drowsiness and invariable nystagmus which follow the intravenous infusion of the pure drug in saline, and also from the observation that spike-and-wave activity in the E.E.G. in cases of petit mal can be reduced (Gammon and Churchill, 1949). We have confirmed this in some cases, but have found others which were resistant to the drug given intravenously. The highest concentration of mephenesin following intravenous injection is in the brain (dogs) (Morrison *et al.*, 1948). However, there is at present no evidence of the site of action above the brain stem, and the mechanism of the beneficial effect in myoclonic epilepsy remains obscure. It has been observed (Hunter and Waterfall, 1948) that mephenesin can subdue status epilepticus.

Mephenesin has a poor reputation in this country, largely owing to its failure to produce good relaxation in surgical anaesthesia and to the occurrence of haemolysis when given intravenously as a 10% solution. It has also proved to be

relatively unsuccessful in the treatment of spastic paralysis, for which condition it was particularly indicated on theoretical grounds. Its failure is due chiefly to the difficulty in getting enough of the drug into the patient without causing gastric or cerebral side-effects and to its brief action: intravenous administration in adequate dosage usually gives complete or almost complete relaxation of the most severe spasticity without any concurrent loss of power, although the effect by this route is too brief to be therapeutically useful.

In the treatment of myoclonic epilepsy we have found it necessary to give up to 48.5 g. of mephenesin a day, and, although this is exceptional, doses of that order should be fairly easily achieved, for short periods at least, if attention is given to the timing of the doses. Where possible they should be given on a full stomach, some as alcoholic elixir and some as tablets, although the latter are absorbed less readily and possibly less completely than the elixir.

In a series of 27 spastic patients one of us found that the maximum tolerated dose of the elixir alone varied between 6 and 18 g. of mephenesin a day; these were high doses at the time (1951), and it is now clear that they can be greatly exceeded in some patients and are safe for a period of months at least.

When mephenesin is given intravenously it should be as a 1% solution in saline. At this strength significant haemolysis does not occur and haemoglobinuria has never been reported. The risk of this complication increases as the solution strength rises, but is probably not serious until 4% has been reached. For solutions of over 1.5% it is necessary to use alcohol or propylene glycol to aid solution. The drug is metabolized very rapidly, and the clinical effects of a single intravenous injection may last as little as 30 minutes, or an oral dose only 60 to 90 minutes.

Mephenesin is also a local anaesthetic, and if a patient cannot swallow easily and sips the elixir this may lead to anaesthetization of the throat and inhalation of the drug (Case 2 above and Newhouse *et al.*, 1950).

Summary

It has hitherto been impossible to control the myoclonus of progressive myoclonic epilepsy with drugs.

Five cases are reported, in four of which helpless patients were restored to activity temporarily by intravenous mephenesin; one less severe case was helped by oral mephenesin.

Owing to the very large doses necessary, various side-effects occurred; these were largely overcome.

The mechanism of the action of mephenesin in this disease remains unknown.

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REFERENCES

- Berger, F. M. (1947). *Brit. J. Pharmacol.*, **2**, 241.
 — (1952). *J. Pharmacol.*, **104**, 468.
 — and Bradley, W. (1946). *Brit. J. Pharmacol.*, **1**, 265.
 Bradshaw, J. P. P. (1954). *Brain*, **77**, 138.
 Dawson, G. D. (1947). *J. Neurol. Neurosurg. Psychiat.*, **10**, 137.
 Gammon, G. D., and Churchill, J. A. (1949). *Amer. J. med. Sci.*, **217**, 143.
 Henneman, E., Kaplan, A., and Unna, K. (1949). *J. Pharmacol.*, **97**, 331.
 Hodakine, M. B., and Yakovlev, P. I. (1929). *Amer. J. Psychiat.*, **9**, 827.
 Hunter, A. R., and Waterfall, J. M. (1948). *Lancet*, **i**, 366.
 Kaada, B. R. (1950). *J. Neurophysiol.*, **13**, 89.
 Morrison, J. L., Saperstein, P., Walker, H. A., and Richardson, A. P. (1948). *Proc. Soc. exp. Biol. (N.Y.)*, **68**, 339.
 Newhouse, M. L., Rochford, J. D., and Royson, G. R. (1950). *British Medical Journal*, **2**, 981.
 Ramsay-Hunt, J. (1921). *Brain*, **44**, 490.
 Unverricht, H. (1891). *Die Myoclonie*. Leipzig.

SPONTANEOUS REGRESSION OF A MALIGNANT MELANOMA

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Cutaneous malignant melanoma has a characteristically unpredictable behaviour, and a melanoma which has already metastasized may undergo spontaneous regression (Willis, 1953).

Bennett (1899) described two such cases. The first was in a woman aged 52 who had a malignant melanoma of the foot treated by local excision, followed by Syme's amputation for a local recurrence. She then developed widespread skin and glandular metastases, and the prognosis was regarded as hopeless. Six months later there was no evidence of malignancy. His second case showed spontaneous disappearance of glandular metastases and skin nodules following removal of the primary tumour, a malignant melanoma of the foot.

Gould (1906) saw a man aged 35 who developed widespread skin recurrences following excision of a malignant melanoma on the chest. The liver was enlarged, there were glandular metastases, and melanogen was present in the urine. He was treated with turpentine and sulphur pills, with considerable local and general improvement and disappearance of the skin deposits lasting for five months, though during this time the melanogenuria persisted. Renewed activity then occurred and he died eight months later. Mathews (1915) saw a man aged 45 who had a malignant melanoma over the scapula, with enlarged axillary glands and a fullness above the corresponding clavicle. After incomplete surgery, when the primary tumour and the axillary glands were removed, he remained well for two years and the supraclavicular swelling disappeared.

The histogenesis of intraocular melanoma is unsettled; amongst other hypotheses Willis (1953) suggests that they are of epithelial origin, arising from split-off epithelial cells analogous to the naevus cells of the skin, and that there is a general similarity between the intraocular and cutaneous melanomas. Ocular melanoma behaves slightly differently from the cutaneous type in producing frequent though long-delayed metastases, and in not usually disseminating so widely throughout the body. If, however, Willis's hypothesis is acceptable, then it is reasonable to expect metastases from a malignant melanoma of the choroid to exhibit the same anomalous behaviour as if the primary tumour were in the skin.

Case Report

The patient, a man aged 60, had the right eye excised at Moorfields Eye Hospital on February 21, 1951. The pathological report on the specimen was as follows: "Arising from the choroid in the superonasal quadrant of the eye is a large lightly pigmented mixed-celled malignant melanoma. Many blood sinuses are present in the growth and the reticulin content is light. There is some infiltration of the adjacent deep scleral lamellae, but in the sections examined there is no evidence of extraocular extension. The retina overlying the melanoma has been invaded and there is a retinal detachment on both sides of the growth. Microscopically this is a malignant melanoma of the choroid."