MYSOLINE IN EPILEPSY: A COMPARISON WITH OLDER METHODS OF TREATMENT.

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THE purpose of this paper is to report on a small series of cases treated with mysoline (5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione) and to contrast the results with those obtained with the established anticonvulsants phenobarbitone and soluble phenytoin.

The 11 patients selected for clinical trial were all subject to major epilepsy and in nine cases minor attacks were also frequent. The selected group represented cases wherein the attacks had been in some instances well and in other instances poorly controlled by these established anticonvulsants. No patient treated with mysoline by us has been excluded from this group. The ages of the patients ranged from 12 to 59. In all cases the physical health was good.

All patients in the series had received treatment with phenobarbitone only for at least one year before commencing treatment with mysoline. The transition to mysoline was achieved slowly and required 3–6 weeks according to what was considered to be the maximum safe dose for the patient. Continuous treatment with mysoline was then given for 80 days, after which time the drug was withdrawn and the series treated for a similar period on phenobarbitone and, where indicated, soluble phenytoin.

TABLE I.—*Dosage of Mysoline.*

Case.	Mysoline per day in grams.	Factors limiting dosage.
1	1·5	Progressive reduction of W.B.C. to 3,000 c.mm.
2	1·5	Reduction of W.B.C. to 3,000/c.mm. Toxic symptoms: ataxia, slurred speech.
3	0·75	Progressive reduction of W.B.C. to 3,000/c.mm.
4	0·75	Progressive reduction of W.B.C. to 2,000/c.mm.
10	0·75	Severe status epilepticus during transition.
11	0·75	Fatal status epilepticus during transition.
5	0·75	Drowsiness persistent
6	0·75	Slight fall in W.B.C. Age (16).
7	0·75	,, ,,
8	0·75	,, ,,
9	0·50	Age (12).

From the above table it will be noted that the estimated maximum safe dose of mysoline was lower than in previous reports, that serious complications occurred during the period of drug transition and that the majority of the

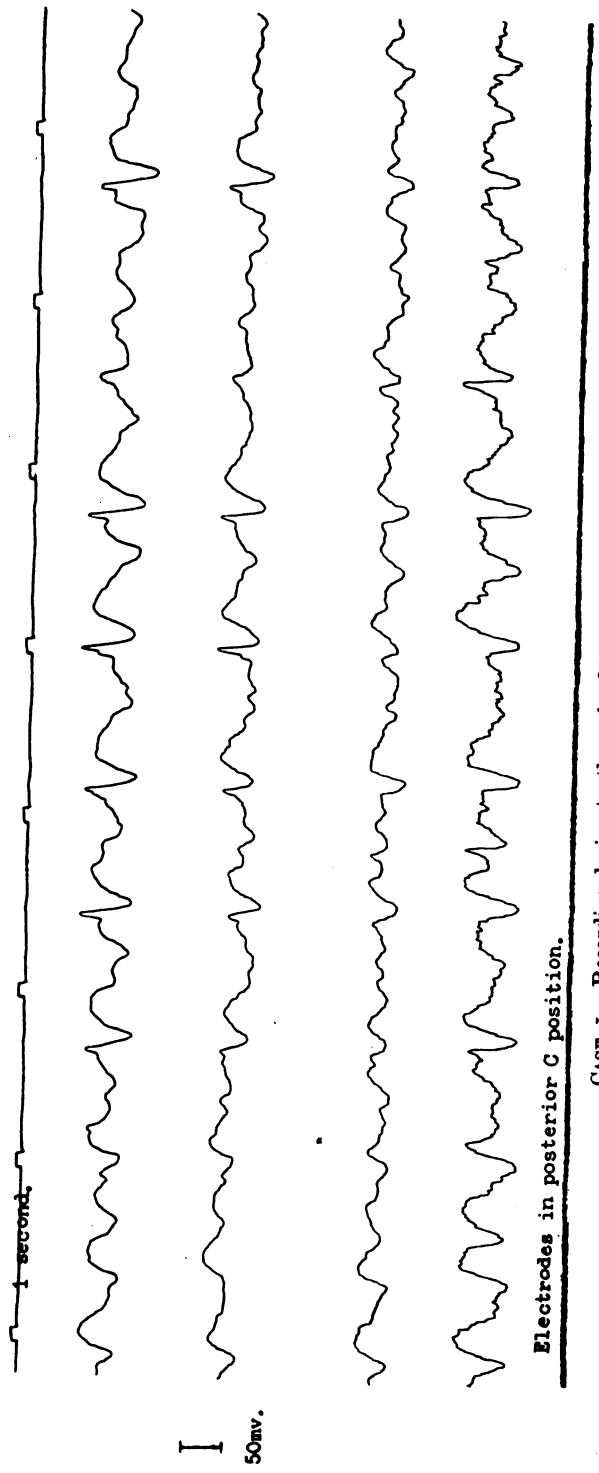
patients maintained on mysoline 0·75 gm./day or more developed either overt toxic symptoms or a clinically significant fall in the white cell count.

During the drug transition to mysoline two patients developed exceptionally severe status epilepticus In the first case the patient was aged 17 and in the previous year had had 10 major and two minor fits while receiving phenobarbitone. The status supervened suddenly 12 days after the commencement of transition at a time when the patient was receiving mysoline and phenobarbitone in divided and balanced doses. After 12 hours this status was eventually controlled with difficulty using ether, parenteral paraldehyde and lumbar puncture. Treatment with mysoline was thereafter discontinued. The patient has since remained controlled by phenobarbitone. The second case developed an equally severe and prolonged status 16 days after the commencement of transition; but, though the status was controlled in four hours, sporadic fits continued until pneumonia developed three days later and the patient, aged 20, died after a further 24 hours. In the previous year there had been good control with moderate doses of phenobarbitone and no major and only seven minor attacks had occurred during this period. This patient had, however, had a severe status two years previously as a result of which there was bilateral loss of vision of central origin which perisisted for several weeks. In both these cases transition had been slow and, as with the other patients in this series the technique of transition was carried out on the lines adopted by earlier observers.

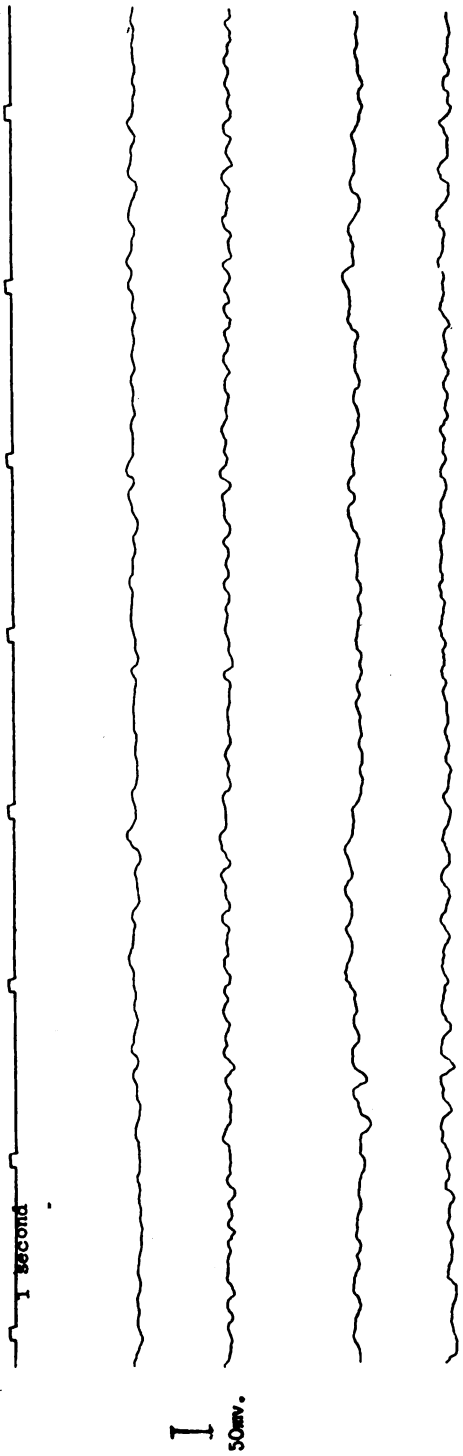
Toxic symptoms were virtually absent during the first two weeks of drug transition. After four weeks, however, one patient became persistently drowsy and for this reason the dosage of mysoline was not increased beyond the 0·75 gm. which was at that time being administered daily in divided doses. In this case some degree of drowsiness persisted throughout the remaining period of clinical trial. In a second case ataxia and slurring of speech developed after six weeks on mysoline 1·5 gm./day. These toxic symptoms were transient but returned again in the eleventh week, appearing in conjunction with a progressively falling total white cell count. On two successive days the count was confirmed to be 3,000/c.mm. and it was decided to discontinue mysoline on the grounds of toxic effects and of clinically increased epileptic activity.

In all patients receiving mysoline it was considered essential to perform a white cell count at least once per week. No significant red cell changes occurred; but four cases out of nine showed a clinically significant fall in the total white cell count, the differential count being unaffected. Three other patients showed a moderate fall in the white count, not clinically significant.

Two patients only were maintained on mysoline 1·5 gm./day. Both developed a leucopenia of 3,000–3,200/c.mm. This degree of leucopenia was reached in one case four weeks and in the other five weeks after treatment was commenced. The counts did not improve until after the mysoline had been discontinued. Of the six patients receiving mysoline 0·75 gm./day, two developed a similar degree of leucopenia, the times being five and seven weeks after the commencement of treatment. The more slowly developing leucopenia was the more severe and three weeks later this white cell count had dropped to 2,000/c.mm. This figure was confirmed after 24 hours and mysoline treatment discontinued.



CASE 1.—Recording during tenth week of treatment with mysoline.



Electrodes in posterior C position

CASE 1.—Recording during fourth week of subsequent treatment with soluble phenytoin.

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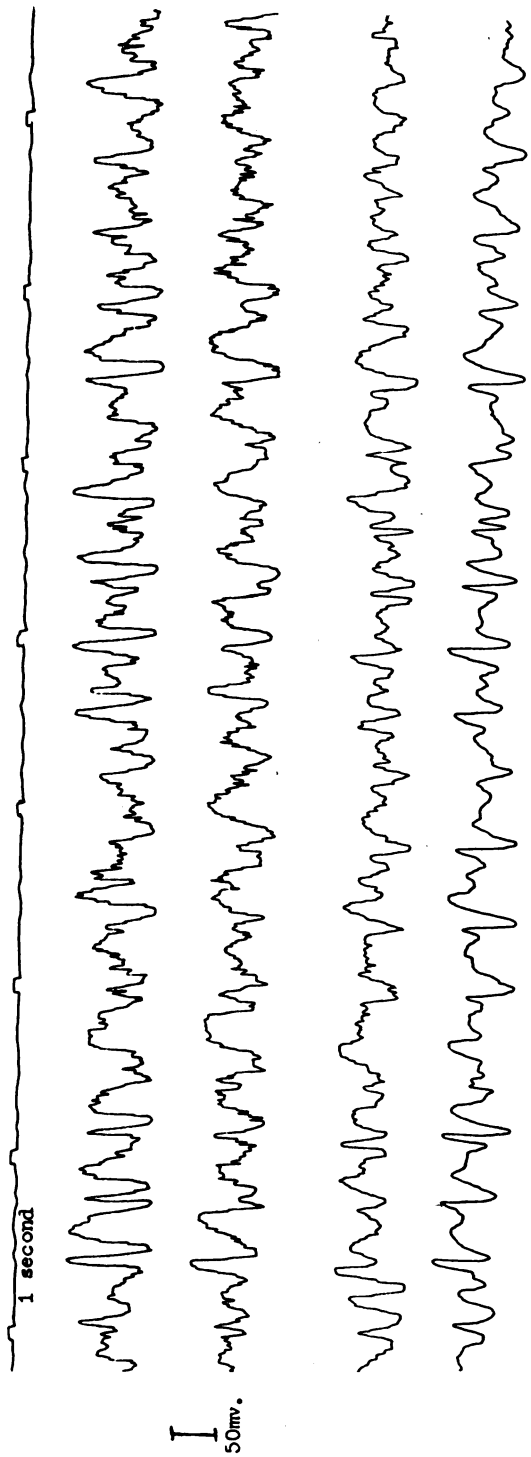

Electrodes in posterior C position.

CASE 5.—Recording during tenth week of treatment with mysoline.

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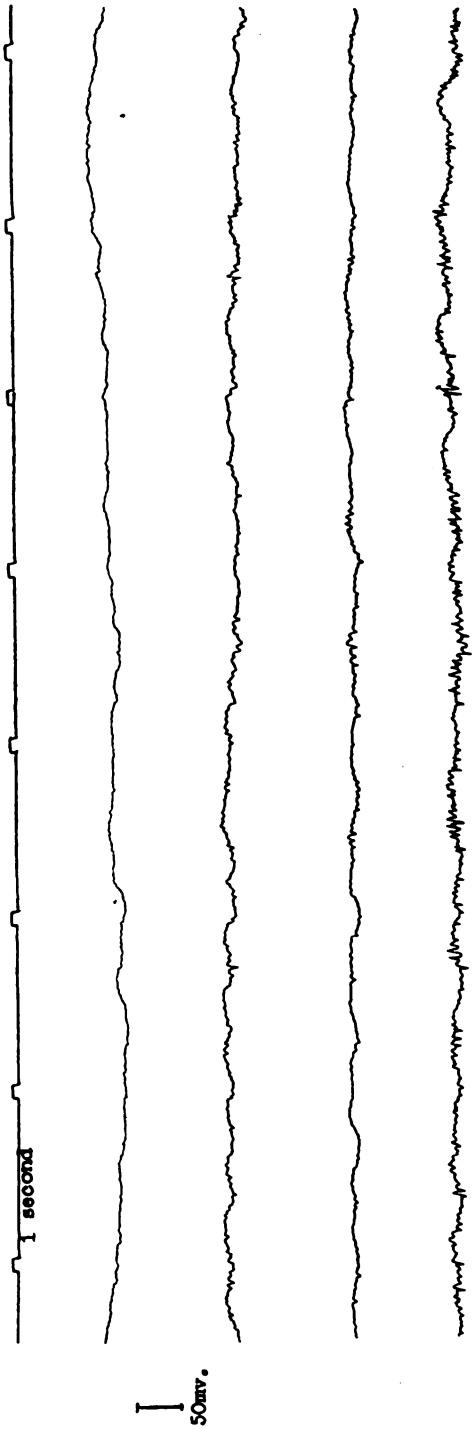

Electrodes in posterior C position.

CASE 5.—Recording during fourth week of subsequent treatment with soluble phenytoin.

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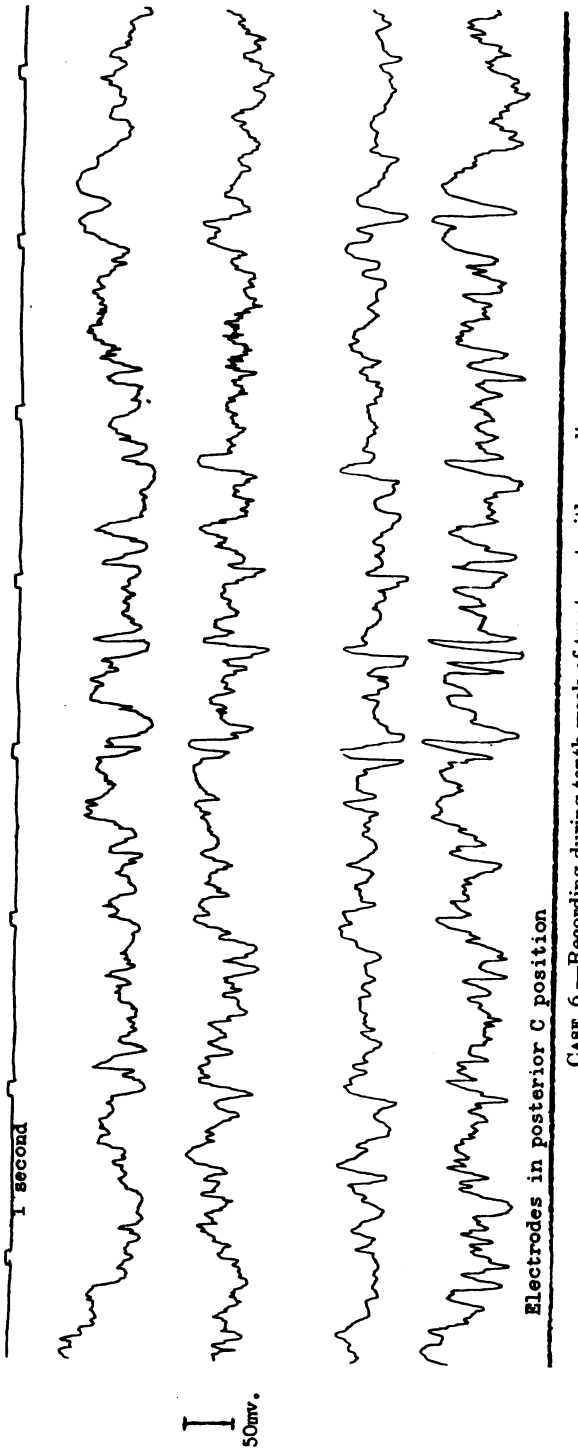
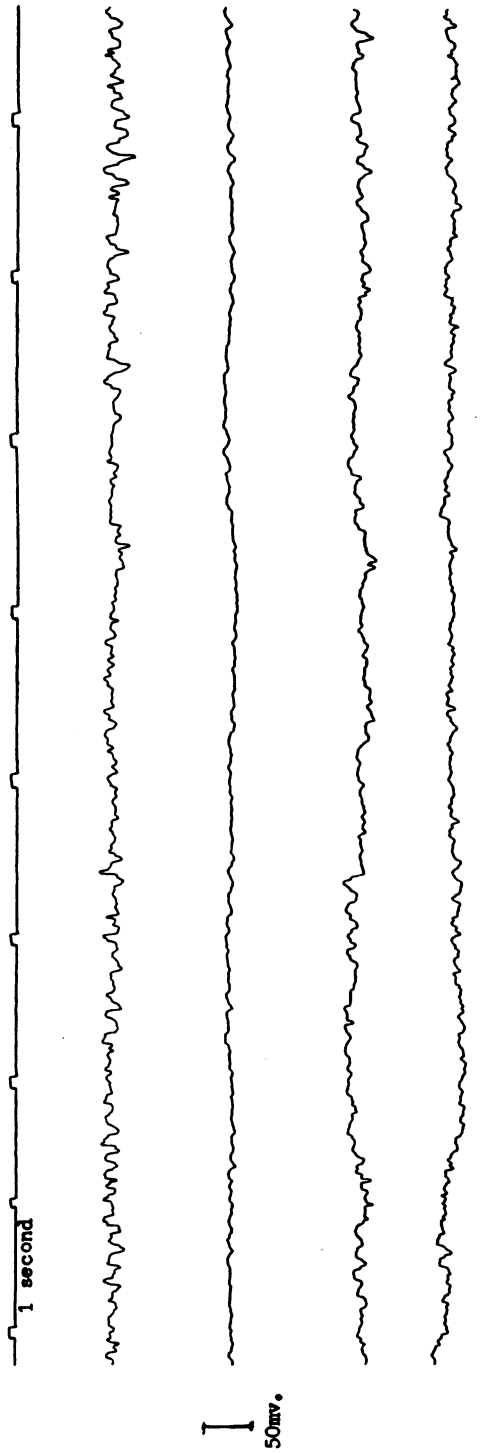


CASE 6.—Recording during tenth week of treatment with mysoline.



Electrodes in posterior C position.

CASE 6.—Recording during fourth week of subsequent treatment with soluble phenytoin.

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TABLE II.—*Total White Blood Counts during Treatment with Mysoline.*

Case.	Mysoline (gm./day).	White count before mysoline course.	Total white blood counts during mysoline treatment. 3rd week.	4th week.	5th week.	6th week.	7th week.	8th week.	9th week.	10th week.	Count one month after conclusion of mysoline treatment.
1	1·5	6,400	4,300	3,200	3,400	3,800	3,500	3,400	3,200	3,000	4,400
2	1·5	5,800	4,800	4,500	3,000	3,000	3,400	4,200	3,600	3,300	5,400
3	0·75	5,500	4,500	4,100	3,000	3,800	3,500	3,400	3,600	3,600	4,700
4	0·75	5,300	5,600	4,600	3,600	3,900	3,000	3,100	3,600	2,000	3,900
5	0·75	7,800	8,000	8,000	6,400	6,200	6,200	5,000	5,000	5,100	6,800
6	0·75	5,000	5,400	5,600	5,000	5,200	5,000	4,600	4,800	4,600	6,400
7	0·75	7,400	8,000	7,500	7,800	7,600	7,200	8,000	8,200	7,600	7,400
8	0·75	8,500	8,300	6,800	7,200	7,400	7,000	7,000	7,100	7,200	7,800
9	0·50	8,200	8,800	5,500	6,500	6,300	6,700	6,700	7,000	7,100	8,100

The blood changes in these patients were unaccompanied by other danger signs but caused anxiety and in some cases made it necessary to examine the patient and blood daily. Toxic symptoms and blood findings were indeed the chief reason why, in five cases out of the nine, the daily maintenance dose of mysoline could not safely be increased beyond the tabled figures. Even so, comparatively low maintenance doses were associated with persistent blood changes sufficiently severe to warrant discontinuation of mysoline at the end of 80 days trial. In our opinion, such blood changes should be regarded as a serious complication liable to occur in mysoline treatment to a greater extent than with the established anticonvulsants for either major or minor epilepsy.

Anticonvulsant Effects of Mysoline.

TABLE III.—*Results of Treatment of Major Epilepsy with Mysoline.*

Case.	Patient. Sex.	Age.	Mysoline per day in gm.	Incidence of major attacks. Rate/year on phenobarbitone.	Rate/year on mysoline.	Per cent. change.
1	M.	25	1·5	66	83	+26
2	M.	59	1·5	8	36	+350
3	M.	49	0·75	10	41	+310
4	M.	57	0·75	5	0	−100
5	M.	28	0·75	28	77	+175
6	M.	16	0·75	24	329	+1,260
7	F.	17	0·75	10	24	+140
8	F.	57	0·75	1	7	+600
9	F.	12	0·50	0	25	> 100

In the above assessment, a major attack was considered to have occurred if there was unconsciousness, convulsion and falling. It was noted that of this small series only one case showed any improvement. He was rendered free from fits but developed a leucopenia of 2,000/c.mm. on account of which mysoline treatment had to be abandoned. In the other eight cases there was a marked increase in the major attacks and in most cases it was an increase not only in the frequency but also in the severity and duration of the fits. Post-epileptic confusion and drowsiness were more prolonged. Behaviour was unchanged. There was no desire for further social activities or work and no subjective feeling of improved well-being. In all nine cases it was decided to discontinue mysoline.

In contrasting the effectiveness of phenobarbitone and mysoline it can be seen that six of the patients were originally well controlled with phenobarbitone having on average 5·7 major attacks per annum: during the treatment with mysoline the rate of major attacks increased in five cases and the average rose to 42 per annum. After a further transition these patients were again returned to phenobarbitone maintenance for a period of 80 days and the incidence of major fits fell to an average of 6·2 per annum. In these cases it was considered that as an anticonvulsant mysoline had proved less effective than phenobarbitone.

In the three cases poorly controlled with phenobarbitone there was with mysoline treatment a slight increase of the major attacks in one case and a marked increase in the other two. After the mysoline trial all three cases were subsequently well-controlled in the absence of toxic symptoms by soluble phenytoin alone. In these three cases the comparative clinical findings were as follows :—

	Major attacks in 80 days.		
Case.	With phenobarbitone.	With mysoline.	With soluble phenytoin.
1	15	18	0
5	6	16	5
6	5	72	6
	26	106	11

For these cases mysoline was assessed as inferior both to phenobarbitone and soluble phenytoin as a major anticonvulsant.

TABLE IV.—*Results of Treatment of Minor Epilepsy with Mysoline.*

		Minor attacks.		
Case.	Mysoline per day in gm.	Rate/year on phenobarbitone.	Rate/year on on mysoline.	Per cent. change.
2	1·5	10	0	−100
3	0·75	8	23	+188
4	0·75	15	9	−40
5	0·75	48	38	−21
6	0·75	1,057	4,628	+320
7	0·75	53	31	−41
8	0·75	9	0	−100

The above seven cases showed minor epileptic activity requiring anticonvulsant control. For clinical purposes a minor attack was considered to have occurred when there was transient loss of consciousness without convulsions. The above figures show that two patients were rendered free from minor attacks by mysoline. In one of these cases, however, there was an associated increase in the incidence of major attacks while the second case reverted to a clinical picture of major epilepsy.

Three other cases did show a 20–40 per cent. improvement whereas the remaining two showed a considerable increase in the minor attacks. This evidence is suggestive of some slight improvement in minor epilepsy following treatment with mysoline.

TABLE V.—*Summary of Results of Treatment of Major and Minor Epilepsy with Mysoline.*

	Free from attacks.	Much improved.	Improved.	Fits increased.
Major attacks	1	0	0	8
Minor attacks	2	2	1	2

Alterations in the Electroencephalograph.

An E.E.G. follow-up was carried out on all patients in this series, records being taken monthly before, during and after all courses of treatment.

TABLE VI.—*Variations in E.E.G.*

Case.	During phenobarbitone treatment (1952).	During mysoline treatment. After 30 days.	During mysoline treatment. After 80 days.	During subsequent treatment. With phenobarbitone.	During subsequent treatment. With soluble phenytoin.
1	++	++	++	..	N
2	N	+−	+−	N	..
3	N	N	N	N	..
4	N	+−	+−	N	..
5	++	++	++	..	N
6	++	++	++	..	+−
7	+−	N	N	N	..
8	+	+	+	+	..
9	+	+	+	+	..

Interpretation of symbols:
N = Recording within normal limits both resting and during hyperventilation.
+− = Non-specific dysrhythmia, negative for epilepsy.
\+ = Recording with characteristic epileptic forms, positive for epilepsy.
++ = Recording strongly positive for epilepsy.

Before mysoline treatment all patients were receiving phenobarbitone and their E.E.G.s were recorded. After eighty days' treatment on mysoline, six patients were replaced on phenobarbitone and three patients on soluble phenytoin and their E.E.G.s again recorded. The three patients treated with soluble phenytoin (and whose previous records had been consistently strongly positive for epilepsy) all gave recordings negative for epilepsy and in two cases the E.E.G. became normal. Of the E.E.G.s of those receiving phenobarbitone four were normal and two remained positive for epilepsy. From the table it will be seen that the E.E.G.s after 30 days and 80 days of mysoline treatment respectively were on the whole worse than the results obtained with phenobarbitone or soluble phenytoin. In no case did a record previously or subsequently positive for epilepsy become normal or negative for epilepsy following the administration of mysoline.

Cost.—In these days when the medical profession is being constantly exhorted to economize in prescribing, it is felt that a comparison of the cost of treating patients with phenobarbitone, soluble phenytoin and mysoline (I.C.P.) should be made.

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TABLE VII.—*Comparison of Treatment Costs.*

Drug.	Maintenance dose per day.	Approximate cost per patient per year.
Phenobarbitone B.P. . .	Tab. gr. 1 *t.d.s.* .	11/-
Soluble phenytoin B.P.C. .	Capsule gr. 1½ *t.d.s.* .	17/6
Mysoline (I.C.P.) . . .	Tab. gm. 0·25 *t.d.s.* .	£8

SUMMARY.

A small group of epileptics have been treated with mysoline. Major epileptic activity was increased in eight cases out of nine. One case was rendered free from fits although his E.E.G. did not improve. There was slight improvement in one-third of cases with minor epilepsy. E.E.G.s were unimproved after mysoline. Mysoline is therapeutically less effective than phenobarbitone or soluble phenytoin.

In this series two cases developed status epilepticus during orthodox drug transition. One status proved fatal. Toxic symptoms, in particular significant falls in the total white blood counts, occurred in more than half the patients and necessitated an uneconomical degree of clinical examination and pathological investigation certainly greater than that required during treatment with established anticonvulsants.

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