FIFTY CASES OF EPILEPSY TREATED WITH "TRIDIONE."

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INTRODUCTION.

Tridione is established as by far the most powerful drug in the control of *petit mal*. Many of its clinical aspects, therapeutic as well as toxic, are as yet not clear. In spite of this there is a remarkable absence of reports on the use of it in controlled clinical experiments.

Most of the reports on clinical trials with tridione have come from the U.S.A. After its anticonvulsant properties were established in animal experiments by Everett and Richards (1944), Lennox (1945) and Perlstein (1945) were the first to administer it in cases of human epilepsy. Lennox (1947) analysed a series of 300 patients who had the treatment over a period of up to two years. De Jong (1946) tried the drug in cases with psycho-motor attacks. Perlstein (1945) tried its effects on cases with gross organic lesions in the central nervous system, such as cerebral palsies of various etiology, tetanus, chorea, etc. He also gave the drug to patients showing behaviour disorders. He did not give a detailed description of the latter, but came to the conclusion that tridione controls the symptoms of lesions in the extra-pyramidal system, in which group he included behaviour disorders. Thorn (1945) also used tridione on a small number of cases with organic lesions of the central nervous system. His series included cases with familial mental deficiency, birth trauma, microcephaly, post-encephalitic cases and deteriorated epileptics. However, he merely observed the effect of the treatment on the major seizures accompanying these conditions. In this country clinical reports are very few, and with one or two exceptions they stress the adverse effects of the drug rather than analyse its therapeutics.* It came about, therefore, that the general trend was always to over-emphasize the dangers of the treatment. It led even to the repudiation of tridione: as it was put in one paper, "In this short series (10 patients) the toxic complications of tridione proved more dangerous than the disease it is used to treat." It is for this reason that it was decided to publish the experience with tridione in a series of 50 patients, treated both as in- and out-patients at the Maudsley Hospital, London. Most of these were patients in the epileptic clinic at that hospital.

* Since this report was written two papers have appeared in the *Brit. Med. J.* and one in *Brain*: Whitty, C. W. H., *Brit. Med. J.*, 1949, 6 August, Haward, F. C., *ibid.* Davies, G. R., and Spillane, J. D., *Brain*, 1949, **72** II, 140.

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Case Material.

The group consisted of 31 adults, their ages ranging from 16 to 52 years, and 19 children aged from 4 to 16 years. Twenty-six were male and 24 female patients.

Clinically this group was heterogeneous. Eight cases had either *petit mal* only, accompanied by a 3 cycle-per-second wave and spike (c/sec. W.S.) pattern in the electroencephalogram (E.E.G.), or else *petit mal*, myoclonic jerks and akinetic attacks, also accompanied by the 3 c/sec. W.S. pattern in the E.E.G. One case had wave-and-spike variant (2 c/sec.). There were a further 5 in whom attacks were clinically indistinguishable from *petit mal*, but the E.E.G. did not show any specific epileptic wave forms. In every patient there were from 5 to 8 E.E.G. recordings done at varying intervals from 1 to 3 months. The largest group consisted of 29 cases who had had in the course of their illness more than one type of attack. All of these suffered from major attacks, although in some cases these were only reported to have occurred once or twice in their lives. Twenty-one of them suffered from *petit mal* attacks, the E.E.Gs. in 7 cases showing the 3 c/sec. W.S. pattern. Four showed the wave-and-spike variant (2 c/sec.). Of those in whom psychomotor attacks were prominent, namely 9 cases, 3 showed W.S. in the E.E.G. recordings, 2 had W.S. variants, and 4 had no specific wave forms. Ten cases of this "mixed" group suffered from myoclonic jerks, 5 with W.S. forms, 5 without. One case had true akinetic attacks. In this case the W.S. was never found in the E.E.G. A further 7 cases showed signs of organic lesions in the central nervous system. These will be described in detail separately.

Dosage.

The recommendations for dosage vary widely in the various reports. Probably, as a result of the preoccupation with the adverse effects, the papers which appeared in this country recommend rather low doses. Butter (1948) suggests that the daily dose should not exceed 4 capsules (1·2 g.). In the present series the following doses were given without serious adverse effects:

8	capsules	(2·4 g.)	per day to	1 patient for 4 months.
6	,,	(1·8 g.)	,,	2 patients for 6 months.
5	,,	(1·5 g.)	,,	9 patients for periods from 1 month to 1 year.
4	,,	(1·2 g.)	,,	13 patients for periods from 2 months to 18 months.
3	,,	(0·9 g.)	,,	25 patients for periods up to 2 years.

In none of the patients was it necessary to reduce the dosage permanently because of toxic or allergic side effects. In 2 cases difficulties arose after the first 2 to 3 weeks of treatment. In one woman glandular enlargement with malaise and slight fever occurred. She had also noticed an erythematous rash, but this had faded before she was seen by a doctor. Tridione was withheld for 2 weeks. The symptoms subsided, and on recommencement of treatment

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no further difficulties occurred. To minimize the number of allergic reactions of this type, treatment was started with 2 capsules per day in adults and 1 capsule in children. This dose was increased weekly by one further capsule until optimum effects had been obtained. This gradual assessment of the most effective dose is the only way to stabilize the treatment. Whereas in many cases 3 capsules and in the majority of cases 4 capsules per day proved sufficient to abolish all attacks of *petit mal* or myoclonus, in 9 cases 5 capsules only produced a satisfactory result. How unpredictable the optimal dosage is becomes apparent if one considers that adults sometimes required small doses only, e.g. 3 capsules per day, whereas some children needed much larger doses, e.g. 5 capsules per day, to reduce the number of their attacks.

Results: General.

Davies and Lennox (1946) in their tables indicate that *petit mal* attacks responded best to the treatment. In a very few of their cases (4 per cent.) an increase in the number of attacks occurred. On the other hand, of the patients with major seizures very few responded favourably (30 per cent.), some remained unchanged (30 per cent.), and many of them showed an increase in the number of fits (40 per cent.). The response of patients with psychomotor attacks was somewhere in between—improved 70 per cent., no change or worse 30 per cent. The results in this series are similar to those of Davies and Lennox as shown in Table I, except in the cases with major seizures, there the results seem to have been more favourable.

1. *Major Seizures.*

Table I may be misleading in regard to the major attacks. These cases were not treated by tridione alone. The patients were usually taking one or several anticonvulsants, such as phenobarbitone or epanutin in doses which had been found optimal, but did not control all attacks. When treatment with tridione was commenced, the other drugs were continued at the same time. In most cases in this series tridicne did not further reduce the number of major seizures.

Table I.

Result of treatment.	Unmixed *petit mal*.		Mixed epilepsy.			
	With 3 c/sec. W.S.	Without 3 c/sec. W.S.	*Grand mal* seizures.	*Petit mal* with W.S.	*Petit mal* without W.S.	Psychomotor attacks.
Worse	..	..	3 (temporarily)	..	..	..
No change	..	..	8	..	..	3
Little improvement	..	..	1	..	..	..
Number of attacks reduced by half	..	..	1	1	2	1
Number of attacks reduced by more than half	..	..	4	..	1	2
Great improvement	2	..	7	3	6	1
No further attacks	6	6	3	3	5	2

This table shows the response to treatment of the various types of attacks encountered. In the "mixed" group the types of attacks are charted, not the patients. It does not include the patients with "organic" lesions in the nervous system.

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In 3 cases out of 27 the major attacks disappeared completely. In 12 they were reduced more or less. In 9 no marked change could be observed, and in 3 the number of attacks increased. In 2 of the latter no other anticonvulsant had been taken with tridione, and the major attacks ceased when phenobarbitone or epanutin was added. In the third case the previous dose of epanutin was slightly increased, and the number of attacks was reduced to its former level.

The results in these three patients are of interest. Even if tridione does seem to reduce major seizures in a small number of patients, it was obvious from the first clinical trials that it was certainly not the drug of choice in this disorder. The observation, however, that it did increase the number of attacks in some patients has often been quoted as another of the adverse effects of the drug. The fact that in these cases the attacks so precipitated were only very few should not deter from the seriousness of this argument for the following reason: some of the patients concerned were young adults and had not had major attacks since their childhood; the sudden unexpected attacks shortly after commencement of a new treatment came rather as a shock, and may well deter the disappointed patient from going on with the treatment. This can be largely prevented by giving any patient who has a history even of rare generalized convulsions a combination of tridione and phenobarbitone gr. ½ *t.d.s.* or epanutin gr. 1½ *b.d.* for a few weeks rather than tridione alone. These drugs can, however, after a few weeks be withdrawn gradually. Major attacks were never precipitated in patients in whom the history had not revealed any such previous attacks.

2. *Psychomotor Seizures.*

The effect on psychomotor attacks was particularly studied by De Jong (1946). He claimed that a combination of tridione and epanutin had a very good effect on this type of attack. In the present series of 9, 4 cases showed some reduction in the number of attacks and in 2 they have quite disappeared, but in 3 cases no apparent change was noted. All these patients took epanutin with or without phenobarbitone together with the tridione. These results are rather similar to those of De Jong, and also of Davies and Lennox (1946).

3. *Minor Seizures.*

In the cases of *petit mal* some improvement always occurred. In most patients attacks before treatment with tridione had been as frequent as 10–15 per day or more. In several cases they were as frequent as 3 per minute. In one case only was the reduction in the number of attacks merely slight. There was reason to suspect a lesion in the central nervous system. The patient will be mentioned again with the "organic cases." In all the other patients improvement was spectacular. In 20 cases attacks ceased altogether. The case in which there was only slight improvement is a young girl who is mildly demented, and shows a number of signs due to organic changes in the central nervous system. She is aged 19, and has a number of epileptics in her family.

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She has always been backward. She began to have both major and minor fits 2 years before menarche. Some of the attacks seem to be of a hysterical nature. She has a right facial weakness and an epilepsia partialis continua of the right arm and leg. The two affected limbs show an increase in tone and tendon reflexes. The plantar reflex is doubtfully dorsiflexor on the right side. There is also some sensory loss of cortical type in the right hand. A full investigation, including an air encephalogram and arteriogram, did not reveal the character of the lesion in the central nervous system. The E.E.G. showed high voltage slow waves, especially on the left side.

4. *Cases with Organic Lesions in the Central Nervous System.*

Tridione was also given to a small number of patients with organic changes in the central nervous system. This aspect of the clinical application of tridione was particularly studied by Perlstein (Richards and Perlstein, 1945). The number of this type of patient in the present series is small, namely 7. They are reported here because the subject has been discussed by others, and the total number of cases reported so far is very small indeed, namely 15 cases.

(1) One patient had congenital diplegia. He is 10 years old. He is somewhat spastic in all limbs, with increased tendon reflexes and bilateral extensor plantar responses. His intellectual ability is at the level of imbecility. He had been unruly at home, dirty, aggressive towards his sister, and had never been to school. He suffered from frequent myoclonic jerks and extremely numerous *petit mal* attacks. From time to time, about once per week, he would have what is best described as *petit mal* status epilepticus. During this there was no appreciable interval between attacks. His E.E.G. was a continuous 2–2½ c/sec. W.S. variant. Phenobarbitone and epanutin were tried, but produced no great change. After treatment with tridione his myoclonic jerks and most *petit mal* attacks ceased. He still goes into the status epilepticus described above, but only once a month or less frequently. He is much more manageable at home, goes now to a play centre, plays with other children and seems much brighter. His neurological signs, however, have not changed.

(2) Another child with cerebral diplegia and W.S. forms on the E.E.G. had no further attacks of *petit mal* when under treatment, but his major seizures increased somewhat in number. They were easily controlled by epanutin. His neurological signs have not changed as the result of treatment.

(3) The next three cases showed evidence of organic dementia, but no persisting localizing signs were present on neurological examination. One of them had epilepsia partialis continua. The pneumo-encephalogram and other methods of investigation did not reveal any cause. She has shown slowly progressing dementia since the age of 14. Tridione reduced the number of her *petit mal* attacks slightly, but did not improve her general condition very much. The other two cases were affected in a similar way: their *petit mal* attacks were greatly reduced, almost abolished; the other aspects of their illness, i.e., the dementia and the other types of fits, were little affected.

(4) One patient was suffering from Unverricht's type of myoclonus epilepsy in an advanced state. Her condition did not change the pace of its progress, but all her attacks, *petit mal*, myoclonus and *grand mal* stopped completely while she was under treatment. They did recur when the tridione was withheld for a few weeks, although treatment by epanutin and phenobarbitone had been continued. Among other marked symptoms this patient had dysphagia. At the height of this she could not swallow at all. With tridione this symptom subsided almost completely, only to recur if the dose was reduced. This patient took 6 capsules daily.

(5) There was one case who suffered from epilepsy due to a cerebral tumour. Attacks were markedly reduced by tridione. Later the tumour was removed by operation, but the fits continued. The fits were mainly of the *petit mal* type. Treatment was again started after operation, and was again helpful.

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The E.E.G. and Efficiency of Tridione.

Lennox (1947) points out that the best results of the treatment can be obtained in cases belonging to the so-called "Triad." By this is meant any of the attacks which are commonly accompanied by the 3 c/sec. W.S. pattern in the E.E.G., namely *petit mal*, myoclonic jerks and akinetic attacks. Lennox goes so far as to describe tridione a specific treatment for this condition. The present series has been analysed from this point of view (Table II).

Table II.

Results of treatment.	Unmixed *petit mal*.		Mixed epilepsy.	
	With 3 c/sec. W.S.	Without 3 c/sec. W.S.	With 3 c/sec. W.S.	Without 3 c/sec. W.S.
No further attacks	6	6	3	5
Less than one attack per month	2	—	3	6
Less than one attack per day	—	—	1	2
Several attacks per day	—	—	—	1

The figures indicate the number of patients in the various groups who have minor seizures.

The patients who have W.S. patterns in their E.E.G. show a slightly better response than those without it. Nearly two-thirds of the cases with W.S. showed a complete disappearance as against half without W.S. forms. Reduction to a level rarer than one attack per month is about equal in the two groups, and the cases who did not improve beyond one attack per day were all without the W.S. The therapeutic efficacy is also slightly less in patients who suffer other types of seizure in addition to *petit mal*. In most of these cases other drugs had been tried, but had little or no effect in reducing the *petit mal* attacks. In a few cases only was tridione used as the first drug to be tried.

It would appear then that tridione can be expected to produce results in patients suffering from *petit mal*, either alone or with other forms of epilepsy. Cases in which the E.E.G. shows W.S. forms have a slightly better prognosis. The danger of precipitating major seizures in mixed cases or in patients who have had a few major convulsions at any time in the past does exist. This can, however, be prevented by adding phenobarbitone or epanutin, and can easily be treated should it occur unexpectedly.

Table III shows that patients in whom the W.S. pattern is present in the E.E.G. do not require smaller doses of tridione to achieve optimal therapeutic success.

Table III.

Type of epilepsy.	Cases showing the 3 c/sec. W.S. in E.E.G.	Cases not showing the 3 c/sec. W.S. in E.E.G.
Unmixed *petit mal*	3–4 caps. per day	4 caps. per day
Mixed epilepsy	5 caps.	4–5 caps.
Symptomatic epilepsy ("Organic" cases)	5–6 caps.	4 caps.

The figures indicate the average number of capsules per day necessary to suppress the largest number of *petit mal* attacks. Each capsule contains 0·3 g. of tridione. The effects of these doses were not necessarily equivalent.

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Tridione and "Backwardness" in Epileptic Children.

Another very striking effect of the treatment was the apparent change in the intellectual abilities of some patients, particularly of children. In a number of children suffering from *petit mal*, the school authorities reported that the children were backward in their class, that they had had to be transferred to a lower stream* in the school, and were still unable to benefit from the instruction. The school authorities were considering their transfer to special schools for backward children.

In four of these children the treatment produced excellent results. The frequent minor seizures ceased and the children caught up quickly with their work. Soon they could be moved up to a higher stream and were able to continue at their schools.

In spite of this striking change in performance in learning, psychometric tests did not show any alteration in their intelligence quotient (I.Q.). This apparent discrepancy may be explained by the fact that in patients suffering from *petit mal* consciousness is more disturbed than is clinically evident. The so-called "subclinical attacks" observed in the E.E.G. probably manifest themselves in this way: that the child cannot cope as well as other children in a competitive situation such as everyday school life presents, but the individual attention of the psychologist during the test helps the child to perform according to his mental age level. It was interesting to note that in these cases the E.E.G. records showed marked improvement as treatment went on. There were fewer bursts of epileptic activity.

Adverse Effects of Tridione.

There are several adverse effects of this drug. They have been described by most of the previous writers on tridione. Most of them are harmless if detected early, and in the case of most, treatment need not even be interrupted.

(1) *Glare or hemeralopia.*—This symptom occurs in a rather large number of patients who take tridione. Lennox (1947) reports that in his series adults only suffered from "glare." In our series 11 patients (20 per cent.) had it. Half of these were patients below the age of 15 years. The symptom is troublesome, as it exposes the patient to the risk of accidents when entering the bright street from a dark house, tube station, etc. The symptom disappears sometimes spontaneously after a few months. If not, a pair of dark glasses will usually help. Most authors report that no retinal changes can be observed. In the present series the patients had repeated ophthalmoscopic examinations, but no abnormalities were found. The cause for the glare, however, is probably not in the retina or optic nerve at all, but more central. The symptom is similar to that which sometimes occurs as a toxic effect of digitalis. Carroll (1945) has described glare in a number of patients, some of whom showed hemianopic distribution of the symptom, or the glare alternating with a hemianopia. Both subsided when treatment was stopped.

* In some schools each age group (class) is subdivided into "streams" A, B, C or D. Those divisions are made on the basis of intelligence tests.

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(2) *Skin conditions.*—In several patients transient maculo-papular rashes appeared particularly on the forehead, behind the ears, on the chest and over the arms. These disappeared even if tridione was only reduced to 2 to 3 capsules per day. The first patient in this country whose death was alleged to have been caused by tridione was a little girl who died of exfoliative dermatitis, reported by Keren (1948). She had a rash which was at first mistaken for scarlatina. When it appeared the dose of tridione was increased and continued for nine days. Blood counts which were done from the peripheral blood near death were normal (personal communication). This is the only case of that kind reported anywhere. In our series mild erythematous rashes occurred in seven cases only. Two further cases had angioneurotic oedema shortly after commencement of the treatment. It is difficult to decide whether tridione was really the cause of the latter.

(3) *Kidney affections.*—These have been reported by two authors (Briggs *et al.*, 1949; Barnett *et al.*, 1948). No such effect was observed in this series. One of the cases reported in the literature was fatal, the other recovered after tridione had been discontinued.

(4) *Behaviour difficulties* are reported in the literature to have been brought on by treatment with tridione in children as well as in adults. In other patients, however, behaviour abnormalities are reported to have been alleviated. In our series two boys were apparently difficult in school. They ill-treated animals, beat other children, etc., and were not improved by ordinary methods. Tridione not only stopped their attacks, but brought improvement in their behaviour. In one case, a boy of 10, the mother reported that after the treatment began he became very restless and noisy and was more difficult to manage. The treatment was continued nevertheless, and after a few weeks the boy's behaviour became normal again; his frequent seizures had ceased.

(5) *Blood*—The blood changes have received more attention than the other side effects of the drug, because the first fatalities following the administration of the drug were due to them. In the present series only one patient had a severe but transient leucopenia of 1600 W.B.C. Tridione was withheld for two weeks and then given again without any ill effects. The white cell-count returned to normal. The patient suffered no symptoms during this period.

Blood counts, including differential counts, were carried out once per month in every patient. In addition every patient was asked to report to the hospital if any of the symptoms which might suggest agranulocytosis, such as sore throat, malaise, petechiae, etc., should occur. This did not happen.

Further investigations of the blood are discussed more fully later.

Course of Treatment.

It has been repeatedly pointed out that tridione is different from most drugs used in epilepsy in that it does not precipitate large numbers of attacks or even status epilepticus if it is suddenly withdrawn. No attacks are precipitated by the withdrawal. On the contrary the therapeutic effect may be maintained for several months. This is important, because the drug can be withheld suddenly if adverse effects are noted, and also because the patient

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is not exposed to any danger if he unexpectedly runs out of capsules and cannot readily replace them.

Lennox (1947) observed that the benefit gained by the treatment was not only held temporarily if the treatment was interrupted, but was often maintained permanently. Quite early on in our series a mother reported that she had deliberately withheld treatment because the patient, a 10-year-old boy, had not had a single attack for many months. He had suffered up to 20 or 30 attacks a day. In spite of the fact that the patient had not taken any tridione for the past month his attacks had not reappeared. He had been taking 4 capsules per day for six months. It was decided that treatment should be withheld until attacks would return. The patient was asked to report monthly to the clinic. He has done so for the past 13 months. This does not, however, occur in many cases. The drug was withheld in a number of patients, but only in a few did the attacks remain abolished. In none, however, did the condition relapse to a pre-treatment level. Some improvement was maintained in all cases. It is also probable that the length of treatment is of significance. Six months appears the minimum for which treatment has to be maintained before one can expect the benefit to remain permanent.

The best way to administer the drug seems to be as follows: The number of capsules per day is gradually increased until the maximum therapeutic effect is obtained. It may be necessary to give as many as 8 capsules per day. Children over 5 years seem to tolerate these doses quite well, although one would observe greater caution. This dose should be maintained for 1 to 2 months if the seizures are abolished. The drug should then be reduced to a lower level by 1 capsule per day every month. Should attacks recur the dose is increased again. After six months the dose can be reduced to 3 capsules per day. One daily capsule should be withdrawn every two months from then on. Should attacks recur at any of these stages no further reductions should be made, or the dose should be increased again if necessary.

Blood Changes.

An analysis from the literature of the cases in which tridione seems to have caused death due to blood changes shows the following encouraging fact: Although tridione must have been administered to tens of thousands of patients, as Lennox states, and has been in clinical use for several years, only five patients are described in the literature in whom the drug was alleged to have caused death by affecting the blood-forming organs or the blood.

One case described by Harrison, Johnson and Ayer (1946) was not taking tridione alone, but also mesantoin. At the time of publication of this case no fatalities had been described following mesantoin, and so the blame for the unfortunate issue in this patient was squarely put on the shoulders of tridione, but since then a case of aplastic anaemia occurring in a patient taking mesantoin alone was published by Bloom, Lynch and Brick (1948).

The second case was described by Mackay and Gottstein (1946), the third and fourth case in this country by Forster, Watson and Neumark (1949), and by Braithwaite (1948); the fifth case was briefly mentioned in *The Lancet*

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(1947). In all the fully reported cases the peripheral blood was very markedly affected. It showed a gross dimunition of granulocytic cells. The red blood cells were also reduced. In one case the bone marrow did not show any gross abnormality, and showed even a hyperplasia of the erythroblastic elements. In the other the bone marrow showed hypoplasia, and in the third the report was inconclusive. In the latter immature granulocytes were found in the peripheral blood. A third case described by Greaves (1946), although not fatal, may well be added here. This patient, who took tridione combined only with phenobarbitone, developed a granulocytopenia. He recovered on discontinuing tridione, but relapsed promptly on attempting to start it again. It was eventually abandoned. Nothing was said about the state of the bone marrow in this case.

Davies and Lennox (1946) found that even when the cell count of the neutrophil polymorphonuclear cells fall to very low levels, grave effects do not always accompany this. They report that in some of their patients the neutrophils fell as low as 1600. Tridione was continued in a number of these, but no ill-effects followed. The patients had no complaints. It appears then that tridione has a selective depressant effect on certain elements in the blood, mainly on the neutrophil polymorphonuclear cells, but that occurs only in a small number of patients, and it is then mostly only transitory and asymptomatic. Only a very small number show symptoms of a grave illness, and in even fewer does it remain irreversible.

Young (1949) states that by the time the peripheral blood shows leucopenia in cases of agranulocytosis the bone marrow changes are well established. If that is so the leucopenia described in our cases is only transitory, and has nothing in common with the severe irreversible type. It is harmless, and does not require any treatment. Indeed recovery occurs even if the drug is not withheld. Young says this type of leucopenia is not due to the toxicity of the drug itself. The fact that the bone marrow in the case of Mackay *et al.* was not very abnormal is not conclusive either. It does not necessarily mean that the case is one of peripheral destruction of the neutrophil polymorphonuclear cells. It may be a true central agranulocytosis in which the bone marrow has begun to recover again.

Eosinophilia.

In only one of our cases did a severe leucopenia occur. The W.B.C. fell to 1600, but there were no symptoms. However, in the present series other changes in the blood have been observed, which may have some important connection with the above group of cases. Sixty per cent. of our cases treated with tridione showed an increase in their eosinophil counts shortly after commencement of the treatment (Table IV).

In about half of those who showed eosinophilia it subsided again after a few weeks or months in spite of continuation of the treatment. In one case it disappeared after cessation of tridione therapy, and did not reappear on resumption of it.

Robinson (1947) in his report on 100 cases mentions occurrence of eosinophilia, and attributes it to other causes unconnected with the drug. In Hall's

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TABLE IV.

Number of case.	Eosinophils before treatment.	Eosinophils during treatment.	Time in which eosinophilia developed.
1	Not taken	11% (1072)	3 months
5	,,	6% (543)	1–2 ,,
6	2% (253)	10% (1475)	4–5 ,,
7	0	19% (1387)	1 month
8	0	7% (505)	5 months
15	1% (101)	3% (529)	1 month
		5% (645)	7 months
16	0	4% (268)	10–11 ,,
17	2% (248)	5% (685)	2–3 ,,
18	3% (150)	8% (824)	3 ,,
19	1% (91)	8% (832)	2 weeks
22	6% (348)	18% (1548)	3 months

The figures in brackets represent the absolute number of eosinophil cells per cubic millimetre.

(1948) cases the percentage of those who showed eosinophilia was about the same as in the present series, and in those reported by Davies and Lennox (1946), 52 per cent. It ranges from 5 to 25 per cent. in the differential blood count. Davies and Lennox showed clearly that the eosinophilia is not incidental, but dependent on the ingestion of the tridione. When administration of the drug was discontinued the number of eosinophil cells fell. On recommencement of the administration their number rose again usually to its former level. In the present series this was not tested. In a number of those who showed eosinophilia tridione had to be discontinued when the drug was temporarily not available, and the results are shown in Table V.

In the first 24 cases of this series the stools of all patients showing eosinophilia were examined. Ova of *Oxyuris vermicularis* were found in all of them in a single test. The stools of the other patients without eosinophilia were

TABLE V.

Number of case.	Duration of treatment.	Eosinophilia at the end of treatment.	Eosinophils after withdrawal of tridione.	Eosinophils after recommencement of treatment.
1	5 months	11% (1072)	3% (174)	9% (598)
5	2–3 ,,	6% (543)	2% (192)	3% (354)
8	5 ,,	7% (591)	3% (195)	3% (270) later 8% (568)
17	5 ,,	5% (644)	1% (96)	4% (482)
18	4 ,,	8% (824)	2% (240)	5% (360)

tested, some of them on several occasions, but no helminthic parasites were found. Since, except in one case, which gave a history of asthma of unknown origin, no other findings were brought to light which could in any way explain the eosinophilia, the following course was taken. The patients were treated with gentian violet for three days, followed by a dose of Epsom salts, and their blood count was repeated after the completion of this treatment. Tridione treatment was continued throughout. The results are shown in Table VI.

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TABLE VI.

Number of case.	Eosinophil cells before treatment with tridione.	Eosinophil cells before antihelminthic treatment.	Eosinophils shortly after antihelminthic treatment.	Eosinophils several weeks or months after antihelminthic treatment.
1	Not taken	5% (515)	4% (84)	..
6	2% (253)	7% (857)	0	3–5% (350)
7	0	12% (1392)	9% (684)	..
8	0	8% (560)	4% (280)	5–8% (480)
18	3% (150)	7% (588)	2% (146)	..
19	1% (91)	8% (832)	0	3% (225)
22	6% (348)	18% (1728)	3–5% (560)	..

The antihelminthic treatment consisted of Gentian violet gr. i–iij *t.d.s.*, according to the age of the patient. This was followed by one dose of magnesium sulphate.

With due regard to the small number of patients, these data seem to allow the following conclusions:

(1) The patients who show an eosinophilia when treated with tridione are also those who are infested with helminths.

(2) They do not show an eosinophilia before tridione is administered. Although no stool tests were taken before this treatment was started, it is most likely that the infestation had existed before. In other words, it is unlikely that all these patients have become infested as soon as treatment with tridione was commenced. Their blood count therefore shows that they were not generally sensitized to the helminths which inhabited their intestinal tract.

(3) When they began to take tridione they showed signs of sensitization; not to the drugs alone nor to the helminths alone, but only to both simultaneously. The tridione, therefore, appears to sensitize the organism to the previously existing infestation with intestinal parasites. The question arises as to whether the other side-effects of tridione therapy are in any way connected with the activation of the helminthic keratins by the drug.

Table VII shows these side-effects in this series of patients, who for this purpose are divided into two groups—those with, and those without eosinophilia. There are neither qualitative differences in the sense that one particular effect would appear in the one and not in the other group. Nor are there quantitative differences in the sense that more ill effects are produced in one group than in the other. The commonly observed side-effects of tridione, therefore, correlate in no way with eosinophilia.

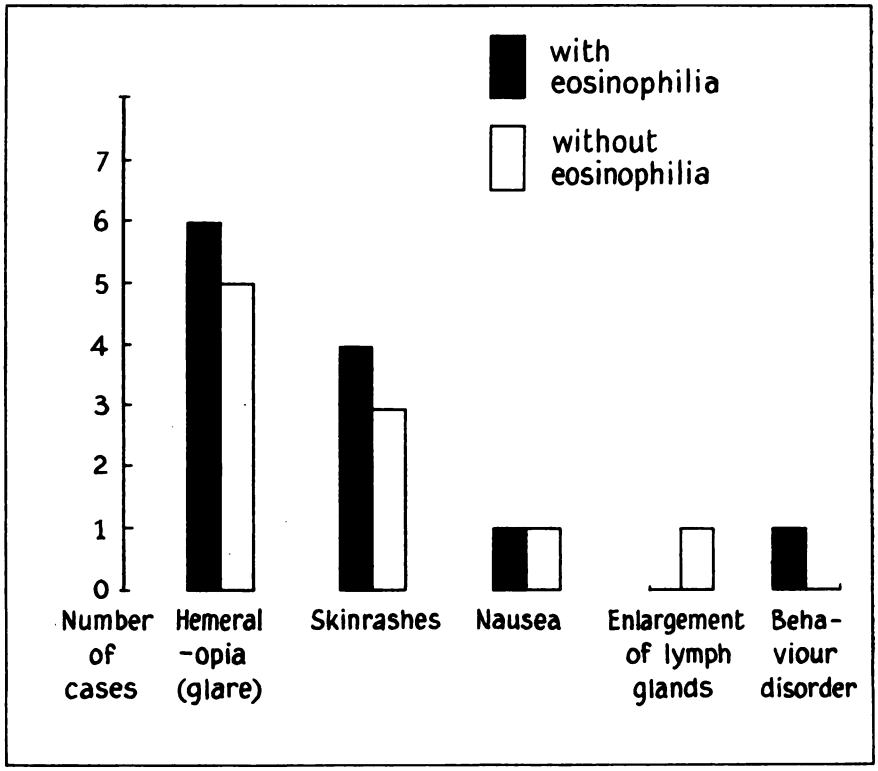
The relationship between neutropenia and the eosinophilia in the series by Davies and Lennox (1946) was as follows: Eosinophilia has not been confined to the group having neutropenia, although the average percentage for this group is 6·2, compared with 3·8 for the entire series. The present group of patients is too small to allow for statistical investigation. We found a slight transitory increase in the W.B.C. during the first 3 to 10 months in all our patients. This leucocytosis was not commented on by Davies and Lennox, but was observed by Hall (1948) during the first 3 months of treatment. In this series the group with eosinophilia showed differences in the differential cell count from the group without eosinophilia. In the first group the increase of W.B.C. was mainly due to lymphocytes. The neutrophil polymorphonuclear cells actually fell in number as soon as treatment was begun. This was

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not so in the control group, where all cells increased in number. These facts would have to be confirmed in a larger series of cases.

The important question is whether this transient granulocytopenia is the precursor of the agranulocytosis found in a few patients. From an analysis of the cases in the literature this question cannot be answered, mainly because the necessary investigations had not been carried out. The interesting findings in the case described by Mackay and Gottstein (1946) are not conclusive

TABLE VII.



(Young, 1949). An investigation of this question would in any event be useful. If the mild transient form is a condition *sui generis* it is harmless and does not require treatment. In that case frequent blood examinations of the patient while under treatment do not seem to be necessary. If it is a precursor of the severe agranulocytosis, the connection with the changes due to allergy may open an avenue to treatment and prevention. It would make this powerful and valuable therapeutic agent, tridione, safer for clinical use.

SUMMARY.

1. Fifty cases of various types of epilepsy were treated with tridione, with or without other anticonvulsants.

2. The best effect was achieved in cases of *petit mal* either occurring alone

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or together with other types of attack. The 3 c/sec. W.S. in the E.E.G. is not a *sine qua non* for successful treatment.

3. Major seizures occurring in addition to *petit mal* do not contra-indicate the use of tridione. They can be suppressed by adding epanutin or phenobarbitone to the tridione.

4. Some of the adverse effects have been discussed.

5. Eosinophilia was observed in 60 per cent. of the patients. This seems to be dependent on the presence of a helminthic infestation, but occurs only if tridione is taken at the same time.

6. The possible implications of this finding for the blood changes in general are discussed.

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