Finally it was decided to test the effect of posture. The patient stated that 20 minutes' vigorous swimming had not precipitated an attack. In our experiment he was instructed to "cycle" on his back, supporting his buttocks on his hands, his flexed elbows resting on the bed. This position over-corrected any possible lordosis. After 10 minutes' vigorous exercise in this position blood was withdrawn from a vein. The serum from this specimen showed no trace of haemolysis, and urine passed shortly afterwards was also clear of protein and of haemoglobin derivatives.

Discussion

Our experiments support the view that exertion haemoglobinuria results from haemolysis during exertion in the erect or extended position. This agrees with the common view. Cases, however, seem to vary in their degree of dependence on the postural factor. Thus in the case recorded by Makin (1944) haemoglobinuria was strictly postural, and did not occur after exercise on a bicycle, whereas in the case recorded by Witts (1936) running with bent back and work on the bicycle ergometer were followed by haemoglobinuria. The postural factor and the common association with lordosis suggest that the condition is allied to orthostatic albuminuria. Bicycle exercise in Makin's case was followed by albuminuria but not by haemoglobinuria. Orthostatic albuminuria was not present in our case.

The failure to demonstrate circulating haemolysin is of little significance and does not rule out the occurrence of intravascular haemolysis; for unless combination with red cells is prevented by special factors, as it is in the case of cold haemoglobinuria, haemolysin liberated into the circulation is likely to be fixed rapidly. In nocturnal haemoglobinuria all efforts to demonstrate circulating haemolysin have failed (Witts, 1936). The failure to demonstrate local haemolysin in muscle is in keeping with the postural features of the disorder and with the view of Witts, who regards the kidney as the source of the haemolysin. He considers intravascular haemolysis "hardly conceivable" in view of the absence of anaemia and the slowness of systemic changes and of haemoglobinaemia; he regards a local haemolysis in the vessels of the kidney as more probable.

According to Whitby and Britton (1944), in exertion haemoglobinuria "there are neither the constitutional symptoms nor the haemoglobinaemia so characteristic of haemoglobinuria from cold." In our case there was a cherry-red concentration of haemoglobin in the serum, and it would seem that the lowering of the blood haemoglobin level was slight because haemolysis was of short duration only, accompanying tiring exertion in the vertical posture. Whitby and Britton state that in cold haemoglobinuria haemoglobin appears in the urine when the free haemoglobin in the plasma exceeds 100 to 140 mg. per 100 ml. This is higher than the plasma haemoglobin level recorded after exercise in Witts's case (46.5 mg.) but considerably lower than that recorded in ours.

History of an injury is another inconstant feature in exertion haemoglobinuria, which, however, helps to incriminate an abnormal kidney as the immediate cause of haemolysin production. No history of injury was elicited in our case, but the disease had come on rather suddenly shortly after a campaign, when slight injuries might have been ignored. In contrast to the usual history, our case resembled that of Witts in showing symptoms for a period (with intermissions) of considerably more than one year. The age at onset of the complaint was much above the average, and it is of interest that the condition recurred with unusual severity when the patient came to the Tropics.

Summary

A case of paroxysmal haemoglobinuria of exertion is described.

Laboratory investigations, including attempts to demonstrate circulating haemolysin, are described and discussed.

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REFERENCES

- Makin, M. (1944). *British Medical Journal*, **1**, 844.
Whitby, L. E. H., and Britton, C. J. C. (1944). *Disorders of the Blood*, p. 258. London.
Witts, L. J. (1936). *Lancet*, **2**, 115.

"TRIDIONE" IN THE TREATMENT OF PETIT MAL

BY

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Tridione, the synthetic anticonvulsant drug (3,5,5-trimethyloxazolidine-2,4-dione), has been extensively used in the treatment of the petit-mal epilepsies by investigators in America since 1944.

A Preliminary Investigation

Recently, when supplies became available in this country, a preliminary investigation was made at St. David's Hospital (for epilepsy), the findings of which are tabulated below. Most of the patients (who are sane males suffering from idiopathic epilepsy, and whose ages range from 17 to 56) have been taking the drug for three months.

Tridione is supplied in 0.3 g. capsules. So far it has been found that the apparently optimum dose in the average case is four capsules daily, in divided doses. One patient aged 17, however, has had his petit-mal attacks abolished by taking only two capsules daily. The drug was given in addition to other medication, such as phenobarbitone and "epanutin" (soluble phenytoin), which the patients had previously been taking.

Convulsive seizures of the grand-mal type did not appear to be reduced by tridione in any case, and one man experienced, possibly as a coincidence, an increase in the number of his fits. All the patients suffered from petit-mal except one whose seizures were of the myoclonic type. This man's condition did not improve. Another, however, who had myoclonic spasms as well as ordinary petit mal, states that he feels better than he has done for years.

It is possible that the patients who showed no improvement might have been benefited had they been given more than six capsules daily. Unfortunately a shortage of supplies precluded an increase of this dose.

No. of patients	23
Entirely free from petit mal	4 (17.4%)
Petit mal reduced by more than half	12 (52.2%)
Definite but slighter improvement	2 (8.7%)
No improvement, or toxic symptoms necessitating withdrawal of drug	5 (21.7%)

Because of the notorious difficulty in obtaining an accurate record of petit-mal attacks each patient was given a notebook, and in this he marked down every attack of which he was aware, or which any fellow patient or member of the nursing staff observed. For the purpose of comparison the patients had kept similar records of their attacks for a period of two months before starting tridione medication.

A few days after beginning to take the drug approximately four-fifths of the patients reported a reduction in the number of their petit-mal attacks. After a week or 10 days no fewer than 19 of the 23 patients mentioned that on walking out of a building into the open air they found the

light too bright. This phenomenon was variously described as "dazzle," or "glare," or "a whiteness like mist over everything." Some patients stated that they found reading in the open air to be impossible, and others said that objects appeared to have changed colour, as, for example, a familiar blue motor-car seemed to be cream-coloured. In most instances the sensation ceased after a short interval, but 10 of the men found it trying and were glad to wear dark glasses to mitigate the effect.

Five men were aware of slight drowsiness, apparently due to the drug; one complained of lack of concentration, and one of restlessness. Two developed slight ataxia; two complained of hiccup, and two of slight epigastric discomfort. One developed a slight rash, similar to acne, on the face; and one, whether *post* or *propter hoc*, had a severe rash of the face, neck, and hands which initially looked like urticaria and proceeded to an acute dermatitis with exudation and desquamation. In this case the drug was withdrawn, as it was in four others in which, although no marked toxic symptoms were present, there appeared to be no improvement in the incidence of petit mal. Most of the other 18 patients were anxious to continue taking the drug, as in their opinion the relief obtained from the reduction in their attacks more than outweighed the slight nuisance of the "dazzle phenomenon" or the other symptoms mentioned above.

Comment

Several important points emerge from a review of some of the literature on the subject. Tridione is said to be contraindicated in patients with severe renal or hepatic damage and in conditions in which optic-nerve disease is already present; but no residual damage to the optic nerve has been detected in patients complaining of the "dazzle phenomenon"; and "histological studies on the optic nerves and retinae of experimental animals receiving large doses of tridione over long periods have failed to reveal any evidence of damage." Several investigators have also recorded that when the drug is withdrawn weeks or months may elapse before attacks of petit mal return.

Obviously more time and greater experience are required before this drug can properly be evaluated, but there is no doubt that tridione has a pronounced inhibitory effect on petit mal and also, in the experience of American investigators, on myoclonic spasms and akinetic seizures.

Summary

The treatment by tridione of 23 cases of the petit-mal epilepsies is analysed.

Approximately four-fifths of the patients improved, but various toxic symptoms and signs were manifested in almost every case.

I wish to express my cordial thanks to the male nurses of St. David's Hospital for their keen and efficient co-operation in conducting this investigation.

BIBLIOGRAPHY

- Everett, G. M., and Richards, R. K. (1944). *J. Pharmacol.*, **81**, 402.
 Lennox, W. G. (1945). *J. Amer. med. Ass.*, **129**, 1069.
 — (1947). *Ibid.*, **134**, 138.
 Richards, R. K., and Everett, G. M. (1944). *Fed. Proc.*, **3**, 39.

The Merseyside Hospitals Council Report for 1946, *Carefree Convalescence*, is a pleasantly illustrated pamphlet with a brief account of the after-care arrangements that the Council has developed during the last twenty years. The Council has continued to acquire houses for convalescent homes, and suggests that the increasing demand for such facilities likely to rise under the National Health Service might be met in part by voluntary assistance. Four members of the Council have been appointed to the Liverpool Regional Hospital Board.

Medical Memoranda

A Fatal Case of Agranulocytosis Associated with "Tridione" Therapy

Now that tridione is being used for the treatment of certain types of epilepsy it is of interest to record the following case. This substance seems to have a high therapeutic value. Nevertheless, until extended use of it proves otherwise, it seems that it should be used with care owing to a possible depressant action on the granulocyte precursors in the bone marrow.

CASE HISTORY

A boy aged 11 had suffered from petit mal for over three years, during which time he had received amphetamine sulphate ("benzedrine") in doses of 0.01 to 0.025 g. daily. For 53 days he received four 0.3-g. tablets of tridione daily. On the 25th day of receiving tridione he developed an urticarial rash on the thighs which faded in two days. On the 51st day of tridione therapy he became ill with gingivitis and a temperature. He lived for 21 days after ceasing tridione. He received sulphathiazole (a small total amount) and penicillin by injection without any helpful effect.

When examined nine days before death he repeatedly complained of sore throat, and was very pale. The mucous membranes were of a good colour, the gums were hypertrophied a little and very red, the tongue was furred and had an ulcer on the left margin. The fauces were somewhat red, but there was no lesion. The upper and lower cervical glands and a gland on the edge of the jaw were enlarged. The left submaxillary gland was enlarged and painful. The trachea was pushed to the right. There was tenderness in the right iliac fossa, where a movable tumour 2 by 2 in. (5 by 5 cm.) was felt. The spleen was slightly enlarged, as were the glands in the groins and axillae.

A radiograph of the chest revealed a shadow in the mediastinum displacing the trachea to the right. A blood count showed: Hb, 44%; R.B.C., 2,730,000; colour index, 0.8; W.B.C., 800 per c.mm. A differential count showed: all lymphocytes and no granulocytes; there were abundant platelets; after a prolonged search no "blast" cells were seen; all the white cells were mononuclears in type, and immature. A trace of albumin was present in the urine. A sternal puncture marrow smear revealed an aplasia of the erythroblastic tissue with a primary agranulocytosis.

Treatment consisted of blood transfusion and administration of pyridoxin and plexan. For two days before death he had profuse yellow diarrhoea. Later blood examination showed no change.

Abnormal Post-mortem Findings.—**Bowel:** Small yellow sloughing ulcers in lower foot or so of ileum in Peyer's patches, which were hyperplastic; gross swelling, redness, and ulceration of lower 3 in. (7.5 cm.) of small bowel, ileo-caecal valve, and caecum; multiple yellow ulcers in ascending colon; mesenteric glands +. **Liver:** Dark from free iron +. **Spleen:** Enlarged; free iron +. **Suprarenals:** Greyish with little lipoid. **Brain:** Greyish, especially cortex. **Bone:** Dark-red marrow in sternum, ribs, vertebrae, femur.

Microscopical Findings from Post-mortem Material.—The tumour in the right iliac fossa showed non-specific ulceration and gross oedema. **Lumbar vertebra section:** Macroscopically the bone marrow is very red; microscopically there is some erythroblastic (normoblastic) hyperplasia, an almost complete absence of myeloid elements, and an approximately normal number of megakaryocytes.

COMMENTARY

The bone section shows that a complete aplasia of the granulocyte precursors in the marrow had supervened. The amount of sulphathiazole seems much too small to have caused this depression (over 30 g. has usually been taken in agranulocytosis due to sulphonamides). Tridione is strongly inculpated. It will be noticed that about half-way through his tridione course (25th day) the patient developed a rash. Two other children on tridione for epilepsy developed rashes and diffuse lymph-gland enlargement. In their case tridione was stopped immediately the rash appeared, and they recovered uneventfully without abnormality in the blood picture.

If during the course of tridione therapy any generalized rash, lymphatic enlargement, undue redness of gums, anaemia, or changes in the white cell count appear it would be wise to cease using tridione.

I have to thank Dr. E. A. Hunter, senior physician in charge of the case, for permission to publish and Dr. T. N. Gledhill for his report on the marrow section.

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