The Tryptophan Load Test in the Syndrome of Infantile Spasms with Oligophrenia

by B D Bower MD MRCP DCH (*Birmingham*)

Pædiatricians are familiar with the rare and tragic type of infantile epilepsy variously known as infantile spasms, lightning fits, salaam spasms or Blitz-Nick-und-Salaam-krämpfe. The tragedy lies in the fact that the malady often strikes an apparently normal infant and causes severe mental regression which is usually permanent even though the epilepsy may finally die out. We are ignorant of the nature of the cerebral insult in infants with such a history (the cryptogenic group), although in some cases immunizing procedures are suspect. An approximately equal number of infants develop these characteristic fits as a consequence of recognizable cerebral disease or damage, which is usually prenatal or perinatal; but the blow is less devastating in this group (the symptomatic group), as these children have been mentally retarded from birth and we have a reason for their epilepsy and mental handicap.

Gastaut (1960) has divided the history of the study of infantile spasms into three periods. The first, the clinical period, was concerned with delineating the clinical features and natural history. Then in 1952 he (Gastaut & Rémond 1952) and Gibbs & Gibbs (1952) in the U.S.A., described the chaotic epileptic EEG pattern called by the latter 'hypsarrhythmia'; this was the start of the second or EEG period. I wish to emphasize that hypsarrhythmia is a descriptive term for an EEG pattern, not a disease, and the terms 'infantile spasms' and 'hypsarrhythmia' are not synonymous. The two characteristics of hypsarrhythmia are chaos and high amplitude and a truly hypsarrhythmic record is, in our experience, found in only a little more than half the first records of cases of infantile spasms (Bower & Jeavons 1959). The remaining cases have an epileptic but not a hypsarrhythmic record. A normal EEG is therefore very much against the diagnosis. A hypsarrhythmic record is almost diagnostic but it is not uncommon to find a less specific epileptic record.

The third period, the period of hormone treatment, started in 1958 with Sorel's discovery that corticotrophin can stop the spasms and produce a normal EEG pattern (Sorel & Dusaucy-Bauloye 1958). This has been confirmed by many, and now in 1961 it is possible to assess the results of treatment with this and other hormones more precisely, although not yet as clearly as one would like. As these results are relevant to what follows, our findings at the Children's Hospital, Birmingham, are briefly described.

We have treated 33 children. Of these 19 are classified as cryptogenic and 14 as symptomatic. Most of the symptomatic group are children with clear evidence of cerebral birth injury. Corticotrophin, prednisolone or dexamethasone was used. A course lasted at least a month, and dosage was at or above the accepted levels for full therapeutic effect in other diseases. There was little difference between the immediate results of each drug and they will not be considered separately. In 31 of the 33 patients the EEG improved on treatment and the spasms became fewer; in 27 spasms stopped altogether. Fig 1 shows a good result. EEGs were taken twice weekly and each record was given a score according to a system devised by my colleague, Dr Peter Jeavons (Jeavons & Bower 1961). Points are given for various abnormal features; hypsarrhythmia scores high (over 12) and more organized epileptic records score lower, while a normal record or one showing a non-specific abnormality scores 0 or 1. After the start of corticotrophin therapy there was a steady fall in score and a cessation of spasms, and in this case the improvement has been maintained for eighteen months. In two-thirds of our cases, however, there has been a relapse after treatment was stopped, and this was most marked in the symptomatic group. The most disappointing feature of treatment is the failure of mental improvement over the period of follow-up in spite of an initial promise during treatment. We have used Griffiths' testing (1954) before and on several occasions after treatment, and in only 3 of the 23 who have been followed longest has there been a significant improvement (Bower & Jeavons 1961). This result is no better than that in our untreated series (Jeavons & Bower 1961).

This very definite effect of corticotrophin and adrenal steroids upon the epilepsy and upon the EEG, even though temporary in many instances, was surprising in 1957 and is still unexplained. It is something more fundamental than the effect of the anticonvulsants, for such an improvement in the EEG appearance is never produced by anticonvulsants, which are clinically ineffective in this condition. It is not due to correction of hypoglycæmia, for this is never present. Nor is there any evidence of any major water-and-salt imbalance (although at the cellular level this would be difficult to detect), and this seems unlikely; dexamethasone, a corticoid with a minimal effect on water-and-salt balance, seems as effective as corticotrophin. An anti-allergic or anti-inflammatory action is also an unsatisfactory explanation, since there is a very definite improvement in some of the symptomatic cases, in whom the brain

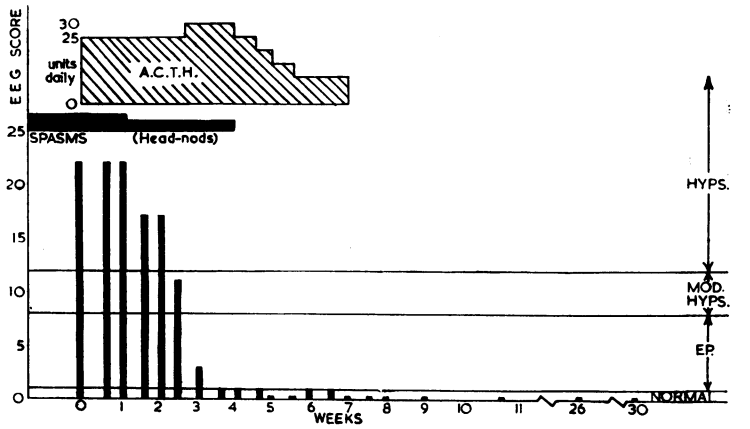

Fig 1 *Improvement of spasms and EEG on corticotrophin*

damage was caused by mechanical or anoxic factors operating several months before the drug was given. A more attractive hypothesis is that adrenal steroids cause maturation of enzyme systems which raise the epileptic threshold, and which have been disturbed by the cerebral insult, whatever its nature. There is experimental evidence that steroids can cause increased enzyme activity in animals (Knox *et al.* 1956).

Cochrane (1959) found evidence of pyridoxine deficiency, that is an abnormal tryptophan load test, in five patients with the syndrome of infantile spasms and mental retardation; and he was satisfied that there was a clinical and EEG improvement after large doses of pyridoxine were given. This report stimulated us to apply the tryptophan load test to our patients before hormone treatment and during treatment to see if the beneficial action of corticotrophin and adrenal steroids could be explained by a corrective action on disturbed pyridoxine metabolism.

Pyridoxine, usually as pyridoxal phosphate, is needed as co-enzyme in an almost embarrassingly large number of cerebral metabolic processes, and it is not difficult to imagine severe disturbance of brain function when it is deficient. For instance, it is needed in the Krebs cycle and for making glucose available as a source of energy. Two metabolic processes seem particularly relevant to the syndrome under consideration. Pyridoxal phosphate is needed for the formation of serotonin (Fig 2), a substance which is probably very important in cerebral metabolism. It has a sedative action and animal experiment has suggested that it is a powerful inhibitor of synaptic transmission (Marrazzi & Hart 1955), so that deficient formation of serotonin might well lead to convulsions. Pyridoxal phosphate is also needed to form gamma-amino-butyric acid (GABA) in the brain from glutamic acid. A large amount of information has recently been acquired about GABA and its inhibitory properties on the C.N.S. It has an anticonvulsant action; by its administration artificially induced convulsions can be prevented in animals (Hawkins & Sarett 1957) and *grand mal* and *petit mal* fits have been prevented in human beings (Tower 1960).

From these data one is not surprised that pyridoxine-deficient animals develop fits, or that the infants who were given a pyridoxine-deficient dried milk in the United States in 1951 and 1952 developed fits which were immediately relieved

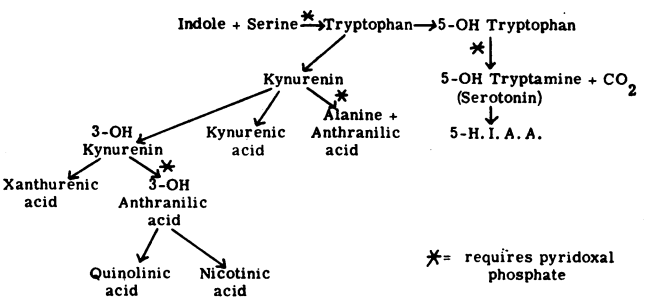

Fig 2 *Tryptophan metabolism* (after *Tower 1956*)

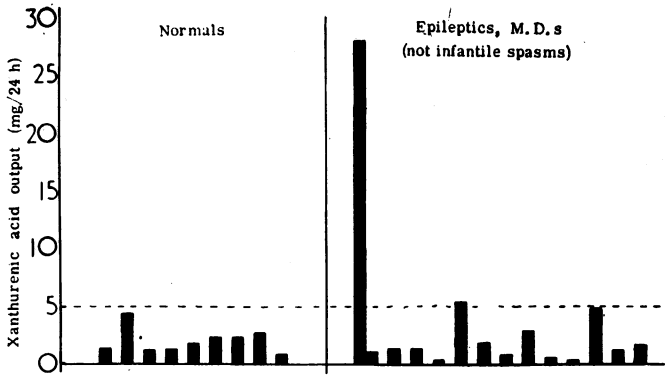

Fig 3 *Results of tryptophan load test – controls. The cross-hatched square shows the result after treatment (i.e. 2·1mg)*

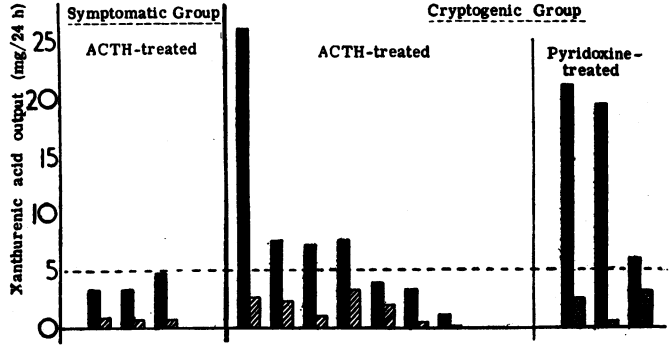

Fig 5 *Results of tryptophan load test – infantile spasms. Solid columns, before treatment. Hatched columns, during treatment. Cross-hatched columns, during treatment with pyridoxine*

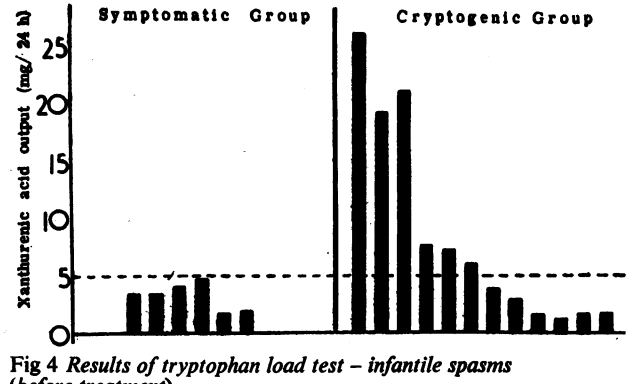

Fig 4 *Results of tryptophan load test – infantile spasms (before treatment)*

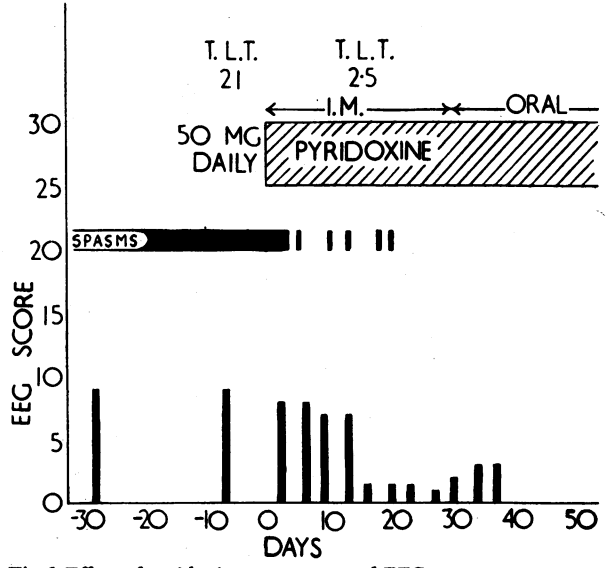

Fig 6 *Effect of pyridoxine on spasms and EEG*

by administration of pyridoxine (*see* May 1954). One of the methods of demonstrating pyridoxine deficiency is to use the tryptophan load test, and the theoretical basis for this test can be understood from Fig 2. Normally one of the paths of metabolism of tryptophan is through kynurenin, 3-OH kynurenin, 3-OH anthranilic acid and nicotinic acid. The third step requires pyridoxal phosphate as a co-enzyme and in pyridoxine deficiency this pathway is blocked. As a result, the alternative pathway is taken and xanthurenic acid is formed. Normally little or no xanthurenic acid is found in the urine, but under these circumstances it can be detected and measured, especially if the patient is given a load of tryptophan beforehand. The details of the test as we have carried it out are as follows:

(1) Collect urine for twelve hours before tryptophan administration. Estimate xanthurenic acid. Multiply by 2.

(2) Give dl-tryptophan: 0·4 g/kg body weight (0–3 years). 0·2 g/kg bodyweight (3 years upwards).

(3) Collect urine for twenty-four hours afterwards. Estimate xanthurenic acid.

(4) Subtract first result from second.

The dose of tryptophan is that which Cochrane (1960) used. Fig 3 shows the result of our attempt to establish a normal figure. Twenty-two children served as controls. On the left are the results in 9 children admitted to hospital for conditions unlikely to be associated with pyridoxine deficiency and with no evidence of disease of the nervous system and no convulsions. On the right are the results in 13 children in whom we had no reason to suspect pyridoxine deficiency but who had convulsions or mental deficiency or both. We excluded children with infantile spasms. The ages range from 2 months to 12 years. Only one result was obviously different from the others, and this child turned out to have pyridoxine deficiency or dependency. He was mentally normal but had had uncontrollable fits since 3 weeks of age. At 18 months the tryptophan load test gave this abnormal result and he was then treated with pyridoxine; his fits were completely controlled and his tryptophan load test result fell from 28·5 to 2·1 mg of xanthurenic acid/24 h. This gave us some confidence in the test. All the other results are below 5 mg/24 h and we felt that this figure should be taken as our normal.

Fig 4 shows the results obtained in 18 children with infantile spasms before corticotrophin or steroid were given. The 6 in the symptomatic group were within normal limits. Of the 12 cryptogenic cases, however, 6 were outside our normal limit of 5 mg; 3 are very definitely abnormal, and 3 are just outside our normal and their significance could be disputed. There is no obvious difference in the history, or in the severity of the epilepsy, the mental defect or EEG abnormality to account for the difference between the patients with an abnormal result and those with a normal one. A severe acute infection can produce an abnormal result but this was not the case here. Nor did their dietary history suggest any deficiency of pyridoxine intake. Our results therefore confirm Cochrane's view that there is some evidence of a disturbance of pyridoxine metabolism in this syndrome, but this applies to only half our cryptogenic cases.

The results of the tests carried out during ACTH or steroid treatment are more uniform. The test was done when there was a diminution or cessation of spasms and a definite EEG improvement: this was usually about two or three weeks after the start of treatment. Nine of the 18 patients whose results were shown in Fig 4 were given a second test during corticotrophin treatment and 1 was tested during dexamethasone treatment. The results of these 10 patients are shown in Fig 5. In every case there was a definite reduction in xanthurenic acid output, whether the pre-treatment result was outside the normal limit or not: in every case but one the treatment figure is less than half the pre-treatment one, and this applied to the symptomatic as well as to the cryptogenic cases. This reduction of xanthurenic acid output on treatment has been confirmed by chromatography of these specimens.

The next logical step was to do what Cochrane had done, use pyridoxine instead of corticotrophin or steroids, but there was an ethical problem here. It seemed most unlikely that these patients had simple pyridoxine deficiency and that a dramatic cure would result. We knew that steroids had a beneficial effect and when we were hopeful that the early use of steroids might improve the mental level, it seemed unjustifiable to withhold hormone treatment, so only 3 children have so far been given pyridoxine. Two were chosen as particularly suitable because they had very abnormal pre-treatment tests (2 of the 3 very abnormal ones in Fig 4) and they were not early cases. In order to get the greatest effect the daily dose of pyridoxine was very large (50 mg daily – the normal requirement is about 1 mg daily for infants) and it was given intramuscularly. All 3 showed improvement in their tryptophan load test during treatment, xanthurenic acid output becoming normal (Fig 5).

The first child showed an encouraging clinical response (Fig 6). Spasms stopped and the EEG improved, although not quite reaching normality. There was no dramatic mental improvement and his development quotient was unaltered, but there was a definite change in his behaviour. Whereas before treatment he had sat in his cot and spent

long periods making bizarre movements with his hands and face, after three weeks these movements stopped and he started to walk round his cot. Unfortunately this improvement was not maintained. He was given the same daily dose of pyridoxine orally and sent home. Two months later his bizarre tics and his infantile spasms started again and his EEG was worse. This time his tryptophan load test was normal. Intravenous pyridoxine produced no change in his EEG over the subsequent two hours and another two months' intramuscular pyridoxine had no effect. In the case of the second child with a very abnormal tryptophan load test, neither intravenous nor seventeen days' intramuscular treatment had the slightest clinical or EEG effect, although the tryptophan load test became normal. In the third child fits stopped and his EEG became normal but he was probably improving spontaneously as one of his previous EEGs had been normal.

More patients must be treated with pyridoxine in order to clarify the question of its usefulness in the infantile spasms syndrome. Already, however, we can say that this is not a matter of simple pyridoxine deficiency. In pyridoxine deficiency there is a rapid response to intravenous injection which is seen in the EEG record within a few minutes. We gave pharmacological doses but the response in the first case took two weeks to occur and during the second period of treatment there was no response. Nor did the second case show any benefit. Nevertheless a definite response occurred in the first case as it did in Cochrane's 5 cases. This fact, and the fact that the clinical and EEG response to hormone treatment was consistently accompanied by an improvement in the tryptophan load test, make one feel that pyridoxine is intimately concerned. Possibly steroids make pyridoxine available to the cell. It is interesting that Low *et al.* (1958) were able to improve a patient with infantile spasms by feeding a diet which was poor in tryptophan. This would suggest that perhaps xanthurenic acid or some other abnormal metabolite is toxic to the brain.

Summary Evidence which suggested pyridoxine deficiency was found in 6 out of 12 patients with the syndrome of infantile spasms and mental deficiency in whom no cause for brain damage was known. In the 6 patients whose brain damage was the result of a perinatal insult there was no such evidence. In all the 10 patients given ACTH or a steroid there was a lower xanthurenic acid output after a tryptophan load, and this coincided with clinical and EEG improvement. It occurred whether the pre-treatment result was normal or abnormal and whether the ætiology was a perinatal insult or was unknown. This suggests that ACTH may improve the patient through increasing pyridoxine availability to the brain. The results of systemic pyridoxine administration to 3 patients show that there is no true pyridoxine deficiency.

Many loose ends remain and I have not answered the question of the ætiology of the condition in the cryptogenic group; nor have I given more than a clue to the mechanism of action of steroids and corticotrophin in this condition. However, such investigations as Cochrane's and ours make one hope that we are now moving into a fourth period in the history of this disorder, the period of biochemical investigation, for this appears to be the most promising field for the future.

Acknowledgments I am indebted to Miss P A M Hughes and Mr Harold Salt for the biochemical estimations, to Dr P M Jeavons for the EEG interpretations and to Professor D V Hubble for helpful advice. My thanks are also due to those pædiatricians who have allowed me to investigate and treat their patients.

REFERENCES

Bower B D & Jeavons P M
(1959) *Lancet* i, 605
(1961) *Arch. Dis. Childh.* **36**, 23
Cochrane W A
(1959) The Syndrome of Infantile Spasms and Progressive Mental Deterioration Related to Aminoacid and Pyridoxine Metabolism. Proceedings of IXth International Congress of Pediatrics, Montreal
(1960) Personal communication
Gastaut H (1960) Personal communication
Gastaut H & Rémond A (1952) *Rev. neurol.* **86**, 596
Gibbs F A & Gibbs E L (1952) Atlas of Electroencephalography, Cambridge, Mass.; Vol. 2
Griffiths R (1954) The Abilities of Babies, London
Hawkins J E jr & Sarett L H (1957) *Clin. Chim. Acta* **2**, 481
Jeavons P M & Bower B D (1961) *Arch. Dis. Childh.* **36**, 17
Knox W E, Auerbach V H & Lin E C C (1956) *Physiol. Rev.* **36**, 164
Low N L, Bosma J F, Armstrong M D & Madsen J A
(1958) *Pediatrics, Springfield* **22**, 1153
Marrazzi A S & Hart E R (1955) *Science* **121**, 365
May C D (1954) *Pediatrics, Springfield* **14**, 269
Sorel L & Dusaucy-Bauloye A (1958) *Acta neurol. belg.* **58**, 130
Tower D B
(1956) *Amer. J. clin. Nutrition* **4**, 329
(1960) In: Inhibition in the Nervous System and Gamma-aminobutyric acid. Ed. E. Roberts *et al.* Oxford; p. 562