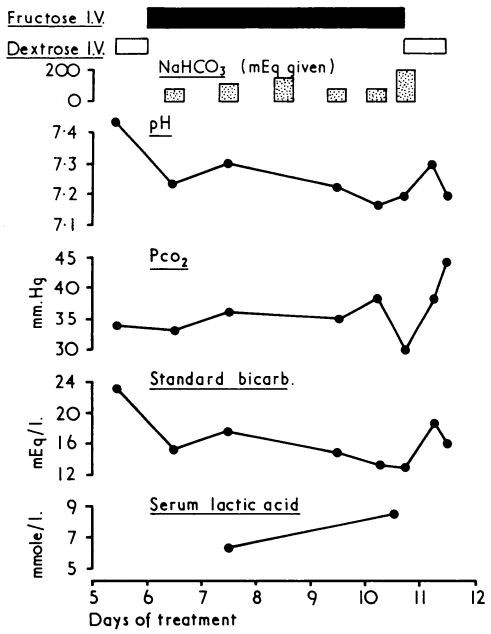

Time relationship between acid-base changes and treatment.

During the terminal 16 hours there was some improvement in acid-base status in spite of anuria. Terminal hypotension and death were due to bleeding from acute gastric erosions. At necropsy the liver was small (weight 870 g), yellow, and necrotic, with no signs of regeneration. The liver necrosis was thought to be due to fulminating infectious hepatitis.

Comment

Since the liver has a major role in removing lactic acid from the circulation defective hepatic metabolism of lactate is likely to be a major cause of lactic acidosis in liver failure. Nevertheless, hypocapnia and hypoxia may contribute. Hypocapnia causes a rise in lactate and pyruvate in proportion to the fall in P_{CO_2} (Mulhausen *et al.*, 1967) and may stimulate lactate production by erythrocytes and muscle. In the presence of hypoxia hepatic anaerobic glycolysis may occur, resulting in lactate production rather than removal (Berry and Scheuer, 1967). Leppla *et al.* (1964) showed that the lactate/pyruvate ratio may be influenced by changes in intracellular H^+ concentration as well as by the proportion of NADH to NAD according to the relationship Lactate + NAD $\rightleftarrows$ pyruvate + NADH + H^+.

Thus if lactate removal is impaired—for example, in diabetes, infection, or alcohol intoxication—minor changes in pH might initiate a severe lactic acidosis. The normal liver metabolizes fructose more rapidly than glucose for two reasons. Firstly, the activity in the liver of fructokinase, an enzyme which initiates fructose breakdown, is four times greater than that of glucokinase, one of the enzymes that initiate glucose metabolism (Heinz *et al.*, 1968), and, secondly, the subsequent steps in fructose utilization are largely independent of phosphofructokinase, whereas this enzyme regulates the rate of glucose metabolism after initial phosphorylation. As a result of rapid fructose breakdown the end products of glycolysis, lactate and pyruvate, accumulate in the blood (Bergström *et al.*, 1968) and the liver may be depleted of enough ATP and inorganic phosphate to reduce protein synthesis to an important extent, thereby impairing the integrity of enzyme systems concerned with lactate removal (Mäenpää *et al.*, 1968).

Magnesium deficiency has been reported in chronic alcoholism and cirrhosis (Flink, 1956) and in hepatic coma. Since many factors concerned with carbohydrate metabolism—in particular coenzyme A (Flink, 1956)—are magnesium dependent magnesium depletion may impair utilization of lactate, but the accumulation of lactate in the present case suggests that it does not impede lactate formation.

We believe that in this patient lactate formation resulting from fructose breakdown initiated the lactic acidosis, since this coincided with fructose therapy and improved slightly when glucose was substituted and the serum magnesium was corrected. The data of Mulhausen *et al.* (1967) show that once established in liver failure lactic acidosis is often irreversible. We feel that fructose is contraindicated in the treatment of liver failure and suggest that ethanol-fructose mixtures should be used with caution if hepatic function is disturbed, since ethanol can also induce lactic acidosis by altering the proportion of NADH to NAD in the liver cell.

We wish to thank Dr. J. Whitfield, of the renal unit, Queen Elizabeth Hospital, for kindly carrying out the lactate analyses.

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Jakob-Creutzfeldt Disease: Treatment by Amantadine

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The subacute spongiform encephalopathy variety of Jakob-Creutzfeldt disease was described in detail by Jones and Nevin (1954). The disorder is characterized by progressive dementia accompanied by pyramidal and extrapyramidal signs, rigidity, and myoclonus, with terminal coma and death usually within a period of weeks or months. Typical E.E.G. changes with repetitive sharp waves appear during the course of the illness, and together with the clinical features constitute a syndrome which may be confidently diagnosed during life (Goldhammer *et al.*, 1971). The discovery by Gibbs *et al.* (1968) that the disease is caused by a transmissible virus has raised hopes that it may prove to be amenable to some specific form of therapy. Idoxuridine, apparently effective in herpes simplex encephalitis, has been tried in one patient in this department (Goldhammer *et al.*, 1971) without benefit. In the case here described the administration of amantadine was followed by encouraging clinical and electroencephalographic improvement.

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Case History

A 65-year-old man was admitted to hospital on 30 March 1971 with a three-month history of increasing mental confusion and

unsteadiness of gait leading to frequent falls. For a year or so previously he had suffered from mild paranoia. Deterioration in his condition led to his admission to a mental hospital, but after a few days of observation he was believed to be suffering from an organic brain syndrome and was transferred to this department. He was conscious on admission but communication was limited and he resented examination. His speech was almost unintelligible; rigidity of the limbs was noted but seemed in part due to voluntary resistance. He was unable to stand or walk but could swallow food offered to him. Routine laboratory examinations showed nothing abnormal. The C.S.F. was under normal pressure and contained 20 mg of protein/100 ml with no cells. The E.E.G. showed a slight generalized abnormality. Cerebral angiography via the right axillary artery showed normal vertebrobasilar and right carotid systems with no evidence of hydrocephalus.

During the next fortnight his condition progressively deteriorated. He sank into stupor, lying mute and immobile on his side in an attitude of flexion, with strong resistance of the limbs to passive stretching. Tube feeding became necessary. The downhill course and the clinical features suggested a diagnosis of subacute spongiform encephalopathy (Jakob-Creutzfeldt disease). The E.E.G. showed typical changes supporting this diagnosis (Fig. 1).

Treatment with amantadine was then begun, 600 mg a day being given in divided doses via the stomach tube. Two days later a dramatic change was seen. He emerged from his stupor, his facial expression showed his awareness of his surroundings, and the limbs were no longer hypertonic. He was fed with a spoon and he even used a napkin to wipe his mouth. An E.E.G. examination four days after the start of therapy showed a slight generalized disturbance only; the sharp-wave pattern of the previous record was not in evidence (Fig. 2).

The improved clinical status was maintained with minor variations for 10 days, when treatment was withdrawn. Within three days he relapsed. He once more sank into stupor and had flexor rigidity and tube feeding had to be reinstituted. The E.E.G. six days after the withdrawal of treatment showed signs of re-emergence of the sharp-wave pattern, though not as distinctly as in the pretreatment phase (Fig. 3). Because of the clinical deterioration amantadine therapy was then restarted, and after a few days improvement was again noted. Within two weeks he was able to sit up in a wheel-chair and exchange a few words of greeting on the daily round. At the time of writing he was no longer tube fed and occasionally fed himself. The E.E.G. three weeks after re-institution of therapy showed a near normal record.

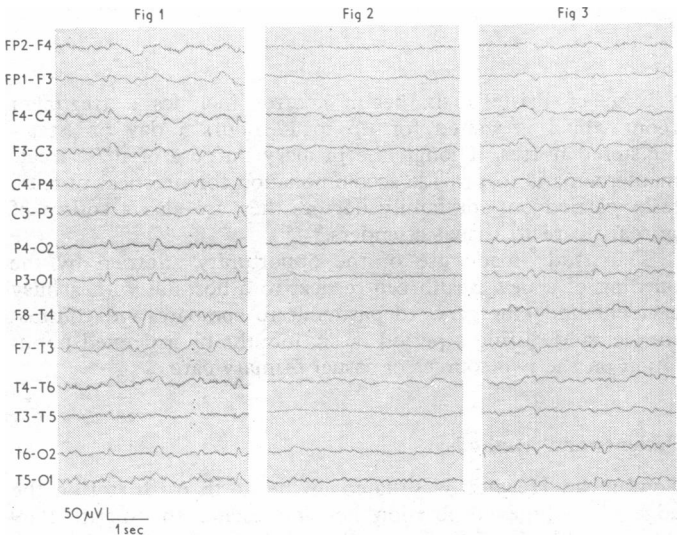

FIG. 1—Record 12 days after admission, with repetitive bisynchronous "triangular" sharp waves. FIG. 2—Four days after start of amantadine. Characteristic sharp-wave pattern no longer seen. FIG. 3—Six days after interruption of amantadine administration. Sharp-wave pattern is seen again though less distinctly than in Fig. 2.

Discussion

The diagnosis in this case is presumptive and lacks histological confirmation. The clinical course and the characteristic E.E.G. pattern, however, were in no way different from those in six other proved cases seen in this department in the past three years and studied postmortem. The expected downhill course in the present patient was halted and partially reversed after the administration of amantadine. Relapse and subsequent improvement were related to withdrawal and resumption of treatment.

Amantadine, originally used as a prophylactic agent against influenza A2 virus, was accidentally found to be efficacious in the treatment of Parkinsonism (Schwab *et al.*, 1969). This combination of properties—namely, an antiviral action and an evident ability to cross the blood-brain barrier—led to its choice as an agent worth trying in Jakob-Creutzfeld disease. Furthermore, it has been shown in Parkinson's disease trials to be suitable for long-term administration. As its mode of action is little understood speculation about the way in which apparent benefit resulted in this case is at present unwarranted. The rather rapid effect, however, could possibly imply a biochemical rather than an antiviral mechanism. In this respect a certain parallelism may be pointed out to the even more dramatic effect reported after massive levodopa administration in hepatic coma; restoration of consciousness and reversal of E.E.G. disturbances were obtained in less than an hour (Parkes, 1970).

Though improvement in the patient treated by this drug continues to be maintained it is of course too early to forecast the ultimate outcome. Nevertheless, as the disease in this form has in my experience been uniformly and rapidly fatal it was considered justifiable to record the results at this stage in the hope that others may be willing to make additional trials.

Amantadine was kindly supplied by Assia Chemical Laboratories, Tel Aviv.

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