Hepatic Encephalopathy

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Because the functional reserve of the liver is large, regulation of blood composition becomes inadequate only if many hepatocytes are destroyed, as in acute hepatic necrosis, or if, in addition to some destruction of hepatocytes, there are circulatory abnormalities that reduce the effectiveness of surviving liver tissue. This is the situation in cirrhosis in which portal blood may bypass functioning hepatocytes through intrahepatic shunts, through the opening up of portal systemic collaterals or through a surgically created anastomosis for the relief of portal hypertension. Nitrogenous substances absorbed from the bowel can thus pass directly into the systemic circulation and it is for this reason that Sherlock introduced the term 'portal systemic encephalopathy'. There is little doubt that intoxication of the brain by such substances is important but, since shunting is not always the major factor, I prefer to use the simpler term of hepatic encephalopathy, distinguishing at the same time acute, chronic, and acute-on-chronic varieties.

ACUTE ENCEPHALOPATHY

This is seen in its most characteristic form in a patient with fulminant viral hepatitis or with an acute toxic hepatic necrosis from an overdose of paracetamol—the commonest cause today. Jaundice may be minimal during the first few days of the illness and, indeed, the first symptoms are often those of the encephalopathy, with disorientation, confusion, and sleepiness, rapidly leading to drowsiness and coma. If only these clinical manifestations were more widely recognised it would prevent such patients being admitted initially to psychiatric wards, unfortunately all too common in my experience, and being given sedative drugs, all of which are potentially harmful and serve only to accelerate the onset of coma. The severity of encephalopathy provides one of the best indices of the likely prognosis. The survival rate recorded by Trey and Davidson (1970) was 66 per cent in those with Stage II encephalopathy, compared with 17·6 per cent in those with Stage IV coma.

Factors in Pathogenesis and their Management

The primary site of action is thought to be on the alerting mechanisms situated in the reticular formation of the brain stem. The responsible metabolic

disturbance is most likely to be multifactorial, which explains why, despite much effort by many research workers in the past decade, all the attempts to isolate a single toxic substance have failed. Certain of the metabolic changes that are of relevance to treatment need to be briefiy mentioned (Table 1).

TABLE 1. Some factors in hepatic encephalopathy

Primary	Ammonia Short-chain fatty acids Neurotransmitters 'False neurotransmitters' Dopamine, Serotonin
Secondary	Anoxia, hypoglycaemia, low pCO_2

Considerable elevation of blood ammonia (because of failure of metabolism by the damaged liver) is one of the most consistent changes, although no exact correlation between blood level and clinical symptoms can be observed. Hyperammonaemia, however, almost certainly has a deleterious effect on cerebral metabolism, leading to an increased formation of glutamine in the brain with diversion of the energy supply on which normal synaptic function and consciousness depend. There may also be an increased formation of the inhibitor neurotransmitter substance gamma aminobutyrate (GABA).

The standard measures used to lower the blood ammonia in these patients, and also the levels of other possible toxic nitrogenous substances of intestinal origin, comprise withdrawal of oral protein, emptying of the bowel by an enema, and neomycin therapy to reduce bacterial growth in the colon. There is little controlled evidence of their value, and their use is based on the beneficial effects observed in chronic encephalopathy.

Ammonia is freely dialysable and blood ammonia can easily be lowered by haemodialysis. Although this is rarely followed by clinical improvement it is important to remember that the rate of passage of substances from the blood to the brain may be much less than into other tissues; for instance, the equilibration of manitol between plasma and CSF may take more than 24 hours.

Failure of the patient to improve with these measures may be due to the persisting effects of other toxic substances such as short-chain fatty acids. These are known to be increased in the blood of patients with hepatic failure and in animals will induce EEG changes similar to those observed in human hepatic coma.

Recent studies in collaboration with Dr G. Curzon have shown changes in the two important neurotransmitter substances—dopamine and serotonin. Dopamine is synthesised in the thalamus from laevo-dopa which, in turn, is

derived from plasma tyrosine and phenylalanine (Fig. 1). Another amino acid, methionine—in its active form S-adenosyl methionine—participates in the

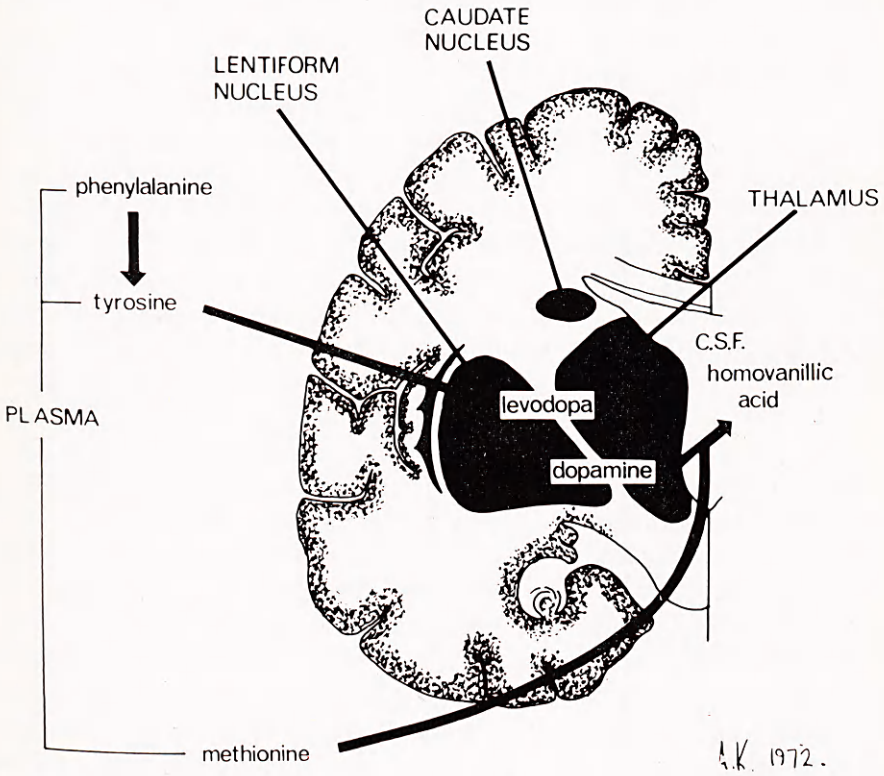

Fig. 1. Simplified drawing of dopamine synthesis and breakdown in the brain (drawn by Dr A. Knell).

degradation of dopamine to homovanillic acid (HVA) which is excreted into the CSF. We have found, as others have done previously, a striking increase in the concentrations of these three amino acids in the blood (Knell *et al.*, 1972). At the other end of the pathway, we have found increased levels of the end product HVA in the CSF of many of these patients (Fig. 1). This indicates an increased metabolic breakdown of dopamine and could be a reflection of an increased production.

In the CSF there were also increased levels of 5-hydroxyindole acetic acid (Fig. 2). This is the end product of the metabolic breakdown of serotonin (5-hydroxytryptamine) which is an important neurotransmitter in the hypothalamus and mid-brain, where it is synthesised from 5-hydroxytryptophan, the precursor of which is tryptophan. But the situation is complex, because

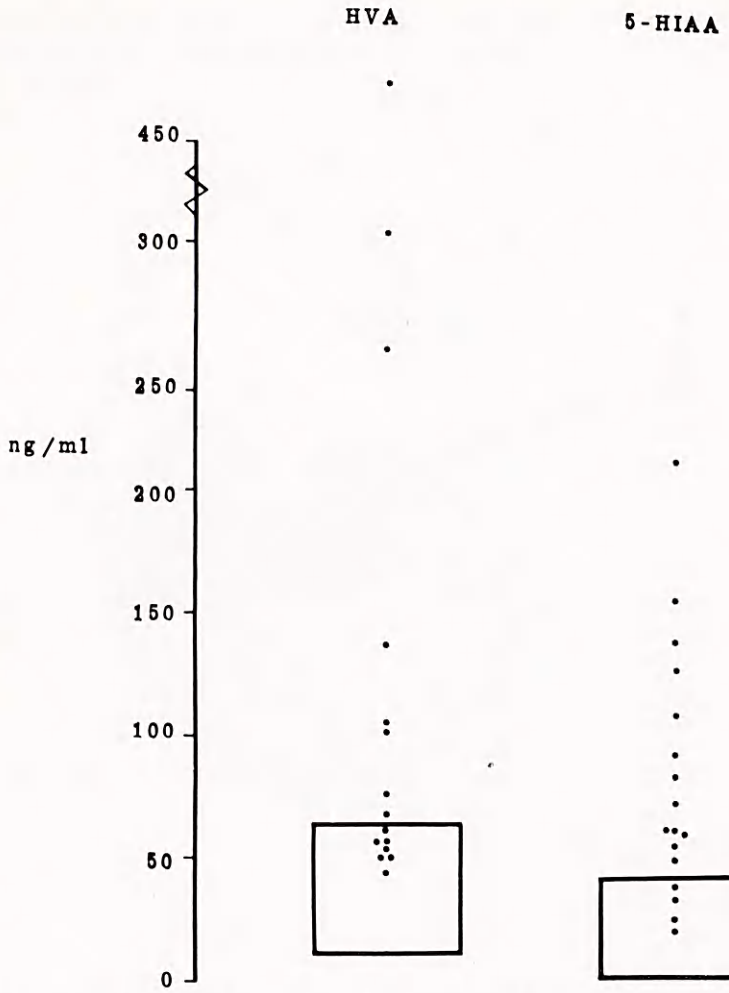

Fig. 2. Homovanillic acid and 5-hydroxyindole acetic acid in the CSF of patients with acute encephalopathy (from Knell *et al.*, 1973),

most of the tryptophan in the blood is in the bound form, and only the free fraction is able to penetrate the blood-brain barrier. However, in preliminary studies, we have found the amount of free tryptophan in the blood to be considerably increased in patients with fulminant hepatic failure. We have also shown in studies on the pig with surgically induced hepatic necrosis that the concentration of tryptophan is increased in the brain (Curzon *et al.*, 1973).

Could this increase in brain tryptophan or 5-hydroxytryptamine turnover have any special role in the development of hepatic coma? Direct toxicity of

tryptophan itself can hardly be responsible, as up to 25 g daily is given by mouth in the treatment of depression and the plasma-free tryptophan of human subjects has been raised almost a hundredfold by tryptophan infusion without grossly apparent effect. Another possibility is that the raised 5-hydroxytryptamine turnover enhances the central toxicity of other substances accumulating in subjects with liver disease. A pharmacological analogy is the apparent role of brain 5-hydroxytryptamine in determining the toxicity of caffeine in the mouse.

The likely increase in dopamine turnover requires further study, and our findings do not explain the beneficial though temporary effect that a large dose of L-dopa may produce in severe encephalopathy, both with respect to the level of consciousness and the EEG pattern. Fischer and Baldessarini (1971) suggested that the effect was due to the flushing away by L-dopa of false neurotransmitter substances. These, they postulate, are derived from various amines of intestinal origin, which, because of failure of metabolism in the liver, reach the brain and, after undergoing beta-hydroxylation locally, replace the normal neurotransmitters. In the rat with hepatic coma, they found increased concentrations of one such substance, octopamine, in the brain as compared with controls. But the fact that these substances accumulate with liver failure does not necessarily mean they cause the encephalopathy.

Damage to the brain may also ensue from secondary influences (Table 1); for instance, from anoxia as a result of the cardio-respiratory arrests so common in fulminant hepatic failure and representing another effect of the brain-stem depression. Hypoglycaemia is an occasional development, and the low pCO_2 resulting from the hyperpnoea—often such a striking feature in the early stages—may reduce cerebral blood flow perhaps even to critical levels. The prevention of such secondary brain damage is one of the major aims of the intensive care and monitoring of these patients.

The course of illness in two patients illustrates certain other aspects of the management of these patients.

Case 1. Occurrence of Cerebral Oedema

The patient was a woman who had taken a large dose of paracetamol in a suicidal attempt (Fig. 3). Hepatic damage was severe, as shown by the very prolonged prothrombin time, but with treatment by fresh frozen plasma and heparin to control the synthetic defect and intravascular coagulation respectively (Williams, 1972), the prothrombin time improved. The blood ammonia and blood free tryptophan fraction also fell. There was no further rise in serum bilirubin, also suggesting that liver function was beginning to recover. Yet her level of consciousness did not improve and the

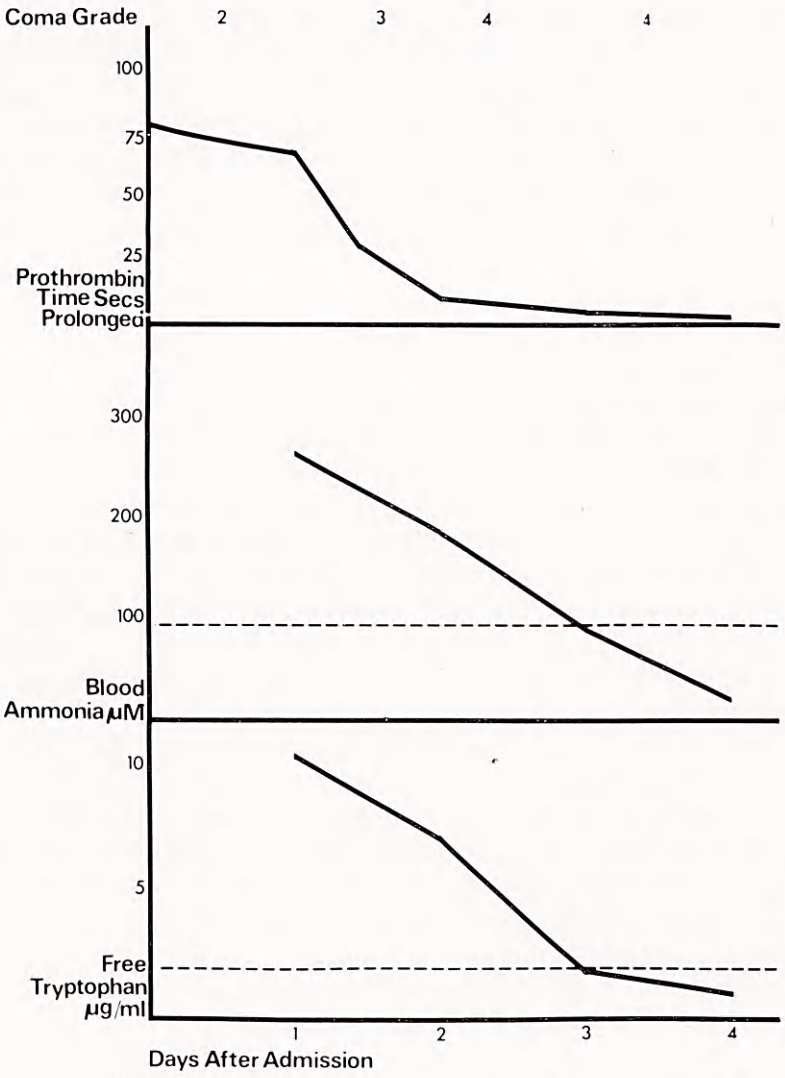

Fig. 3. Course of patient with acute encephalopathy in whom the coagulation defect and liver function improved but conscious level deteriorated due to cerebral oedema.

EEG, which initially had shown some electrical activity, became flat. Death occurred on the fourth day after admission. At autopsy, the liver showed considerable areas of surviving liver; indeed, it seemed that complete restitution of normal structure and function was possible. Section of the brain showed gross oedema. This has also been reported by others, but what

relation it bore to the initial encephalopathy and impairment of liver function, which from all the tested biochemical measurements was improving, is uncertain.

Case 2. Use of Temporary Liver Support

In contrast, in this patient, who had a fulminant viral hepatitis, liver function did not improve. Indeed, it continued to deteriorate despite full supportive therapy (Fig. 4). At this stage it was felt that some form of

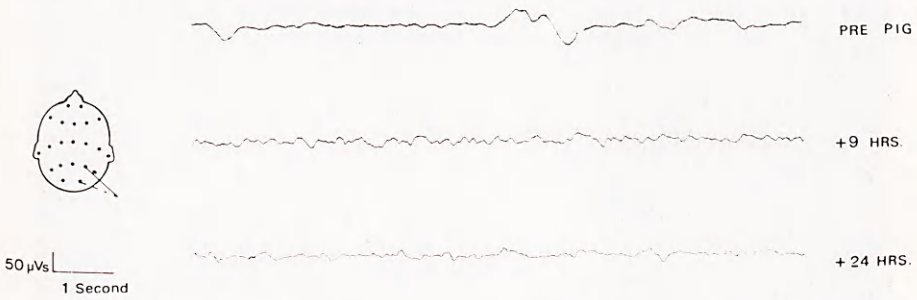

Fig. 4. Beneficial but temporary effect of extracorporeal pig liver perfusion on the EEG of a patient with acute encephalopathy.

temporary liver support was needed to provide the time necessary for the liver to regenerate. To do this, Mr John Winch set up an extracorporeal pig liver perfusion. The pig's liver functioned satisfactorily for a period of $7\frac{1}{2}$ hours. This was associated with very considerable improvement in the biochemical changes of liver failure present in the patient, as shown by a fall in serum bilirubin from 18 to 6 mg/100 ml and improvement in the prothrombin time from 26 to 9 sec. Indeed, direct synthesis of fibrinogen from the pig's liver into the patient's circulation could be demonstrated. There were also striking falls in the blood levels of methionine, tyrosine, and ammonia. The patient's EEG also improved but at the end of 24 hours it was back to the pre-perfusion trace, and she died the following day. However, one can hardly expect such a relatively short period of liver support to restore the severe metabolic derangements that have developed in patients by this stage of the encephalopathy. Our efforts now are directed towards the development of an artificial system to provide the type of reproducible and repeatable liver support that these patients need.

CHRONIC AND ACUTE-ON-CHRONIC ENCEPHALOPATHY

This condition can effect all parts of the nervous system, and may mimic many unrelated psychiatric or neurological diseases. It is often missed because the

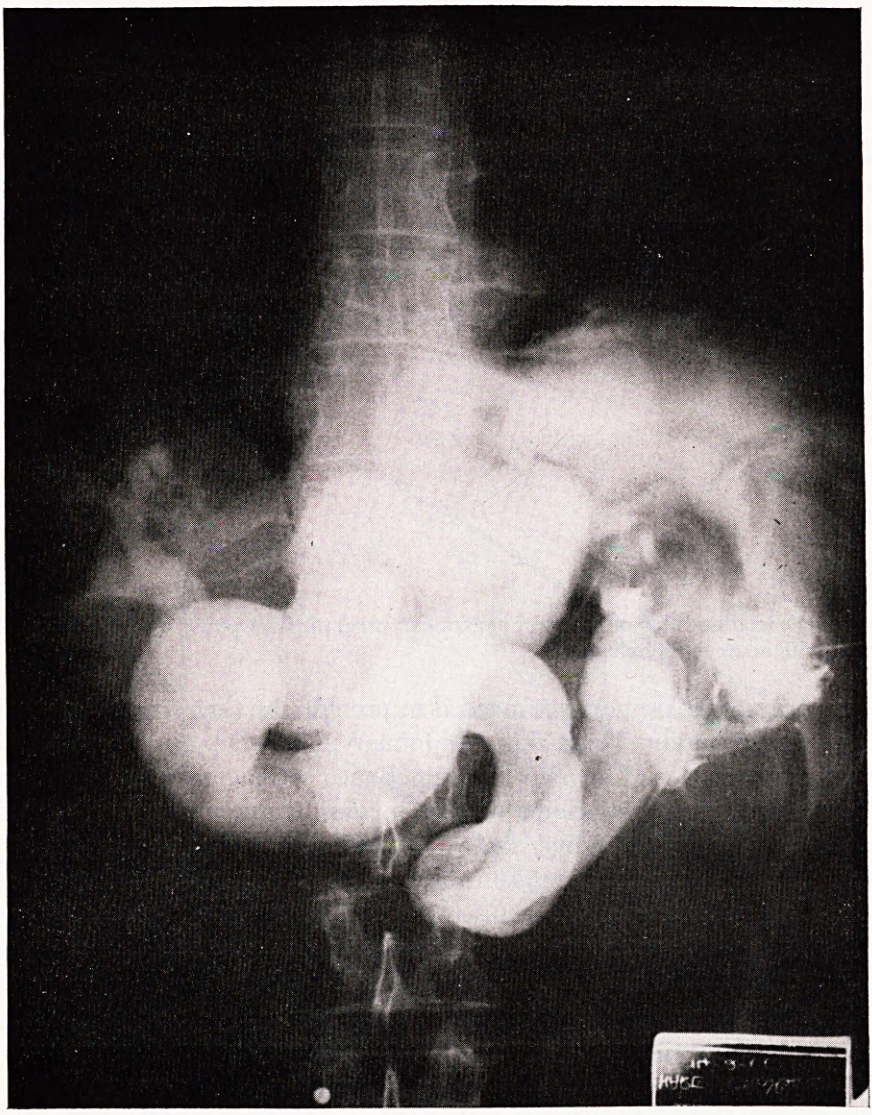

Fig. 5. Splenic venogram of a patient with chronic encephalopathy, who presented as an unexplained brain-stem lesion, showing the enormous portasystemic collateral circulation present.

neurological features may be disproportionate to the manifestations of hepatic failure. I well remember being asked to see a patient in a well-known neurological centre who was being investigated for an unexplained and rather bizarre brain-stem lesion. The only signs of the underlying cirrhosis were a

few spider naevi, but there was no doubt on the splenic venogram about the enormous collateral circulation (Fig. 5).

The first symptoms are often personality deterioration, abnormal behaviour, euphoria or irritability, and altered sleep rhythms. Patients may notice loss of concentration and intellect, and this can be assessed conveniently by the Reitan trail test (Zeegen *et al.*, 1970). Handwriting deteriorates, and a daily specimen is a useful guide to clinical progress. This is in part due to a difficulty of co-ordination of visual and motor processes called constructional apraxia, which can be assessed by asking the patient to copy a five-pointed star, or a match-stick pattern, although these tests may be difficult even for the doctor.

Involvement of the extrapyramidal system is another feature. Facial expressiveness and spontaneous movements are reduced, and there is often increased muscle tone and a coarse tremor, to be distinguished from the better known 'flapping tremor'. The latter is a periodic, transient collapse of posture most obvious in the outstretched hands: it is sometimes seen in renal or respiratory failure. The pyramidal system is often spared, but spasticity may occur and sometimes paraplegia dominates the clinical picture (Pant *et al.*, 1968). Other unusual manifestations include schizophrenia-like reactions, cerebellar atrophy, and focal neurological signs (Read *et al.*, 1967).

Acute exacerbations can be easily provoked by simple factors such as constipation, injudicious protein in the diet, and stopping lactulose or neomycin, or by major events such as an acute infection, excessive use of sedatives or diuretics, or by bleeding from varices. The clinical features and biochemical changes during an acute exacerbation of chronic encephalopathy are very similar to those disorders seen in acute encephalopathy developing in fulminant viral or toxic hepatitis. These patients can deteriorate extremely rapidly: for instance, a patient seen recently was alert in the morning, confused in the afternoon, delirious during the night, and unrousable next morning. Recovery can be similarly abrupt and unpredictable, and this is one reason why it is difficult to assess the effectiveness of therapy.

Treatment

The measures shown to be of most value in these patients are avoidance of constipation by mild purgation, reduction of dietary protein, and the use of neomycin and lactulose (Table 2).

Although lactulose is a laxative, its beneficial effect in chronic encephalopathy is also related to a decreased pH of the faeces, causing a fall in blood ammonium. In addition, it is essential to avoid any of the factors that can cause an acute exacerbation, and here sedatives constitute one of the main

TABLE 2. Management of chronic encephalopathy

Mild purgation, Low protein diet ↓ Neomycin, Lactulose ↓ ?? L-dopa, Colonic exclusion ↓ Liver transplantation	*Avoid*	Sedatives, hypokalaemia Excess diuresis
	Control	Variceal bleeding
	Beware of	Infections—septicaemia —ascitic fluid

problems. Morphine is notoriously dangerous, but in fact all sedatives are harmful. If sedation is absolutely necessary, then phenobarbitone or diazepam are probably the safest. The increased effect of sedatives in these patients probably does not result from reduced metabolism by the liver but from an increased sensitivity of the brain.

Diuretics are also harmful if the induced diuresis causes a weight loss of 0·5 kg/day or more, or if potassium depletion results.

If these measures do not control the encephalopathy, two other possible approaches need to be considered, both of uncertain value. The first is surgical exclusion of the colon, which has given good results in selected cases with well-preserved liver function. But even then, there is a substantial early mortality and the overall prognosis is not improved (Resnick *et al.*, 1967).

The second followed on from the observed arousal effect of L-dopa in acute encephalopathy. It may also have an effect in chronic encephalopathy. Two of the four patients we have treated showed substantial objective signs of improvement. One did not respond, and the fourth, even on small doses, developed severe vomiting and an exacerbation of the encephalopathy. The drug must be given with considerable caution.

Acute exacerbations of chronic encephalopathy are treated by complete withdrawal of dietary protein and intravenous dextrose supplemented with potassium. Several groups have reported on the use of intravenous glutamate or arginine to stimulate the synthesis of urea from ammonia, but no carefully controlled studies of their value have been reported. We have recently given ornithine-alpha-ketoglutarate to 16 cases of chronic and acute-on-chronic encephalopathy: the EEG improved in nearly every case and, in some, the clinical response was encouraging.

Liver Transplantation

Finally, I must mention transplantation of the liver, for there comes a stage in chronic encephalopathy when the patient's life is a misery to himself and his family. Initially, we thought that the manifestations of chronic

encephalopathy would be irreversible because of structural changes in the brain, but this has not been our experience. We have now seen two patients with severe chronic encephalopathy and one with an acute exacerbation of a chronic encephalopathy who have made a complete neurological and electroencephalographic recovery after transplantation (Parkes *et al.*, 1970).

The patient I would mention briefly could serve as a summary of the management of chronic encephalopathy, indeed of cirrhosis (Fig. 6). This man

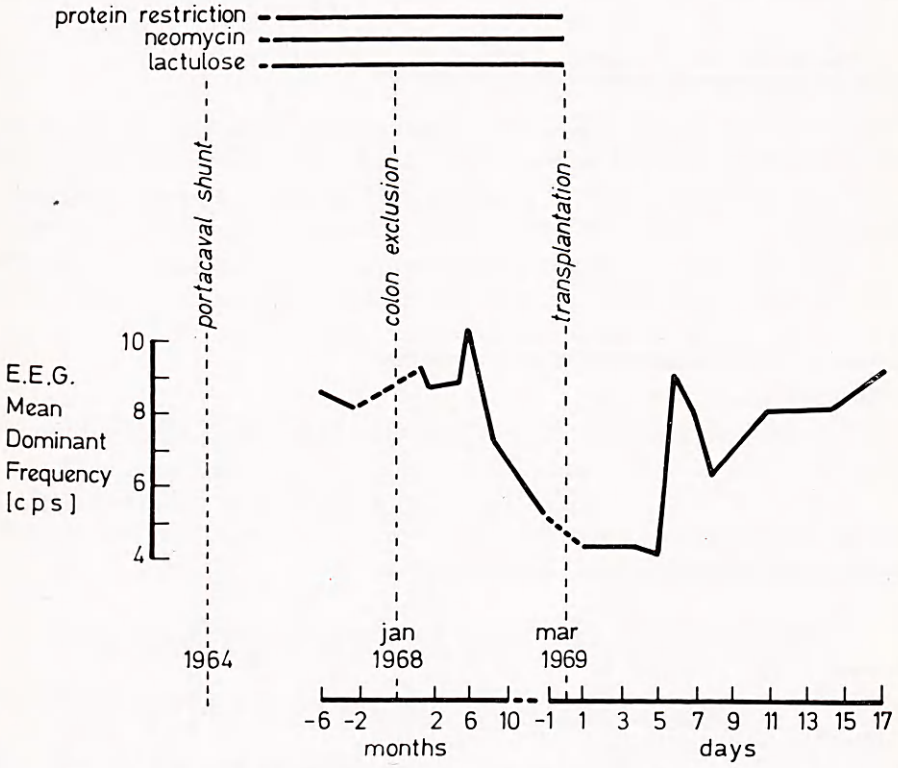

Fig. 6. Course of chronic encephalopathy in patient G.K. during the years preceding and immediately after liver transplantation (from Williams, 1970, courtesy *British Medical Journal*).

had contracted serum hepatitis while in the Far East during the Second World War, but the first manifestation of the cirrhosis following this infection was not until 1963 when he bled from oesophageal varices. For this, a portacaval anastomosis was carried out. Subsequently he developed encephalopathy, initially not too severe and controlled by a low-protein diet, neomycin, and lactulose. When his condition began to deteriorate, a colonic exclusion

operation was carried out, with some improvement both clinically and in the EEG, as shown by the rise in the mean dominant frequency, a measure of the electrical activity of the brain. Finally, because of increasing incapacity, transplantation was performed, with very rapid improvement in the EEG and striking improvement clinically.

CONCLUSIONS

In acute encephalopathy due to fulminant hepatic failure, our main concern is the prevention of the secondary brain damage from hypoglycaemia, hypoxia and cerebral oedema. Control of the primary cerebral intoxication at present depends on spontaneous recovery of liver function and there are no adequate means by which this can be hastened. In the patient with an acute exacerbation of chronic encephalopathy rapid control of precipitating factors such as oesophageal bleeding, hypokalaemia, or excess diuresis, is of major importance. In chronic encephalopathy, some symptomatic improvement can be obtained by protein restriction, neomycin, and lactulose. This may be maintained for some years but often there is a slow deterioration and in such patients liver transplantation merits serious consideration.

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