Progress report

Progress in the treatment of chronic portasystemic encephalopathy

Hepatic encephalopathy resulting from acute episodes of hepatic decompensation in patients with chronic liver disease is to be distinguished clinically from the chronic variety – less common and seen in its most characteristic form in patients with large portasystemic shunts.¹⁻⁵ Although such shunting can develop spontaneously, it is more frequently seen in association with a surgical shunt procedure. With the presently favoured selective shunt procedure, where portal flow to the liver is maintained, the development of severe encephalopathy is lower. When measured by psychometric tests, however, it may be as high as 80%.⁶ This clinically latent impairment in mental function may affect a patient's daily functions. Indeed, in a recent study only 15% of patients with chronic liver disease and portal hypertension who were not clinically encephalopathic were regarded as fit to drive as judged by a battery of psychometric tests.⁷ The toxic factor or factors responsible for encephalopathy, whether occurring acutely or in the chronic syndrome, are not yet known. Candidates include the synergistic effects of ammonia, fatty acids and mercaptans, aminobutyric acid (GABA), and plasma amino acid imbalance.⁸⁻¹¹ Although our understanding of the basic pathophysiological mechanisms is still incomplete, recent research has provided reasons for the effectiveness of certain treatment modalities and a theoretical framework for manipulation of the amino acid profile.

Protein restriction

Several potential toxins are thought to arise from the action of intestinal bacteria on gut protein and both Sherlock¹ and Summerskill³ found that encephalopathy improved with dietary protein restriction, whereas excess dietary protein precipitated deterioration. Recent studies have shown that protein breakdown rates in cirrhosis with or without encephalopathy are significantly higher than normal and are associated with lower rates of protein synthesis.¹² The minimum protein requirement of such patients is about 50 g/day.^{12 13} Thus, although protein restriction has become a cornerstone of treatment of portasystemic encephalopathy, failure to provide adequate protein may lead to progressive depletion of body protein, a situation which is associated with reduced host defence to infection.¹⁴ Attention has therefore been focused on alternative ways of providing adequate protein without precipitating encephalopathy.

NON-MEAT SOURCES OF PROTEIN

Dairy protein

Early studies have suggested that the type of dietary protein may be as

important as the quantity in terms of its ability to produce hepatic encephalopathy.^{15 16} In an uncontrolled study of three patients with chronic encephalopathy from cirrhosis Fenton *et al*¹⁵ found that 50 g of milk and cheese protein were tolerated better than an equivalent amount of protein from meat. It was thought that dairy protein had a lower ammonia content than meat protein. Similarly, Bessman *et al*¹⁶ showed that blood was more ammoniagenic than an equivalent protein meal of casein.

Vegetable protein

Greenberger *et al*¹⁷ compared the effect of a vegetable protein diet with an animal protein diet in a controlled crossover study of three patients with chronic portosystemic encephalopathy. All three patients treated with the vegetable diet showed an objective improvement (measured on an hepatic encephalopathy index). Furthermore, addition of lactulose to this diet allowed an increase of protein intake to 90 g without encephalopathy. The design of the study, however, makes interpretation of the findings difficult.

Some patients in whom blood ammonia concentrations fell had significantly lower hepatic encephalopathy index scores – that is, improvement – despite a lack of improvement in coma grade or trail test scores. The apparent improvement with vegetable protein would have been less marked if a lower weighting had been attached to the blood ammonia concentration. Nevertheless, the trend seemed to be in favour of vegetable protein, although the greatest improvement was with the addition of lactulose.

In recent controlled trial, de Bruijn *et al*¹⁸ studied eight stable cirrhotics with mild chronic encephalopathy. Equal amounts of mixed protein were alternated with animal protein or vegetable protein for five consecutive one week periods. Patients were assessed on a 25 item routine neurological examination and by computer assisted EEG. The mean dominant EEG frequency was significantly lower (6.6 ± 0.45 Hz) on the animal protein diet than on the vegetable (7.0 ± 0.5 Hz) or mixed protein diet (6.9 ± 0.22 Hz) ($p < 0.05$). The neurological score was not significantly different, although there was a trend towards higher scores on the animal protein diet. Greater differences might have been found if more severely encephalopathic patients had been studied.

A further controlled cross-over study by Uribe *et al*¹⁹ compared two week treatments of a 40 g meat protein diet with 40 and 80 g of vegetable protein in 10 cirrhotic patients with chronic portosystemic encephalopathy. There was improvement in mental state, EEG, asterixis, and number connection test, although only the latter improvement was significant. Hypoglycaemia was recorded in two patients on the 40 g vegetable diet. During treatment with the vegetable diet, neomycin and laxatives which had been given with the animal protein were discontinued; this may have unfairly mitigated against the beneficial effect of the vegetable diet. In a further trial, improvement was noted in six patients with chronic encephalopathy switched to a vegetable protein diet. One patient improved considerably but the other five showed only minimal benefit. The addition of lactulose resulted in some further benefit (Morgan, Sherlock, Greenberger, personal communication).

Methionine, which is metabolised in the gut to mercaptans (reputedly

comagenic compounds), is present in significantly greater amounts in meat protein than vegetable protein,²⁰ but such beneficial results are unlikely to result from the lower methionine content of vegetable diets as gram quantities of methionine are needed to induce coma and these diets differed by only 200–500 mg quantities.¹⁷ Furthermore, Morgan *et al* added methionine to the patients' vegetable diets with no resultant deterioration. Vegetable diets may contain less, as yet unidentified, comagenic substances, may change bowel flora or bioavailability of other amino acids or, because of their bulk, alter bowel transit time and smooth out absorption from the bowel lumen. The major disadvantage of vegetable diets, especially if they need to be combined with salt restriction (which is invariably the case) is that they are very bulky and may not be well tolerated because of abdominal bloating and gaseous distension. A vegetarian diet can be varied and interesting, but for good compliance expert dietetic advice is invaluable.

Branched chain amino acid supplements

Hepatic failure associated with cirrhosis is accompanied by a two to four-fold rise in the plasma concentrations of the aromatic amino acids, together with a decrease in the plasma concentrations of the branched chain amino acids, valine, leucine, and isoleucine.²¹ A combination of catabolism and impaired hepatocellular function is probably responsible. Raised plasma concentrations of glucagon stimulate muscle catabolism with release of amino acids for gluconeogenesis.^{22 23} When hepatic function is poor, however, the uptake and metabolism of aromatic amino acids is impaired. In contrast, branched chain amino acids are preferentially metabolised in muscle and fat and their low concentrations can be partly explained by their enhanced uptake as a result of hyperinsulinism.^{23–25}

Most attention has been focused on phenylalanine and tyrosine because increased intracerebral concentrations may result in decreased synthesis of true neurotransmitters and accumulation of false neurotransmitters, such as octopamine.¹⁰ In addition tryptophan is thought to be converted to the inhibitory neurotransmitter serotonin.^{26 27} Normally, phenylalanine, tyrosine and tryptophan compete with branched chain amino acids for entry through the blood brain barrier *via* a single carrier system.²⁸ The transport of these 'toxic' aromatic amino acids may be enhanced by the low plasma concentrations of branched chain amino acids found in chronic liver failure and result in an imbalance of the synthesis of cerebral neurotransmitters and the development of hepatic encephalopathy.²⁹ Thus normalisation of the abnormal amino acid profile by infusion of a mixture high in branched chain amino acids and low in aromatic amino acids might be expected to be beneficial in hepatic encephalopathy.^{30 31}

Encouraging results were initially reported from studies using intravenous branched chain enriched amino acid solutions in dogs with portacaval anastomoses and in acutely decompensated cirrhotic patients.^{30 31} The uncontrolled nature of these studies, however, and the fact that the composition of the therapeutically active amino acid mixture (FO80) differed from the amino acid mixture (Freamine II) used experimentally for induction of encephalopathy, not only in branched

chain amino acid content but in the amount of ammonia generating, as well as ammonia processing, amino acids, presented difficulty in the interpretation of these studies.

Analysis of six recently reported studies comprising nearly 200 patients show an overall improvement in the amino acid profile and claim arousal from coma in up to 60% of patients with intravenous infusions of branched chain amino acids.³²⁻³⁷ In some of these studies, however, details of case material and exact randomisation are inadequate and comparison with conventional amino acid solutions was lacking. In a recently completed and well documented controlled trial,³⁸ complete mental recovery was achieved in 70% of cirrhotics with encephalopathy treated with branched chain amino acid infusions, compared with 47% receiving lactulose plus isocaloric glucose.

In contrast, another controlled study³⁹ in 30 patients with encephalopathy showed no benefit from branched chain amino acids when compared with conventional amino acid mixtures. This paper, however, has been subject to criticism not least for its inadequate randomisation.⁴⁰

Continuous intravenous branched chain amino acid therapy is not practicable in chronic encephalopathy. In a number of controlled trials, however, the effect of an oral branched chain amino acid supplement has been studied. Horst⁴¹ reported the development of encephalopathy in 58% of cirrhotics consuming an ordinary protein diet, whereas this occurred in only 7% receiving the branched chain amino acid supplements. Despite this clinical benefit there was no change in the trail test, EEG, or blood ammonia. Improvements in psychometric tests occurred in Egbert's trial,³⁵ although the patients were never encephalopathic and the EEG remained within the normal range.

Herlong *et al* (see section on keto analogues) were unable to show any significant clinical improvement in eight patients with chronic portasystemic encephalopathy treated with a daily 10 g branched chain amino acid supplement.⁴² Similarly Eriksson, in a double-blind crossover study could not show any clinical, psychometric or EEG improvement over a 14 day period in seven patients treated with a 30 g branched chain amino acid supplement when compared with placebo.⁴³ In four patients given branched chain amino acids for longer periods (five to 22 weeks), psychometric tests remained unchanged. The findings in two other studies^{13 44} failed to substantiate a beneficial effect of branched chain amino acids. Experience in the Liver Unit, King's College Hospital showed no significant difference in the rate of recovery from encephalopathy due to severe alcoholic hepatitis in patients receiving branched chain amino acid supplements or conventional protein (Calvey, Davis, Williams, unpublished observations).

The apparent failure of oral branched chain amino acids to improve chronic portasystemic encephalopathy may reflect the lack of continuous high plasma concentrations of branched chain amino acids which are obtained with continuous intravenous infusions. After oral administration plasma concentrations of branched chain amino acids remain raised for only three hours.⁴³ Despite this, oral branched chain amino acid supplementation has not been shown to be deleterious and may provide a way of increasing nitrogen intake without precipitating encephalopathy.

Controversy also surrounds the mode of action of branched chain amino

acids, the significance of the altered plasma amino acid profile and the relationship of neurotransmitter imbalance to the development of hepatic encephalopathy. Intravenous administration of branched chain amino acids results in the lowering of the concentrations of 'toxic' aromatic amino acids.^{45 46} Studies in animals and man have shown that branched chain amino acids and leucine in particular decrease the brain uptake of aromatic amino acids.^{47 48} In addition, branched chain amino acids have been thought to play a regulatory role in the efflux of amino acids from muscle,²⁵ and as endogenous protein catabolism contributes significantly to the plasma amino acid imbalance in liver failure, their ability to suppress muscle catabolism would be beneficial.^{49 50}

Several investigators have shown that the plasma branched chain amino acid concentrations are decreased with the onset of encephalopathy but do not change significantly as coma deepens and that plasma and the cerebrospinal fluid, aromatic amino acids, phenylalanine, tyrosine, free tryptophan, methionine and the false neurotransmitter octopamine increase progressively with coma with an associated fall in the branched chain amino acids/phenylalanine and tyrosine ratio.^{31 51-55}

In many other studies no correlation has been found between the changes in plasma AAs, BCAA/AAA ratio and the presence or degree of coma.^{56 58} The normal functions of the carrier mechanisms and the integrity of the blood brain barrier, however, are disturbed in coma and a lack of correlation between plasma concentrations and coma grade may therefore not be surprising.

Furthermore, although at least partly dependent on the plasma concentration, it is the concentration of amino acids and neurotransmitters within the brain which are of final importance in the development of hepatic coma.

Persuasive experimental studies have recently shown that combined intracarotid infusions of high doses of phenylalanine and tyrosine in normal dogs induce the characteristic CSF abnormalities and coma, which is prevented by simultaneous infusion of branched chain amino acids.⁴⁸ Nevertheless, confirmatory evidence that changes in the final effector pathway – that is, an increase in false neurotransmitters and/or a decrease in true transmitters cause coma – is lacking. Direct infusion of octopamine into the lateral ventricle of the rat raised brain octopamine considerably without causing coma, despite a fall in brain dopamine and noradrenaline concentrations to well below those observed in hepatic coma.⁵⁹ Measures of synthesis of the inhibitory neurotransmitter serotonin or the excitatory neurotransmitter dopamine do not show any change during hepatic coma,⁸ and, finally a recent necropsy study has shown that there are no significant differences in the dopamine or noradrenaline concentrations in the brain of cirrhotics with or without encephalopathy, and octopamine concentrations were not raised.⁶⁰

Keto analogues

A different approach to the treatment of portosystemic encephalopathy has been adopted by Maddrey⁶¹ who has shown that keto analogues of essential amino acids can offset hyperammonaemia and protein deficiency by combining with amino group donors to yield essential amino acids.

Amination may occur in tissues other than the liver. Eight of 11 patients with encephalopathy infused with keto analogues showed clinical improvement although nitrogen balance did not change significantly. The formulation used was the sodium or calcium salts of keto acids, and in patients with chronic liver disease and sodium retention it is unclear whether sufficient quantities could be administered to improve nutritional status.

A more recent double blind crossover study from the same group showed clinical and electro-encephalographic improvement in eight patients with chronic portosystemic encephalopathy treated orally with ornithine salts of branched chain keto acids.⁴² When compared with branched chain amino acids the ornithine salts were considerably more effective. The formulation with ornithine was clearly important as calcium salts of the branched chain keto acids were not as effective. The reason for this synergistic effect was unclear, but might be explained by the peripheral anabolic effects of branched chain keto acids and the stimulatory effects of ornithine on the urea cycle.

A further study suggests that α -ketoisocaproate, an α keto analogue of leucine, reduces the arterial concentration of the aromatic amino acids and may be useful in encephalopathy.⁶²

Agents affecting colonic amine/ammonia production

NEOMYCIN

As toxins are thought to arise from bacterial action on gut protein, antibiotic treatment to eliminate such organisms has been advocated. It had previously been assumed that aerobic gut flora, against which neomycin was active, were the major producers of ammonia and other toxins.⁶³ Subsequently neomycin was shown to be of value in several controlled and uncontrolled studies.⁶⁴⁻⁶⁹ While it is of undoubted value in acute episodes of hepatic decompensation as well as chronic encephalopathy, its place may be limited by complications. It is partially absorbed and ototoxicity and nephrotoxicity may result particularly in patients with impaired renal function.⁷⁰⁻⁷¹ Malabsorption, staphylococcal and clostridium difficile enterocolitis have also been described.⁷²⁻⁷³

METRONIDAZOLE

Recent bacteriological studies have shown that gram negative anaerobes are the most numerous gut bacteria and make a major contribution to the generation of ammonia⁷⁴ and possible other toxins from dietary protein degradation. Neomycin, however, has very limited activity against these organisms. Hence a recent trial has evaluated the effect of metronidazole which is active against anaerobic bacteria in the treatment of chronic hepatic encephalopathy.⁷⁵ In 18 cirrhotic patients with various grades of encephalopathy it was shown to be as effective as neomycin, while in a further five patients combination therapy resulted in further improvement in the EEG mean dominant frequency, suggesting that this may be a worthwhile regime in the patient with refractory chronic encephalopathy. Although no adverse reactions were reported in this particular study, CNS toxicity, which is dose related, is the most serious and caution is advised with long courses, especially in patients with liver disease.

LACTULOSE

Lactulose (1–4 galactoside fructose), a synthetic non-absorbed disaccharide which was first described in 1966, has been shown to be effective in several controlled studies.^{76–79} Its mode of action has been exhaustively studied. It passes unchanged to the lower bowel where it is metabolised by bacteria with the production of lactic, acetic and formic acids, carbon dioxide and diarrhoea. Initially it was thought that acidification favoured the growth of lactobacilli and other fermentative bacteria and the suppression of acidophobic proteolytic bacteria.⁷⁶ Quantitative studies have failed to substantiate this.^{77 80} It has also been suggested that its beneficial effect results from the trapping of ammonia and other toxins owing to the pH gradient across the intestinal wall.^{77 81} A reduction in pH will also reduce ammonia formation by inhibiting the deaminating enzymes.⁶³ More recently, Vince *et al* have shown that lactulose inhibits ammonia formation irrespective of the change in pH and this may be because of the incorporation of ammonia into bacterial proteins.⁸² In an extension of this study they have shown *in vitro* that lactulose and other carbohydrates such as lactose may repress the formation and inhibit the activity of bacterial enzymes (catabolite repression) which generate ammonia.⁷⁴ If bacterial uptake of ammonia continues normally but production falls then the net concentration of ammonia will fall.

Subsequent studies in cirrhotics have investigated the effects of lactulose on gut ammonia production by measuring urea metabolism in gut and liver.^{83 84} Urea production is dependent in part on the quantity of substrate nitrogen, especially ammonia reaching the liver from the gut. Lactulose decreased urea production by increasing the faecal output of nitrogen. Although urea degradation decreased, this was accounted for by a fall in the urea pool rather than by inhibition of bacterial urease activity within the gut lumen. These findings are consistent with those of Vince⁸² and indicate that the major effect of lactulose was to trap nitrogen in the bowel. As previous studies have not shown an increase in faecal ammonia with lactulose⁸⁵ it is probable that the increase in stool nitrogen was in the form of ammonia precursors rather than ammonia and suggests that the beneficial effects seen with treatment may not be exclusively related to reduction in gut ammonia metabolism.

Three controlled clinical trials have compared the effects of lactulose and neomycin in hepatic encephalopathy. Conn studied 29 patients with chronic portosystemic encephalopathy in a double-blind crossover trial and found lactulose was effective in 90% and neomycin in 83% of patients. Lactulose resulted in a significantly greater improvement in the portosystemic encephalopathy index than neomycin and its efficacy was related to its ability to acidify stool pH.⁶⁹ Atterbury found similar results with both treatments in acute encephalopathy.⁶⁷ A study comprising 173 patients reported by Orlandi⁶⁸ showed similar effectiveness of the two agents, although there was a trend in favour of neomycin when coma was deep.

COMBINED LACTULOSE AND NEOMYCIN THERAPY

In theory, neomycin may suppress the activity of the bacteria necessary for the hydrolysis of lactulose. Pirotte *et al*,⁸⁶ however, have reported a

decrease in blood ammonia and an increase in ammonia tolerance which was greater with combination therapy than with either agent alone. Similarly, Weber⁸⁷ has shown that the addition of neomycin (4 g/day) to treatment with lactulose further reduced gut ammonia production by inhibition of bacterial ureolysis. Faecal pH remained low with combination therapy indicating ongoing metabolism of lactulose. Such synergism suggests that the effect of each drug was mediated by different bacterial populations. As yet there are no clinical trials which suggest that combination therapy is more effective in hepatic encephalopathy, although Conn has suggested that the response may be unfavourable in 27% of patients.⁸⁸

LACTOSE

A variety of carbohydrates such as lactulose, lactose, and glucose may inhibit ammonia formation by gut organisms and suggests that such substances given by enema may be therapeutically effective.⁷⁴ A study comparing 1 litre 20% lactose enemas three times per day plus placebo tablets with neomycin tablets plus starch enemas in acute portosystemic encephalopathy lends support to this idea.⁸⁹ Although considerably cheaper than lactulose, lactose enemas are unlikely to win a place in the long-term treatment of chronic portosystemic encephalopathy.

Use of dopamine agonists

LEVODOPA

As the neurotransmitter hypothesis postulates an imbalance of cerebral neurotransmitters with decreased synthesis of dopamine, a beneficial effect of levodopa was predicted because of the central effects of its derivative, dopamine, although more recent evidence suggests that it also increases renal excretion of ammonia.⁹⁰ Several uncontrolled studies have shown arousal from acute coma^{10 91} with levodopa. There have, however, only been two controlled studies of its use in chronic encephalopathy. Lunzer *et al*⁹² reported a significant improvement in three of six patients with chronic portosystemic encephalopathy treated with levodopa. Patients were maintained on levodopa for 12 weeks before entering a double blind crossover study with placebo (lactose). After treatment with L-dopa three patients improved clinically, but only one of these was able to tolerate the drug sufficiently long enough for double blind assessment. He deteriorated on placebo and improved again on L-dopa. In the other patients in the crossover study there was no difference between L-dopa and placebo.

The second study⁹³ involved 75 patients with chronic decompensated liver disease. Encephalopathy resulted from gastrointestinal bleeding, alcoholic hepatitis, and infection in 41%, 28%, and 7% respectively. In the remainder the cause was not determined. No significant differences were found between placebo and active treatment. It should be noted that patients in this study did not have chronic portosystemic encephalopathy. Furthermore, the high percentage of patients with severely decompensated liver disease and the 50% death rate in both groups may have masked any beneficial effects of treatment.

BROMOCRIPTINE

Two recent controlled studies have evaluated the use of bromocriptine – a dopamine agonist – in the treatment of patients with chronic portosystemic encephalopathy. The first study,⁹⁴ a double blind crossover comparison of bromocriptine (15 mg/day) and placebo in seven cirrhotics with chronic portosystemic encephalopathy did not show any significant improvement. The numbers were small, however and any beneficial effect of the drug may have been masked by constipation which developed in three patients. In addition, two of the patients had decompensated liver disease which may have attenuated any beneficial effect.

The second study⁹⁵ showed overall improvement in all six patients treated with bromocriptine, although improvement was definite in only three of the six and probable in the rest. This was a single blind study in patients with well compensated liver disease. Improvement also coincided with increased cerebral oxygen and glucose consumption, together with increased cerebral blood flow.

Possible sequence of therapeutic regimes

In the management of chronic encephalopathy the first requirement is a careful search for, and correction of, precipitating factors such as constipation, administration of sedatives and electrolyte imbalance due to overzealous diuretic therapy. Initial treatment comprises moderate protein restriction and oral lactulose or neomycin. In older patients or those with renal impairment or constipation lactulose is the drug of choice. Its cost for a week's treatment in hospital is £1.47 (15 ml tds) compared with £2.32 for neomycin (4 g daily). Otherwise there is little to choose between them.

Protein intake should, if possible, be maintained above 40 g/day so as to avoid progressive muscle wasting. If there is no symptomatic improvement neomycin can be combined with lactulose. Clinical deterioration and a rise in stool pH will require withdrawal of combined therapy. Substitution of metronidazole for neomycin or combination of the two may then be tried, followed by dietary protein restriction to 40 g daily.

In the patient whose symptoms are not relieved and where more strict protein restriction seems necessary, a 40 g vegetable protein diet may be tried. Some patients will improve and protein intake can then be increased progressively to 60 and 80 g/day. The help of a dietitian is essential, as lack of variety of food, invariable salt restriction and gastrointestinal side-effects limit compliance.

Supplementation of a low protein diet or vegetable protein diet with branched chain amino acids may be tried next, although there is little direct evidence of a beneficial effect and the cost of Hepaticaid (four sachets daily) is currently £182 per week. When symptoms are still not relieved the next approach is a trial of bromocriptine (15 mg/daily costs £11.37 per week).

Finally, no review of therapy for chronic encephalopathy would be complete without mention of liver transplantation. This should be considered in patients under 50 years of age with advanced cirrhosis and without contraindications to major surgery in whom the symptomatic measures described do not control encephalopathy and in whom no further specific therapy for underlying cirrhosis is possible. Despite the

histological changes described in the brain in chronic encephalopathy, the condition may be completely reversible and a return to normal, including changes in EEG, has been described in patients with severe chronic encephalopathy who were treated in this way.⁹⁶

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