HEPATIC COMA IN LIVER FAILURE AND GASTRO-INTESTINAL HAEMOR- RHAGE TREATED WITH NEOMYCIN

BY

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The introduction of protein withdrawal, oral broad-spectrum antibiotics, and enemata as a basis for treating hepatic impending coma and coma (Sherlock *et al.*, 1954) has been supported by encouraging results in larger groups of patients (Sherlock *et al.*, 1956; Summerskill *et al.*, 1957a). However, the relative contribution of each measure to the therapeutic response is uncertain, and protein deprivation, which may have to be long-continued, is particularly undesirable when liver disease is associated with undernutrition. No comparative studies are available to indicate the most effective antibiotic in hepatic coma, but the recent use of neomycin in three patients by Fisher and Faloon (1957) is important, as temporary clinical improvement was compatible with continued protein administration. Dawson *et al.* (1957) treated acute hepatic coma in 12 patients with neomycin, protein deprivation, and other measures. No conclusions were drawn in regard to its specific therapeutic action in either series, as coma was often due to multiple factors and additional methods of treatment were employed simultaneously. In this paper the effect of neomycin is compared with that of other antibiotics under controlled conditions, and the degree to which protein withdrawal and other procedures may be modified as a result of neomycin therapy is also studied.

Material

Six patients (three male and three female) with impending hepatic coma or coma complicating cirrhosis were studied (Table I). Cirrhosis was thought to be the

TABLE I.—*Biochemical Findings*

Case No.	Sex and Age	Serum Bilirubin (mg./100 ml.)	Serum Albumin (g./100 ml.)	Thymol Turbidity (Units)	Serum Sodium (mEq/l.)
1	F 60	6.0	2.2	16	137
2	F 75	4.0	2.8	10	112
3	F 77	1.5	3.5	5	127
4	M 24	20.0	2.9	2	99
5	M 55	0.8	4.8	1	142
6	M 49	0.9	3.1	1	125
Normal values		<1.0	>4.0	<5	(137-144)

sequel of virus hepatitis in Case 1 and of long-standing cardiac failure in Case 3; in Cases 5 and 6 it was possibly associated with alcoholism; and in Cases 2 and 4 the cause was uncertain. All except Case 6 had stigmata of chronic liver disease, and the relevant biochemical findings are shown in Table I. Case 2 gave a history of poor nutrition, and the serum albumin concentration was below 3 g./100 ml. in Cases 1, 2, and 4.

Coma was attributed to liver failure in Cases 1, 2, and 3, as all had developed ascites and two had become jaundiced shortly before the onset of neuropsychiatric disorder. The presence of a portal collateral circulation facilitating the onset and perpetuation of coma in these patients could not be excluded, but splenomegaly or superficial abdominal collateral veins were not found and there was no radiological evidence of oesophageal

varices in Case 1. Additional factors which may contribute to coma, such as high protein feeding, gross or occult gastro-intestinal bleeding, drugs, or intercurrent infection, were excluded. Ascites in Cases 2 and 3 was accumulating despite treatment, and was associated with serum sodium concentrations below 130 mEq/l., findings suggesting advanced liver damage and a poor prognosis (Hecker and Sherlock, 1956).

In Cases 4, 5, and 6 coma followed major gastro-intestinal haemorrhage. Gastro-oesophageal varices were demonstrated by barium swallow and meal, portal venography, and oesophagoscopy in Cases 4 and 5, while Case 4 also had intractable ascites, hypoalbuminaemia, and was deeply jaundiced (Table I). In Case 6 bleeding originated from a chronic gastric ulcer and there was no evidence of portal hypertension at laparotomy.

Methods

Daily assessment of the neuropsychiatric state was based on the observations of Walshe (1951), Adams and Foley (1953), and Summerskill *et al.* (1956). Because of the characteristic fluctuations in the syndrome, a distinction was made only between "coma" (absence of response to strong stimuli), "impending coma" (personality changes with objective signs, of which a flapping tremor was the most prominent), and the absence of gross psychiatric or neurological disorder.

Diets with calculated protein and sodium contents were supplied by the hospital dietetic department; antibiotics were given by mouth or intragastric drip in equally divided doses three or four times in the 24 hours; and enemas were administered when necessary to ensure daily bowel movements.

The biochemical tests, including the nitrogen balances, and bacteriological investigations reported were routine laboratory procedures.

Results

Case 1 (Fig. 1).—A woman aged 60 was admitted to hospital unconscious, and initial treatment by protein withdrawal, intragastric glucose, and enemata was followed within 48 hours by emergence from stupor, but tremor and confusion continued. Protein was added cautiously, but a daily intake of 30 g. was followed by gross neuropsychiatric disorder. Reduction of the amount to 20 g. failed to bring improvement. The patient's behaviour was incompatible with her retention in a general ward when neomycin (6 g. daily) was started, 12 days after admission to hospital. Within 24 hours normal mental function was restored and tremor and the other neurological abnormalities disappeared. The protein intake was then raised by 10-g. increments every three or four days to a total of 50 g. daily without neuropsychiatric deterioration. Simultaneously the daily dose of neomycin was reduced, and after two weeks it was discontinued. Five days later the patient again became drowsy, confused, and tremulous, but it was possible to raise the protein intake to 70 g. daily. Chlortetracycline (2 g. daily) did not improve the neuropsychiatric state. Accordingly, neomycin (6-4 g. daily) was substituted for it without alteration in dietary protein. After three days there was a striking improvement in response to neomycin, and after a further six days it was possible to withdraw chemotherapy. There was no further relapse, the jaundice and ascites subsequently disappearing.

Case 2 (Fig. 2).—A woman aged 75 was admitted to hospital for the treatment of ascites, but her condition slowly deteriorated and she developed impending coma and then lost consciousness. She remained in deep coma for five

days despite therapy with protein withdrawal, "sigmamycin" (tetracycline and oleandomycin in proportions of 2:1) (2 g. daily) and enemata. The following day she

regained consciousness, although confusion and tremor continued for a further day. After the neuropsychiatric state had remained normal for 24 hours, 20 g. of protein was added to the diet. The next day confusion, drowsiness, and tremor reappeared, but the amount was increased to 40 g. daily. Neuropsychiatric disorder persisted, and neomycin (6 g. daily) was substituted for sigmamycin. Within 24 hours the patient had returned to normal consciousness, although remaining on 40 g. of protein daily. Neomycin was discontinued after a four-day course, being replaced by sigmamycin (2 g. daily). Two days later there was a return of drowsiness, confusion, and tremor. Chloramphenicol (2 g. daily for four days) was substituted for sigmamycin for the treatment of an infection of the urinary tract, but it had no effect on the neuropsychiatric condition. Neomycin (8 g. daily) was therefore reintroduced, and within three days there was again a striking response, the patient becoming orientated and more alert. Subsequently the dosage was reduced slowly without deterioration in her condition.

FIG. 1.—Case 1. Neuropsychiatric state in relation to treatment and protein intake.

FIG. 2.—Case 2. Neuropsychiatric state in relation to treatment and protein intake.

FIG. 3.—Case 3. Neuropsychiatric state in relation to treatment and protein intake.

Case 3 (Fig. 3).—While in hospital for treatment of congestive cardiac failure, a woman aged 77 became confused, tremulous, and intermittently stuporous. Ammonium chloride (1 g. t.d.s.) had been included in her treatment, but its cessation failed to influence her condition. Chlorotetracycline (2 g. daily) was then given without altering the diet, and the patient regained consciousness, although confusion, apathy, and tremor persisted. Neomycin (6 g. daily for four days) was substituted for chlorotetracycline and further improvement occurred after two days. Tremor was no longer apparent and she was alert enough to sit out of bed and feed herself. Two days after neomycin treatment was stopped some tremor and apathy returned.

Case 4.—A man aged 24 was admitted to hospital with melaena and impending hepatic coma. A portacaval anastomosis, which had subsequently become occluded, had been constructed 16 months previously. Neomycin therapy (6 g. daily) was started immediately, but balloon compression of the gastro-oesophageal region was not undertaken. Haemorrhage, with the daily passage of loose melaena stools, continued for six days and the haemoglobin concentration was 8.9 g./100 ml. (60%) after 6 pints (3.4 litres) of blood had been given during this time. A protein intake of 40 g. daily was allowed throughout, and, despite progressive liver failure, with increasing jaundice (serum bilirubin 20 mg./100 ml.), the accumulation of tense ascites, and hyponatraemia (serum sodium concentration 99 mEq/l.), there was no neuropsychiatric deterioration. Normal consciousness was re-established 36 hours after admission and subsequently maintained. After the cessation of bleeding, liver function improved quickly.

Case 5.—A man aged 55 with known portal hypertension was admitted to hospital following the passage of melaena stools. Irrational, violent behaviour prevented the immediate introduction of a gastro-oesophageal compression balloon, and neomycin (6 g. daily), together with routine treatment, was started. Bleeding continued for four days and, after 6 pints (3.4 litres) of blood had been given in this time, the haemoglobin concentration was only 10.2 g./100 ml. (64%). Grossly abnormal conduct and a "flapping" tremor persisted for three days and some confusion continued for a further two days. Protein was withdrawn from the diet for two days, but it was then introduced in

daily increments of 10 g. without apparently prejudicing improvement in the neuropsychiatric state.

Case 6.—A man aged 49 was admitted to hospital following haematemesis and melaena of three days' duration. The next day he developed impending hepatic coma. Although standard biochemical tests of liver function showed no abnormality (Table I), 50% of injected bromsulphthalein was retained in the blood after 45 minutes, thus supporting the possible presence of liver disease. Neomycin therapy (6 g. daily) was instituted immediately. Profuse bleeding continued, and, despite the rapid transfusion of 7 pints (4 litres) of blood, his condition deteriorated. Although impending hepatic coma had been present for 12 hours, surgical treatment was thought necessary to arrest the haemorrhage. Accordingly Mr. K. Lloyd Williams undertook a laparotomy under general anaesthesia (Dr. L. Khan) with thiopentone, pethidine, gallamine triethiodide, nitrous oxide, and oxygen. The liver was cirrhotic, but no splenomegaly or portal collateral veins were found, and three chronic gastric ulcers were present. A Polya partial gastrectomy was performed. His recovery from the anaesthetic and his post-operative progress were uneventful, and no further neuropsychiatric disorder occurred.

Bacteriological Studies

Stool cultures were examined at various stages of treatment in Cases 1-5. A "sterile" stool was obtained after four to six days' neomycin (6 g. daily) in Cases 2, 4, and 5, although faecal organisms persisted in Case 3 after the same treatment. Stools from Case 1 and 2 which were examined after longer courses of neomycin (6-14 days) grew an apparently normal faecal flora in three instances despite continued clinical improvement. The average daily dose of neomycin was less than 6 g. on these occasions. Faecal organisms were also present after chlortetracycline in Cases 2 and 3 and after both sigmamicin and chloramphenicol in Case 2.

Additional Observations

Hepatic fetor was present initially in all patients, but it disappeared within 36-48 hours of treatment with protein withdrawal or antibiotics. Despite the subsequent addition of dietary protein and the reappearance of neuropsychiatric signs, fetor was not detected during the intermittent administration of antibiotics. The patients had loose stools with neomycin, but troublesome diarrhoea did not occur and no other toxic effect was observed.

Following a period of equilibration on the appropriate diet and antibiotic, four-day nitrogen balances were carried out on Case 1. During treatment with chlortetracycline (2 g. daily) there was a total nitrogen output of 46.1 g. with a positive balance averaging 2.2 g. daily. When neomycin (6-4 g. daily) was substituted for chlortetracycline, the urinary nitrogen loss was reduced and the positive nitrogen balance improved to 3.5 g. daily (Table II).

TABLE II.—Nitrogen Balance During Treatment with Chlortetracycline and Neomycin in Case 1

Drug	4-day Collections (g./Nitrogen)			
	Dietary Nitrogen	Urine Nitrogen	Stool Nitrogen	Balance
Chlortetracycline	54.9	34.2	11.9	+ 8.8
Neomycin	55.1	29.4	11.6	+14.1

Discussion

Treatment with antibiotics, protein withdrawal, and enemata in hepatic coma is based upon evidence that nitrogenous compounds of intestinal origin are a cause of the neuropsychiatric disorder. The object of therapy is therefore to reduce the amount of nitrogenous material in the intestines and, with antibiotics, to inhibit bacterial enzyme activity by suppression of the gut flora. The regime is of proved therapeutic value when coma results from intolerance of nitrogenous substances, such as gastro-intestinal

bleeding or high-protein feeding, in patients with adequate liver function. In coma due to liver failure there is more widespread clinical and metabolic disturbance and consequently a much poorer prognosis (Sherlock *et al.*, 1956; Summerskill *et al.*, 1957a). Moreover, the issue is rarely sufficiently prolonged or uncomplicated to permit controlled observations in relation to specific therapy.

Cases 1, 2, and 3 are of interest, as comparative studies were possible, although coma resulted from hepatic failure. In two patients relapses occurred after initial treatment when relatively small amounts of protein were added to the diet, and they responded successfully on four occasions to neomycin without alteration of the diet. In the third patient, recovery occurred when neomycin was given, despite the continued administration of protein. Other antibiotics (chlortetracycline, sigmamicin, or chloramphenicol) proved less effective with the identical protein intake and general management, although chlortetracycline was followed by improvement in one patient. The therapeutic action of neomycin occurred within 24-72 hours and deterioration took place on withdrawing the drug after a similar interval. These results stress the importance of oral antibiotic therapy even when coma is due to hepatic failure and, in the absence of other comparative data, suggest that neomycin is the most effective of currently recommended antibiotics in hepatic coma. This accords with the experience of Dawson *et al.* (1957) with neomycin in the management of chronic or recurrent neuropsychiatric disorder due to protein intolerance in patients with extensive portal-systemic collateral circulations, and with the improvement in E.E.G. appearances following use of the drug in patients with liver disease (Parsons-Smith *et al.*, 1957).

In Cases 4 and 5, with impending coma due to bleeding varices, deterioration to coma was prevented and full restoration of consciousness occurred when neomycin was given, although the haemorrhage was not controlled. Recovery was particularly striking in Case 4, in which deep jaundice and ascites were present, especially as an adequate protein intake was allowed throughout. The improvement in Case 6 was predominately due to surgical arrest of the bleeding, but the use of neomycin before operation probably ensured the smooth post-operative course, as impending coma had been present for at least 12 hours prior to general anaesthesia and constituted an important contraindication to surgery.

The close relationship between protein feeding and hepatic coma (Phillips *et al.*, 1952) is particularly important when coma complicates liver disease associated with malnutrition. Neomycin was superior to other antibiotics tested in permitting an adequate protein intake despite neurological disorder. Moreover, the nitrogen balance was positive during neomycin therapy, whereas the tetracycline antibiotics increase nitrogen catabolism and may cause a negative nitrogen balance (Faloon *et al.*, 1954, 1957).

A nutritious diet is important in the management of many patients with cirrhosis (Patek *et al.*, 1948), and the extent to which neomycin therapy will obviate protein deprivation in the treatment of hepatic coma is not yet clear. Clinical improvement with neomycin appears within 72 hours and temporary elimination of protein from the diet for this period is still prudent if coma is established or anticipated. When consciousness returns, an adequate protein intake (40 g. daily) may be tolerated, and if protein undernutrition is thought to be of aetiological significance in the liver disease larger amounts can be tried. As the presence of blood in the intestines has an effect similar to that of protein in precipitating hepatic coma (Sherlock *et al.*, 1954), balloon compression of the gastro-oesophageal region (Sengstaken and Blakemore, 1950) is of prophylactic use in patients with bleeding varices. However, the tube is often difficult to introduce in the uncooperative pre-comatose patient, hard to tolerate, and apt to cause ulceration of the oesophagus (Sherlock, 1958). The control of neuropsychiatric complications with neomycin during bleeding in Cases 4 and 5 indicates that compression can be reserved for patients in

whom haemorrhage is catastrophic or results in progressive neuropsychiatric deterioration. The smooth recovery of Case 6, despite preoperative impending coma, suggests that neomycin is also effective as a prophylactic measure in patients with liver disease prior to operation.

The relative significance of various organisms in the production of toxic nitrogenous substances in the human intestine, and therefore the specific action of neomycin, remains uncertain. Although the faecal flora is qualitatively and quantitatively normal in cirrhosis and hepatic coma (Phear *et al.*, 1956), some organisms, particularly coliforms and *Str. faecalis*, extend abnormally far up the intestines (Martini *et al.*, 1957). Neomycin, being poorly absorbed from the intestines, is relatively non-toxic, and doses of 8-12 g. daily were shown by Fisher and Faloon (1957) to "sterilize" the stools within 36 hours to 5 days. With the lower dosage employed in this study, the stools were "sterile" in three patients after four to six days' treatment. Reappearance or persistence of the faecal flora was not necessarily accompanied by clinical deterioration, and this agrees with the more extensive bacteriological studies of Dawson *et al.* (1957). Neomycin presumably exerts some specific effect on bacterial growth and metabolism under these circumstances that explains its clinical superiority to the other antibiotics used.

Toxic agents derived from nitrogenous material in the intestines, and of possible causal significance in hepatic coma, include methyl mercaptan (Challenger and Walshe, 1955) and tertiary amines (Butt and Mason, 1954), but evidence accumulates to incriminate ammonia in particular (Kirk, 1936), although its effect on brain metabolism has been variously interpreted (Bessman and Bessman, 1955; Summerskill *et al.*, 1957b). Ammonia from food, blood, and other nitrogenous material in the intestines can reach the systemic circulation by passing through a diseased liver or by way of portal collateral vessels (White *et al.*, 1955), and this accords with clinical experience, which relates hepatic coma to inadequacy of liver function, the extent of the portal collateral circulation, and the amount of nitrogenous material in the intestines (Sherlock *et al.*, 1954). Oral neomycin reduces portal blood ammonia levels effectively in dogs (Silen *et al.*, 1955), and Fisher and Faloon (1957) showed that both peripheral and portal vein ammonia values were lowered in patients with cirrhosis, even when protein was given. However, during long-term treatment, Dawson *et al.* (1957) found that ammonia concentrations in the blood tended to rise, although this was not necessarily associated with clinical deterioration.

Conclusion

These cases have been reported because, as is rarely possible in acute hepatic coma, objective assessment of the efficacy of a single therapeutic agent has been possible. Wider experience with neomycin in this department has confirmed its usefulness but has also emphasized two disadvantages. The first is its cost, although in these patients it was effective in doses well below the 12 g. daily used by Fisher and Faloon (1957). The second, if paradoxical, sometimes constitutes a practical dilemma and involves irreversible hepatic failure due to terminal chronic liver disease. Neomycin is sometimes so effective in prolonging normal consciousness in such patients that the distressing and unequal struggle appears to be unduly prolonged.

Summary

Neomycin was more effective than chlortetracycline, sigmamyacin, or chloramphenicol in treating three patients with hepatic coma due to liver failure under controlled circumstances. Neomycin therapy permitted an adequate protein intake, which, with the other drugs, caused neuropsychiatric deterioration.

Impending hepatic coma was precipitated by haemorrhage from gastro-oesophageal varices in two other

patients, one of whom also developed liver failure. Restoration of consciousness followed neomycin treatment despite persistent bleeding and continued protein-feeding. Balloon compression of the gastro-oesophageal region was not necessary. In another patient, impending coma resulted from massive bleeding from a gastric ulcer. Despite the neuropsychiatric disorder, general anaesthesia and surgical treatment were followed by an uncomplicated post-operative course with neomycin therapy. The influence of these findings on the management of hepatic coma is discussed.

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The British Council for Rehabilitation has set up a working party under the chairmanship of Dr. ELFED THOMAS, director of education for the City of Leicester, "To investigate the needs of physically and mentally handicapped school-leavers; to study the means of meeting their difficulties, and to make recommendations." The work is expected to take about two years and will be on a nation-wide basis. The composition of the working party includes educationists, representatives of the medical services, the voluntary organizations engaged in social work of an educational and medical nature, the Trades Union Congress, industry, and observers from the Ministries of Education, Health, and Labour and National Service, and local authorities. While it is recognized that the statutory services show an enlightened approach to the problem, states the council, and, as promulgated, appear to make reasonable provision, there still remain gaps. There are, continues the council, far too many handicapped school-leavers who, for one reason or another, miss the opportunities they should have and are left in what could become a hopeless position. The British Council for Rehabilitation (Tavistock House South, Tavistock Square, London, W.C.1) would therefore welcome evidence relevant to the above terms of reference from any source.