CHLOROTHIAZIDE IN CONTROL OF ASCITES IN HEPATIC CIRRHOSIS

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Ascites in cirrhosis of the liver is associated with a raised portal venous pressure and a lowered serum albumin level. Sodium is retained in the body as ascites accumulates, and urinary sodium is extremely low, most of the dietary intake passing into the peritoneal cavity. The urinary sodium/potassium ratio is reduced; this probably reflects the effects of aldosterone, increased amounts of which may be found in the urine of some cirrhotics with ascites (Wolff *et al.*, 1956). Ascites can often be controlled by rigid restriction of sodium intake and the use of diuretics (Eisenmenger, 1952; Atkinson *et al.*, 1954). The organic mercurials have been consistently useful, their only drawback being the necessity for parenteral administration; toxic effects are rare. An equally powerful but oral diuretic with no toxic properties would be of great value.

The new oral diuretic, chlorothiazide (6-chloro-7-sulphamyl-1-1,2,4-benzothiadiazine-1,1-dioxide; "saluric," "chlotride," "diuril") has been successfully used in patients with chronic cardiac failure (Moyer *et al.*, 1957; Bayliss *et al.*, 1958; Slater and Nabarro, 1958), and this prompted us to give it to patients with cirrhosis complicated by ascites. Chlorothiazide is chemically an aromatic sulphonamide derivative. Experimentally, in dogs, intravenous administration results in increased sodium and potassium excretion (Ford *et al.*, 1957). Its primary action, like that of the mercurial diuretics, seems to be potent inhibition of tubular reabsorption of sodium with no significant effect on renal blood flow or glomerular filtration rate. The increased excretion of sodium is balanced partly by increased chloride loss and also by an increased bicarbonate excretion. This anion excretion pattern is reminiscent of the carbonic anhydrase inhibitors such as acetazolamide ("diamox"), and chlorothiazide *in vitro* is a potent inhibitor of carbonic anhydrase. Unlike acetazolamide, however, its action does not depend only on bicarbonate excretion, and renal loss of bicarbonate is not profound enough to cause a metabolic acidosis and so inhibit further diuretic action by limiting the availability of the bicarbonate ion.

Patients Studied and Methods

Chlorothiazide was given orally in a dose of 2 g. a day (0.5 g. six-hourly) in 15 courses to 13 patients with Laennec's (portal or post-necrotic) cirrhosis complicated by ascites and peripheral oedema (12 patients) or gross peripheral oedema alone (1 patient) (Table I). A history of the neuropsychiatric complications of liver disease (confusion, flapping tremor, and disturbed consciousness) was obtained in seven instances. Four out-patients were also studied. The in-patients were investigated in a metabolic ward and received a sodium-

TABLE I.—*Cirrhotic Patients Treated with Chlorothiazide in Hospital*

Case No.	Age and Sex	Aetiological Factors	Duration of Ascites (Months)	Previous Treatment	Serum Bilirubin (mg./100 ml.)	Serum Albumin (g./100 ml.)	Past Hepatic Precoma or Coma
1	69 M	Alcoholism	18	Low Na diet. Mersalyl. Multiple paracentesis	0·5	2·7	–
2	38 M	Past hepatitis	36	Low Na diet. Mersalyl. Paracentesis × 3	1·1	3·3	–
3	50 M	—	5	Low Na diet. Mersalyl. Paracentesis ×10	0·8	2·2	–
4	53 F	—	14	Low Na diet. Mersalyl. Paracentesis ×25	0·4	3·1	–
5	50 F	—	3	Low Na diet. Mersalyl	2·5	2·5	–
6	39 M	Past hepatitis	3	Low Na diet. Mersalyl. Paracentesis ×2	4·0	2·7	+
7	47 F	Past hepatitis (porta-caval anastomosis)	12	Low Na diet. Mersalyl	1·2	2·4	+
8	50 F	—	6	Low Na diet. Mersalyl	2·1	2·2	+
9	65 F	—	15	Low Na diet. Mersalyl	1·2	3·1	+
10	47 M	Alcoholism	16	Low Na diet	0·4	2·3	+
11	66 F	Past hepatitis	1	Nil	2·6	2·5	+
12	10 F	—	1	Low Na diet	0·7	2·2	–
13	42 M	—	3	,, ,, ,,	0·3	3·8	+

TABLE II.—*Effects of Chlorothiazide on Urine Volume, Electrolytes, and Body Weight*

Case No.	Before Chlorothiazide (Mean of 3 Days)				During Chlorothiazide (Mean of First 3 Days)				Duration of Treatment (Days)	Weight Loss (Kg.)	Diuretic Response	Complications
	Na	K	Cl	Vol. (ml./24 Hrs.)	Na	K	Cl	Vol. (ml./24 Hrs.)				
	mEq/24 Hours				mEq/24 Hours							
1	0·3	53	34	1,510	5·9	117	97	1,840	6	0	Poor	Hepatic precoma
2	0·5	27	2·9	1,175	53	62	90	1,410	6	0	,,	
3	0·3	25	1·3	500	3·8	83	44	1,040	7	0	,,	
4	0·5	25	1·2	920	5·9	67	60	1,410	6	0	,,	
5	0·7	16	1·0	400	9	44*	18	430	7	0	,,	
6 (1)	0·8	21	4·0	750	40	214*	163	1,640	2	4·4	Good	Hepatic coma
6 (2)	0·2	25	29	730	2·8	197*	172	990	6	0	Poor	
7 (1)	7	41	26	920	131	104	160	2,200	3	3·5	Good	Hepatic precoma. Epileptic fit
7 (2)	7	52	21	920	113	275*	225	2,200	5	3	,,	Hepatic precoma
8	12	53	27	2,200	256	240*	342	4,300	7	6·1	,,	
9	9	57	44	1,440	139	148*	206	2,700	7	2·3	,,	
10	20	55	53	1,610	237	138	279	3,700	2	5·2	,,	Hepatic coma
11	6·3	32	10	1,100	105	56	133	1,900	7	2·6	,,	,, ,,
12	8	60	16	2,100	66	112	74	3,600	4	2	,,	E.E.G. slowing
13	11	62	23	2,060	73	123	160	2,530	6	2·8	,,	Hepatic precoma

* Given potassium supplements.

restricted diet (22 mEq/24 hours) and approximately 70 mEq of potassium daily with a daily protein intake of 80 g.; one patient in impending hepatic coma (Case 11) could tolerate only 50 g. of protein daily.

The 24-hourly urine was measured and the sodium, potassium, and chloride content estimated, using standard and flame photometry techniques. Serum electrolyte levels were estimated so far as possible in the fasting state.

Electroencephalograms (E.E.G.s) were recorded serially. Slowing of the mean frequency was used as an indication of hepatic coma (Foley *et al.*, 1950; Parsons-Smith *et al.*, 1957; Laidlaw, 1958).

On six occasions oral potassium supplements in the form of potassium chloride in gelatin-coated capsules and/or potassium bicarbonate as an effervescent mixture were added (see Table V), and these were given routinely to the four out-patients. 1 g. of potassium chloride contains 13 mEq of potassium.

Results

On 9 of the 15 occasions the diuretic response to chlorothiazide was regarded as good (Table II). These patients showed a weight loss of at least 2 kg. and the urinary sodium output increased by more than 39 mEq. In the remaining six instances the response was poor, the weight showing no change, and, with one exception (Case 2), the urinary sodium output little or no increase. With one exception—Case 6 (1)—the patients who were refractory had a very low initial urinary sodium output (less than 1 mEq daily). This avid sodium retention with a low urinary sodium/potassium ratio indicates a profound degree of secondary hyperaldosteronism. Patients with a good diuresis showed a higher urinary sodium output and sodium/potassium ratio in the pre-treatment period, evidence of a less profound aldosterone effect.

In all patients chlorothiazide resulted in a twofold to threefold increase in urinary potassium output, and this was associated with a fall in serum potassium level in every patient not receiving potassium supplements (Table III). The increased urinary potassium and the drop in serum potassium level were most rapid and conspicuous in those having the greatest diuresis. The fall in serum potassium level was associated with the expected increase in the serum alkali reserve and a fall in serum chloride values (Table III).

TABLE III.—*Serum Electrolytes Before and Following Chlorothiazide, 2 g./day*

Case No.	Before Chlorothiazide				At Completion of Chlorothiazide				Duration (Days)
	Na	K	Cl	HCO_3	Na	K	Cl	HCO_3	
	mEq/l.				mEq/l.				
1	125	4·7	95	21·4	125	2·3	92	28·8	6
2	138	4·2	98	29	133	2·7	97	32	6
3	135	4·2	98	27	130	3·0	91	32	7
4	133	4·4	96	22	137	2·5	89	31	6
5	130	3·2	96	30	130	4·7*	98	25	7
6 (1)	128	4·5	102	20·7	127	2·4*	94·5	26·7	2
6 (2)	120	3·7	87	25	118	4·0*	87	22·2	6
7 (1)	133	4·0	106	21·8	137	2·9	99	26·4	3
7 (2)	138	3·9	103	26·1	133	3·1*	101	22·6	5
8	137	3·6	107	24	130	2·9*	104	25	7
9	135	4·5	105	27	138	3·7*	95	31·4	7
10	137	3·8	103	24·8	128	2·5	95	26·9	2
11	137	4·3	105	28	140	2·7	90	33	7
12	133	3·9	96	27	133	2·2	85	33·6	4
13	136	4·2	103	26	128	2·6	96	29	

* Potassium supplements given.

TABLE IV.—*Urinary pH and Bicarbonate Excretion on Chlorothiazide*

Case No.	Before Treatment (Mean of 3 Days)			During Chlorothiazide (Mean of First 3 Days)		
	Vol. (ml./24 hrs.)	*p*H	Bicarbonate (mEq/24 hrs.)	Vol. (ml./24 hrs.)	*p*H	Bicarbonate (mEq/24 hrs.)
13	2,060	6·9	6	2,530	7·1	26
1	1,510	5·9	3	1,840	6·8	23
14	900	6·5	2	800	6·8	5
15	1,020	6·4	3·2	2,030	6·9	21

Anions excreted consisted mainly of chloride, but there was a considerable deficit between the total urinary cations and the chloride output. In two control and two cirrhotic patients chlorothiazide resulted in a rise in urinary *p*H with a fivefold increase in bicarbonate excretion (Table IV). These results suggest that chlorothiazide was behaving not only as a choluretic (mercurial-like action) but also as a carbonic anhydrase inhibitor. The increase in bicarbonate and in potassium loss was reminiscent of the action of the carbonic anhydrase inhibitor acetazolamide.

Results obtained in a patient who proved refractory to chlorothiazide are shown in Fig. 1.

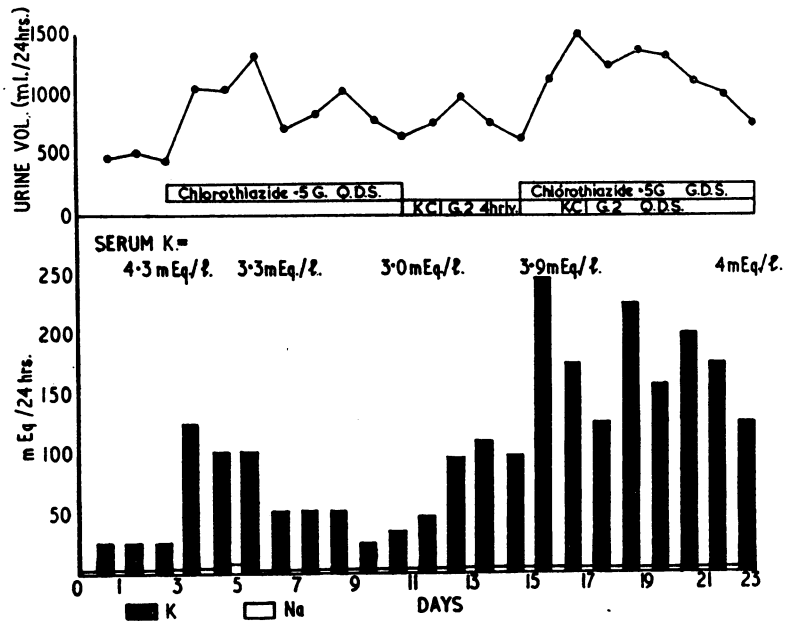

FIG. 1.—Case 3, cirrhosis and ascites. Urinary sodium excretion during the control period was less than 1 mEq daily and the Na/K ratio was low. Chlorothiazide increased the urinary sodium excretion to only 6 mEq/24 hours. The predominant cation lost was potassium, and as its excretion proceeded the serum potassium level fell. There was a small diuresis but insignificant weight loss. The addition of potassium supplements did not increase the urinary sodium excretion, but the serum potassium level did not fall.

Complications

Hypokalaemia, defined as a serum potassium below 3.5 mEq/l., was noted in all nine patients receiving chlorothiazide without potassium supplements. This state, although sometimes symptomless, is potentially dangerous. In six cases studied the changes of potassium deficiency developed in the electrocardiogram, and in two of these cases ventricular extrasystoles were a further manifestation of hypokalaemia.

Potassium supplements (78–250 mEq/24 hours) were given six times (Table V). On four occasions this proved insufficient to balance the urinary loss, and serum potassium values fell. The other two patients showed a poor diuretic response to the drug; urinary potassium loss was balanced by the extra potassium, and hypokalaemia was not seen.

TABLE V.—*Effect of Potassium Supplements.*

Case No.	Duration of Treatment (Days)	K supplements (mEq/24 hrs.)	Before Chlorothiazide: Serum K mEq/l.	Before Chlorothiazide: Urinary K (mEq/24 hrs.) (3-day Mean)	After Chlorothiazide: Serum K (mEq/l.)	After Chlorothiazide: Urinary K (mEq/24 hrs.) (3-day Mean)	Diuretic Response
5	7	78	3·2	16	4·7	44	Poor
6 (1)	2	100	4·5	21	2·4	214	Good
6 (2)	6	256	3·7	25	4·0	197	Poor
7 (2)	5	256	4·0	52	3·1	275	Good
8	7	256	3·6	53	2·9	240	"
9	7	78	4·5	57	3·7	148	"

Hepatic Precoma and Coma

This syndrome was noted in 7 of the 13 in-patients treated (Table II). It was usually associated with a good and rapid diuretic response to the chlorothiazide. Two patients passed into deep coma after only two days' therapy.

Case 10.—A man of 47, an alcoholic with cirrhosis, was admitted to hospital for assessment for porta-caval anastomosis following haemorrhage from oesophageal varices. Examination revealed hepatosplenomegaly and moderate ascites with ankle oedema. Slight hepatic fetor and "flapping" tremor disappeared within a few days of admission to hospital. Neuropsychiatric complications had not followed the haemorrhage, but there was a history of previous hepatic precoma. Chlorothiazide resulted in a massive diuresis, 5 kg. in weight being lost in two days. However, within 24 hours of commencing the drug the fetor and tremor returned and the E.E.G. showed slowing. The next day he became violent, requiring considerable restraint, and passed into deep coma, regaining consciousness only after 36 hours.

Case 6 (1).—This patient with cirrhosis and a past history of hepatitis had considerable ascites. He responded to chlorothiazide with a good diuresis, but soon exhibited hepatic fetor, tremor, and confusion, and passed into coma. A further course of chlorothiazide given later in his illness—Case 6 (2) in Table II—when he had developed even greater retention of sodium with a fall in his serum sodium level, was not accompanied by a diuresis, and neither was there any neuropsychiatric electroencephalographic deterioration.

Three other patients exhibited the features of hepatic precoma while receiving chlorothiazide, and in one of these there was an associated major epileptic fit. A further patient developed only gross slowing of the E.E.G., and the chlorothiazide was then stopped. The E.E.G. proved the most sensitive record of impending neuropsychiatric disturbance, but major electrical abnormalities were always accompanied by clinical evidence of hepatic precoma.

Only one patient (Case 11) developed hepatic coma without a coincident gross diuresis. This complication was noted six days after beginning the drug.

Two patients—Cases 6 (1) and 7 (2)—developing neuropsychiatric changes were receiving supplements of 100 and 256 mEq of potassium daily (Table V). Supplements were also given on four other occasions and to four out-patients, and the changes of hepatic precoma were not seen.

Continued Treatment in Out-patient Department

Four cirrhotic patients with ascites were previously well stabilized as out-patients on a low-sodium diet and mersalyl twice weekly. Chlorothiazide (2 g. daily) was substituted for the mercurial and was given continuously for two to three days in the week. All the patients received 3 to 6 g. of potassium chloride daily in capsules. Two responded well, the ascites being controlled or regressing; and two showed a poor response, the ascites increasing (Table VI). One of those who became refractory to chlorothiazide after four weeks had been followed previously for four years and had continuously responded to mersalyl. She was very disappointed to return to the injection treatment, for it had caused her considerable diarrhoea.

TABLE VI.—*Results of Chlorothiazide Therapy in Four Cirrhotic Out-patients with Ascites. The Drug was Given Continuously for Two to Three Days Weekly. No Neurological Complications were Seen*

Case No.	Duration of Treatment (Weeks)	K Supplements (mEq/24 Hours)	Serum K (mEq/l.): Before	Serum K (mEq/l.): After	Result
14	4	39	4·1	3·3	Slow gain of 3 kg.
8	4	39	3·6	2·9	" " 2 "
15	4	39	4·5	3·7	Good. " Lost 2 " kg.
7	2	78	4·4	4·7	Good. Weight constant

There was a tendency to develop hypokalaemia when chlorothiazide was given on more than two days in the week and when potassium supplements were less than 78 mEq daily (6 g. of KCl). Neurological complications were not seen, the serum potassium not reaching as low levels as in the patients on continuous therapy.

Comparison of Chlorothiazide with Mersalyl

In five patients the sodium and potassium excreted after 0.5 g. of chlorothiazide six-hourly for four doses was compared with that following 2 ml. of mersalyl intramuscularly (Fig. 2). On three occasions mersalyl therapy preceded

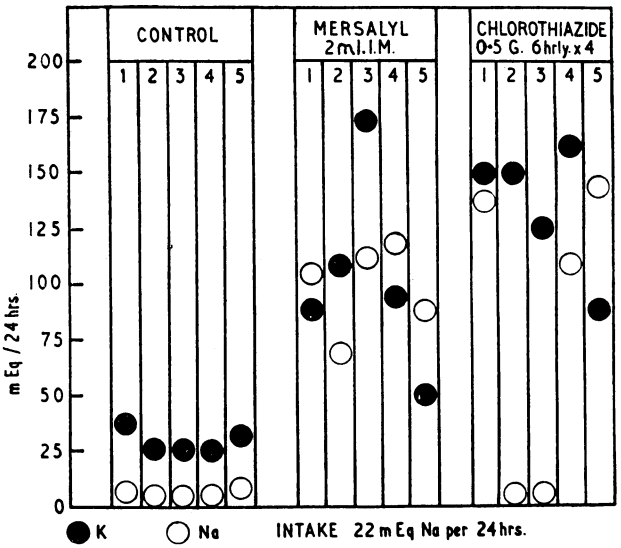

FIG. 2.—Cation excretion in five cirrhotic patients with ascites before and after chlorothiazide or mersalyl.

chlorothiazide and on two occasions the regime was reversed. In all five patients mersalyl increased the sodium excretion, an effect that was noted in only three patients after chlorothiazide. Potassium excretion after mersalyl was lower than the sodium loss in three patients. With chlorothiazide the reverse situation was noted, with a 24-hourly loss of sodium exceeding that of potassium in only one case. All these patients showed a very low initial sodium excretion in the urine. Chlorothiazide seemed less able than mersalyl to promote sodium excretion in such patients, but potassium loss was greater.

Discussion

Chlorothiazide has had only limited clinical trials in patients with ascites and cirrhosis. In a series of nine cirrhotic patients Laragh *et al.* (1957) found a good diuresis in three, a partial response in three, and no effect in three. Other authors have described only one or two cases, and the results are variable. In our patients the response was proportional to the severity of the fluid retention, and those with very low initial urinary sodium outputs showed little or no diuresis. These patients were by no means in a "terminal state" (Hecker and Sherlock, 1956), and the majority responded well to a mercurial diuretic. Patients with less avid sodium retention often showed a dramatic diuresis after chlorothiazide. All these in-patients were receiving a strict low-sodium diet. Out-patients cannot usually achieve such a regime, and here chlorothiazide may be useful, although two such patients became refractory to

the drug after a few weeks' treatment. In such instances alternation with mercurial diuretics may be valuable. Chlorothiazide is convenient to use and patients prefer it to mercurials. The cost, however, must be remembered, for 2 g. of chlorothiazide for three days costs 7s. 6d., in contrast to 2 ml. of mersalyl, which costs 2d.

Hypokalaemia has been well recognized as a complication of chlorothiazide treatment of congestive heart failure (Bayliss *et al.*, 1958) and has also been reported in cirrhotic patients (Laragh *et al.*, 1957; Richards, 1957; Schreiner and Bloomer, 1957; Slater and Nabarro, 1958). It was a consistent finding when our patients had a good diuresis. Hypokalaemia can be partly controlled by potassium supplements, and 3 g. of potassium chloride daily should be given to all patients receiving the drug. In some instances, however, the potassium loss far exceeds this amount and with continued therapy hypokalaemia becomes inevitable. The potassium supplements can be increased to 6 g. of potassium chloride daily, but the patient may not tolerate even this amount of an essentially nauseating substance.

The large number of patients developing impending or actual hepatic coma was unexpected, although single instances have been reported by Richards (1957) and Castro (1957). The high incidence of a past history of hepatic coma in our patients (7 out of 13) was not more than is usually encountered in cirrhotic patients with ascites. Fluid retention can be regarded as a bad prognostic sign, and other signs of liver failure such as jaundice or neuropsychiatric complications are therefore common. Precoma of minor degree can easily be overlooked if the possibility is not considered. Abnormal electroencephalographic recordings are even more frequent. This distinction of patients with a past history of precoma was of practical importance, for no patient treated with chlorothiazide developed these complications unless there was this tendency. The drug should be given extremely cautiously if such a history is elicited or if neuropsychiatric abnormalities can be detected.

The mechanism of the hepatic coma is uncertain and will be discussed more fully later (Read *et al.*, 1958). It could not be related to failure of the diseased liver to metabolize chlorothiazide, for blood levels in cirrhotic patients did not differ from those obtained in normal subjects after a similar loading dose. Chlorothiazide *in vitro* has carbonic anhydrase inhibitor properties (Beyer *et al.*, 1957), and this is confirmed by the finding of an increased urinary excretion of bicarbonate and an accompanying rise in urinary *p*H after its administration. The carbonic anhydrase inhibitor acetazolamide induces hepatic precoma in some patients with liver disease (Webster and Davidson, 1956), and this has been related to a blockage in uptake of ammonium by peripheral tissues (Dawson *et al.*, 1957). Chlorothiazide might act in a similar way, although perhaps with less potency. Episodes of hepatic coma and precoma associated with chlorothiazide therapy have usually been accompanied by an elevation of the fasting arterial ammonium level (Read *et al.*, 1958). It seems unlikely that this is the only way in which chlorothiazide is toxic, for the effects are not proportional to the dose, and in some instances recovery may ensue when potassium is given.

A correlation was noted between the extent of the diuresis and the development of precoma. Patients with cirrhosis and ascites may develop hepatic precoma after abdominal paracentesis, and, although the mechanism is not clear, alterations of osmolarity and loss of electrolytes must be considered. A diuresis of comparable amount may act similarly. Potassium loss may be of particular importance (Read *et al.*, 1958). The potassium deficit associated with neuropsychiatric complications in cirrhotic patients is of the order of 300 mEq. This is a relatively small amount, but the brain of a patient who has experienced hepatic precoma may be particularly sensitive to many metabolic insults, of which hypokalaemia may be one (Sherlock, 1958). It is unfortunate that therapy is particularly dangerous in the group having the most satisfactory diuresis.

Summary

Chlorothiazide, 2 g. daily, was administered on 15 occasions to 13 patients with cirrhosis of the liver and ascites. On nine occasions the diuretic response was regarded as good; in the remaining six instances the response was poor. Refractory patients had an initial urinary sodium output of less than 1 mEq daily. Two refractory patients to chlorothiazide responded well to mersalyl.

Urinary potassium output increased and all patients not receiving potassium supplements developed hypokalaemia. Impending or actual hepatic coma was noted in 7 of the 13 patients treated. It was usually associated with a good diuretic response to chlorothiazide and in those with a previous history of hepatic precoma. The possible mechanisms of this reaction to chlorothiazide are discussed.

Four out-patients were treated for longer periods with intermittent chlorothiazide and continuous potassium supplements. Neuropsychiatric changes were not seen, but two patients became refractory to the drug.

Continuous chlorothiazide therapy should not be given to cirrhotic patients outside hospital. Potassium chloride (3–6 g. daily) should be given to all patients with cirrhosis receiving the drug. Particular care should be taken in patients with a previous history of the neuropsychiatric complications of liver disease.

We wish to thank Merck, Sharp and Dohme Ltd. for generous gifts of chlorothiazide (" saluric "), Miss Janet McLaren, B.Sc., for biochemical assistance, and Miss A. M. Lees for taking the electroencephalograms. We are also indebted to the Medical Research Council for a personal grant to one of us (J.L.) and for help with expenses.

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At a meeting of the Huntingdon Rural District Council on March 28 the council said farewell to Dr. J. R. GARROOD, who had been their part-time medical officer of health for 34 years. He took office on the death of his father-in-law, Dr. L. Newton, who was appointed as the council's first M.O.H. in 1894. Dr. Garrood was 84 when he retired.