ALDOSTERONE ANTAGONIST (SPIRONOLACTONE) AS AN ADJUNCT IN THE MANAGEMENT OF ASCITES IN CIRRHOSIS OF THE LIVER.

By C.C.S. Toh and O. T. Khoo
(Department of Clinical Medicine, University of Singapore.)

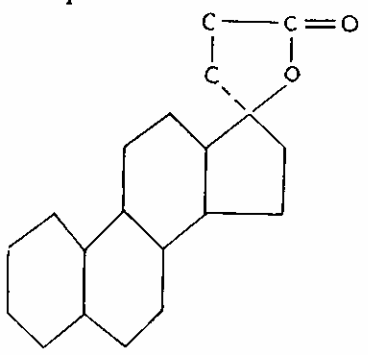
INTRODUCTION

One of the major problems in the management of cirrhosis is ascites. Paracentesis has been practised from ancient times and, though dramatic, it results in excessive protein loss. By some unknown mechanism it may lead to hepatic encephalopathy. The response to the standard diuretic agents is generally good initially, but becomes less satisfactory as time goes on. Furthermore, prolonged treatment with benzothiadiazine derivatives or organic mercurials tend to produce hypokalaemia by causing excessive urinary loss of potassium (Bayliss 1958, Read 1958). This frequently leads to hepatic encephalopathy (Sherlock 1957, Misra 1960) and even death. Only large oral supplements of potassium will replenish the loss and counteract this dangerous side effect.

In 1954, Luetcher and his associates observed sodium retaining activity in extracts from urine of oedematous patients with nephrotic syndrome, cardiac failure, and hepatic cirrhosis. This led to the suggestion that secondary aldosteronism might play an important role in the pathogenesis of oedema. Indirect evidence in support of this hypothesis is the observation that oedema and ascites may be severe in cirrhosis in spite of insignificant hypoalbuminemia. However, Hood et al (1960) observed that in oedema states responding to spironolactone, the aldosterone level may only be slightly raised. This suggests that it is important in maintaining oedema even though the secretion is normal or slightly raised.

PHARMACOLOGY

Since Kagawa and his associates (1957) synthesized the group of Spironolactone compounds with aldosterone-like structures, these have been widely tried and used with good results (Liddle 1958, Slater 1959, Clowders 1960, Shaldon 1960, Edmonds 1960). The basic "Spironolactone" configuration is represented thus:



* Marketed as ALDACTONE.

It acts by antagonising aldosterone, hence does not work in adrenalectomised animals. The effect is the same as the withdrawal of aldosterone. It has no effect on aldosterone, 17-ketosteroid and 17-hydroxysteroid secretion. It has no effect on the glomerular filtration rate (Coppage and Liddle, 1960). Unlike the benzothiadiazine compounds which act primarily on the proximal tubules (Vander 1959) the Spironolactones act on the distal tubules. Hence by combining both, an enhanced diuresis was achieved (Shaldon, 1960).

The preparation used in the present investigation is the orally administered Spironolactone SC 9420 (Searle*). Absorption is good. Apart from very occasional rash and drowsiness, no serious toxicity has been reported. Hepatic encephalopathy may occur but there is no evidence to prove that it is directly responsible. There was no rise in the blood ammonia levels during treatment (Hood 1960).

OBJECTS OF INVESTIGATION

The aim of the present investigation was to find out the effect of this drug used in conjunction with the standard measures in the treatment of resistant ascites in our local cirrhotic patients. It was also hoped that the results might throw some light on the extent of secondary hyperaldosteronism in our cirrhotics as we do not have as yet a laboratory method for estimating aldosterone output.†

METHOD

Six patients with hepatic cirrhosis were studied. All had unequivocal features of cirrhosis with abnormal bromsuphthalein retention. Liver biopsy was not done in view of hypersplenism and thrombocytopenia. In two patients, subsequent necropsy confirmed the diagnosis. Investigations included liver function tests, haemoglobin, total white count, platelet count, bleeding time, clotting time, prothrombin time, serum electrolytes, daily weighing, intake and output, and in 4 cases daily excretion of electrolytes before and during spironolactone therapy. All patients were put on a low salt diet containing 20 milli-equivalents of sodium and 40 to 60 milli-equivalents of potassium. All were initially treated for a variable period with low salt diet, one of the benzothiadiazine compounds

† A method is now available.

TABLE 1

CASE	SEX	AGE	HAEMATOLOGY LIVER FUNCTION TESTS									Results of Treatment	Side-effects
			Hb%	TW/cmm	Platelets/ cmm	T.T. Units	S Bil. mgm%	S. A. Ph. Units	B.S.P. (R)%	S.Alb. gm%	S.Glob. gm%		
1. T. A. C.	F	42	50	2,000	30,000	2	1.3	20	—	3.5	3.0	Excellent	Nil
2. C. A. K.	M	67	70	3,400	—	6	2.3	12	12	2.1	3.4	Good	Generalised Erythema
3. R. R.	M	37	81	5,000	60,000	4	1.8	25	33	3.2	4.1	Fair diuresis but died of cerebellar haemorrhage	
4. I. S.	M	84	84	6,800	100,000	6	2.6	1.6	—	3.0	3.8	Good	Nil
5. T. P.	F	48	40	1,500	40,000	3	0.4	20	7	3.6	3.6	Fair	Nil
6. A. B. D.	M	56	71	6,300	68,000	6	1.5	8	23	2.6	4.7	Good	Nil

Explanation:
T. T. = Thymol Turbidity
S. Bil = Serum Bilirubin
S. A. Ph. = Serum Alkaline Phosphatase
B. S. R. (R) = Bromsulphthalein (Retention)
S. Aib. = Serum Albumin
S. Glob. = Serum Globulin

(Chlorothiazide or the Trifluomethyl derivative, "Rontyl" or the 3-cyclopentylmethyl derivative, "Navidrex") and with intermittent injections of 2 c.c. mersalyl. Oral potassium chloride in divided doses of 3 grams to 4 grams daily were given if the serum potassium levels were subnormal. Once weight reduction had reached a stationary level, spironolactone SC 9420 was added in divided doses of 400 mgm. daily. When there was hyponatremia initially prednisolone in divided doses of 15 mgm. daily was also given.

RESULTS

The results of treatment are summarised in Table 1.

Case I. T. A. C.

Following an initial response to the standard measures, the weight actually increased. The Sodium/potassium ratio was below 1. Four days after adding spironolactone, the excretion of both sodium and potassium was increased enormously. However, the ratio exceeded 1 in only one day. Serum potassium levels were maintained at normal.

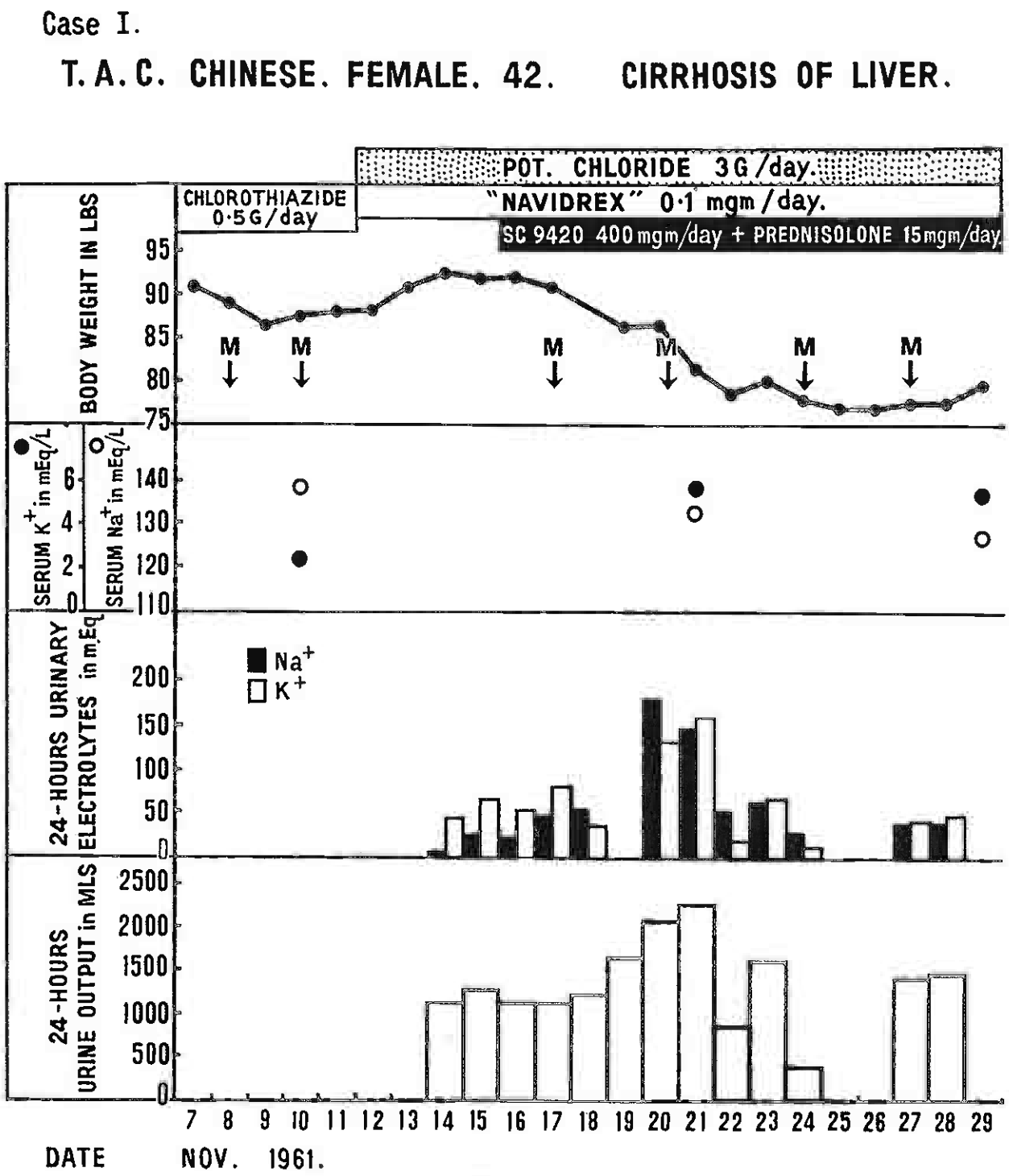


Fig. 1.

Case II. C.A.K.

The response was immediate. The urinary concentrations of electrolytes were raised. The sodium/potassium ratio was increased from just over 1 to 3 or more during the period of massive diuresis. Note that the absolute amount of potassium lost was not significantly increased during this period. The serum sodium and potassium were maintained at normal values. Total weight loss amounted to 12 lbs.

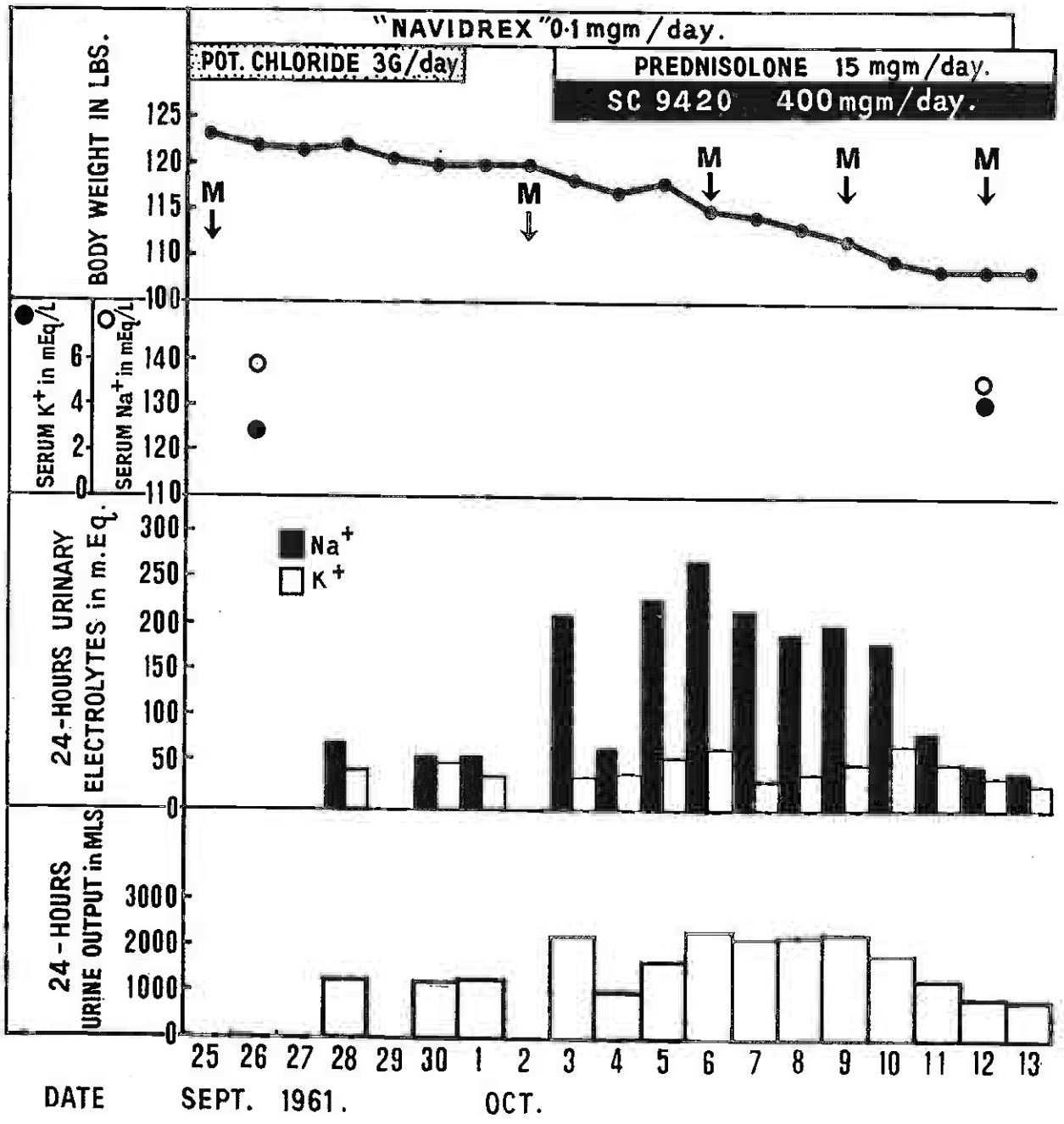


Fig. 2.

Case III. R.R.

Response to standard measures was fair. Just prior to the addition of spironolactone, the sodium and potassium excretion levels were very low. Within 24 hours of commencement of spironolactone therapy, the total sodium excretion rose to 80 milli-equivalents with a less proportionate rise in potassium excretion.

Patient developed a flapping tremor and generalised weakness on the eighth day. Prednisolone was given, but he lapsed into coma on the eleventh day. Lumbar puncture revealed normal C.S.F. He died on the fourteenth day. Necropsy showed gross portal cirrhosis and haemorrhage into the cerebellum extending into the fourth ventricle.

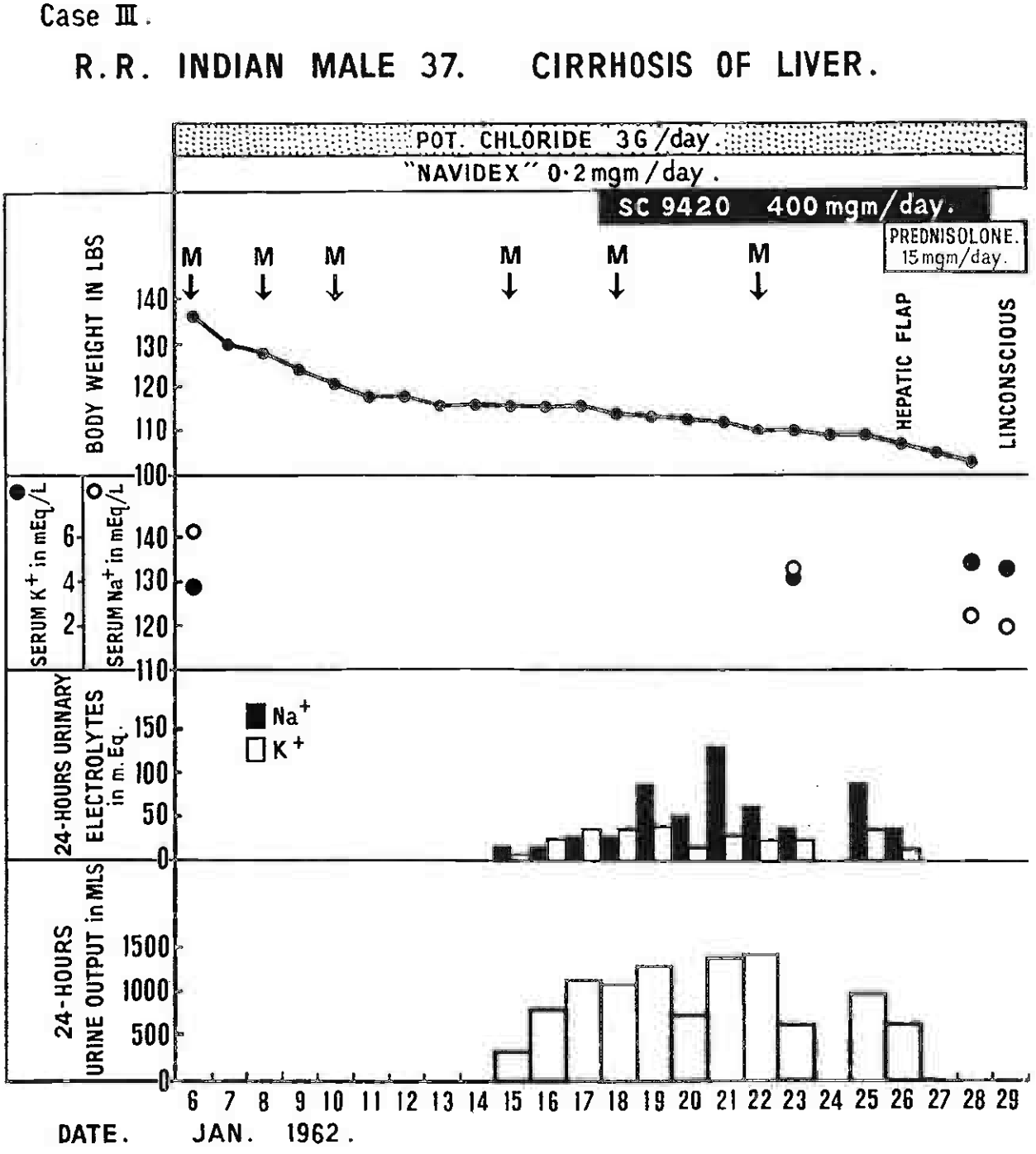


Fig. 3.

Case IV. I.S.

With 1.5 grams of chlorothiazide and mersalyl there was no diuresis. In fact, the weight increased. Ten days treatment with Spironolactone and additional "Rontyl" produced a weight loss of 30 lbs. without any side effect.

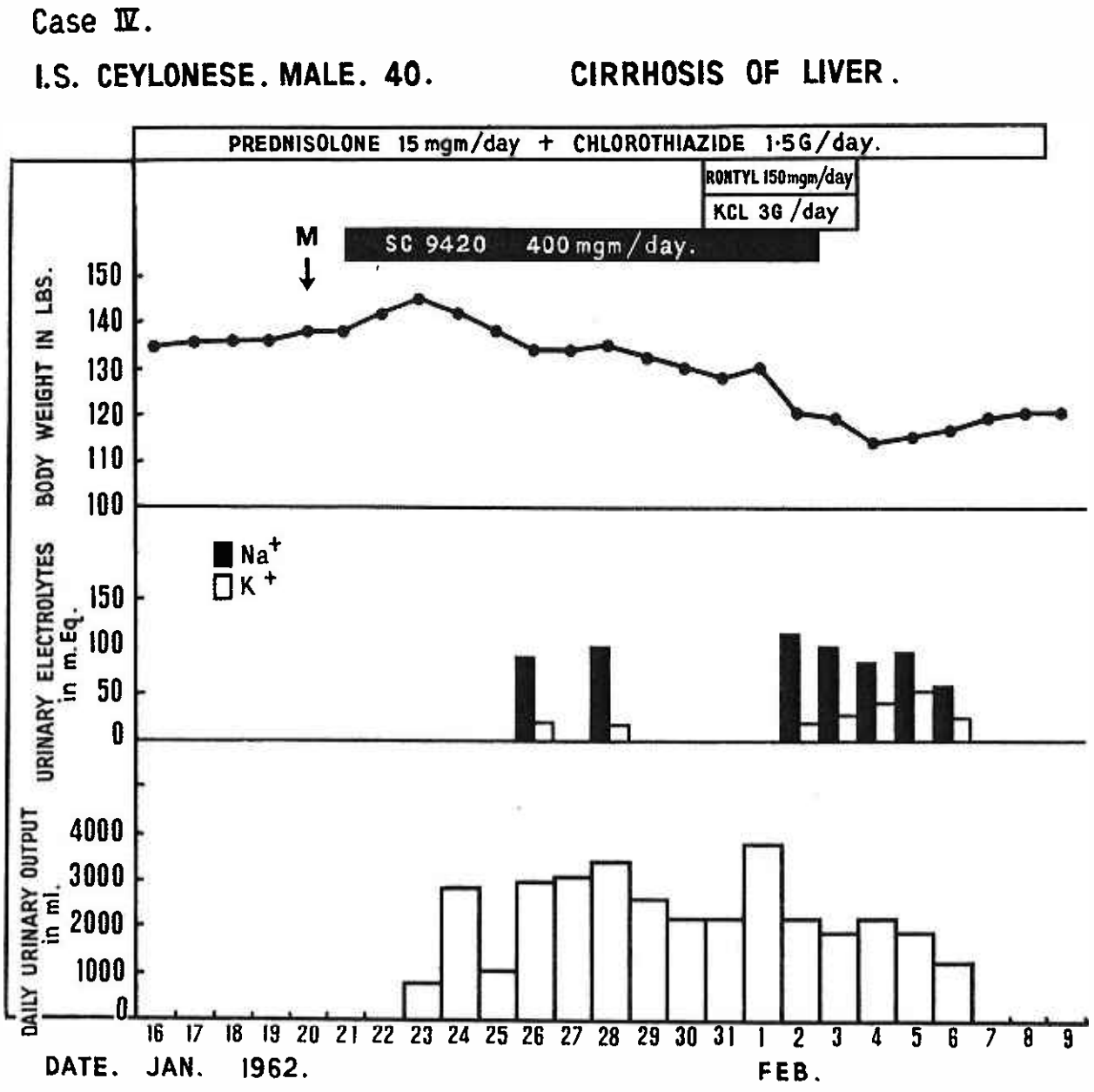


Fig. 4.

Case V. T. P.

The response to mersalyl and chlorothiazide was poor. Six days' treatment with added spironolactone produced a weight loss of only 6 lbs. A second course of three days with a bigger dose of chlorothiazide considerably enhanced the diuretic response. Serum sodium and potassium levels remained normal.

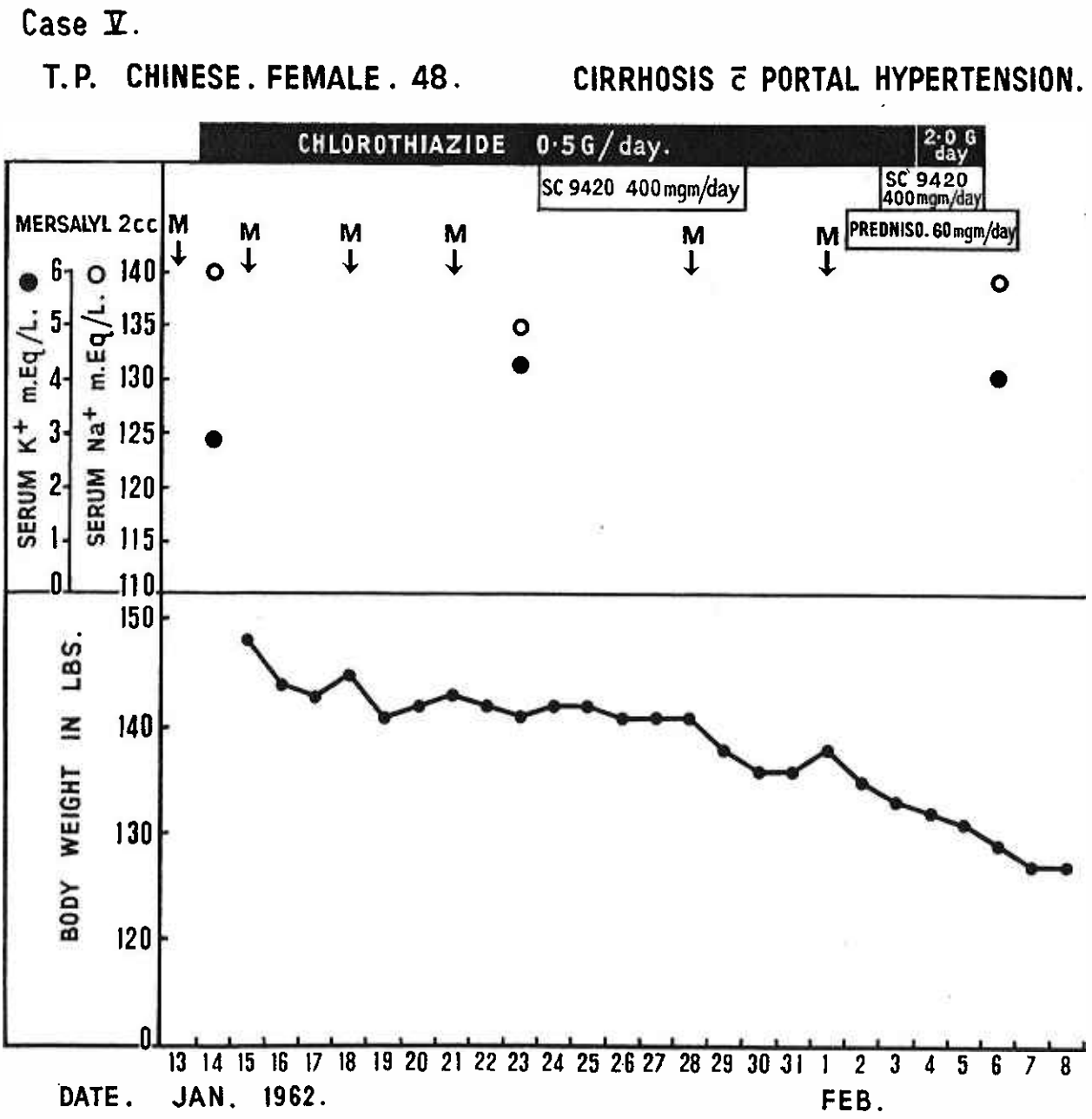


Fig. 5.

Case VI A.B.D.

Initial ascites was gross and distressing. Four paracenteses at close intervals at another hospital produced only transient effect. Response to mersalyl was fair; but while on 0.2 mgm. "Navidrex" daily, excretion of sodium fell to well below 1.0 mEq. Response to Spironolactone appeared on the third day and reached its maximum on the fifth day. The sodium/potassium ratio rose to nearly five on the sixteenth day. Good response to diuretics continued for four to five days after the stopping of spironolactone. 24 lbs. were lost in the seventeen days of combined spironolactone therapy. In spite of the 4 grams of potassium chloride supplement daily, the serum potassium level was only 2.7 mEq/Litre at the end of treatment. After another seventeen days in hospital, the patient regained 10 lbs. in spite of salt restriction and diuretics. A further course of eleven days of combined spironolactone, prednisolone and diuretic therapy resulted in a fall in weight of only 6 lbs.

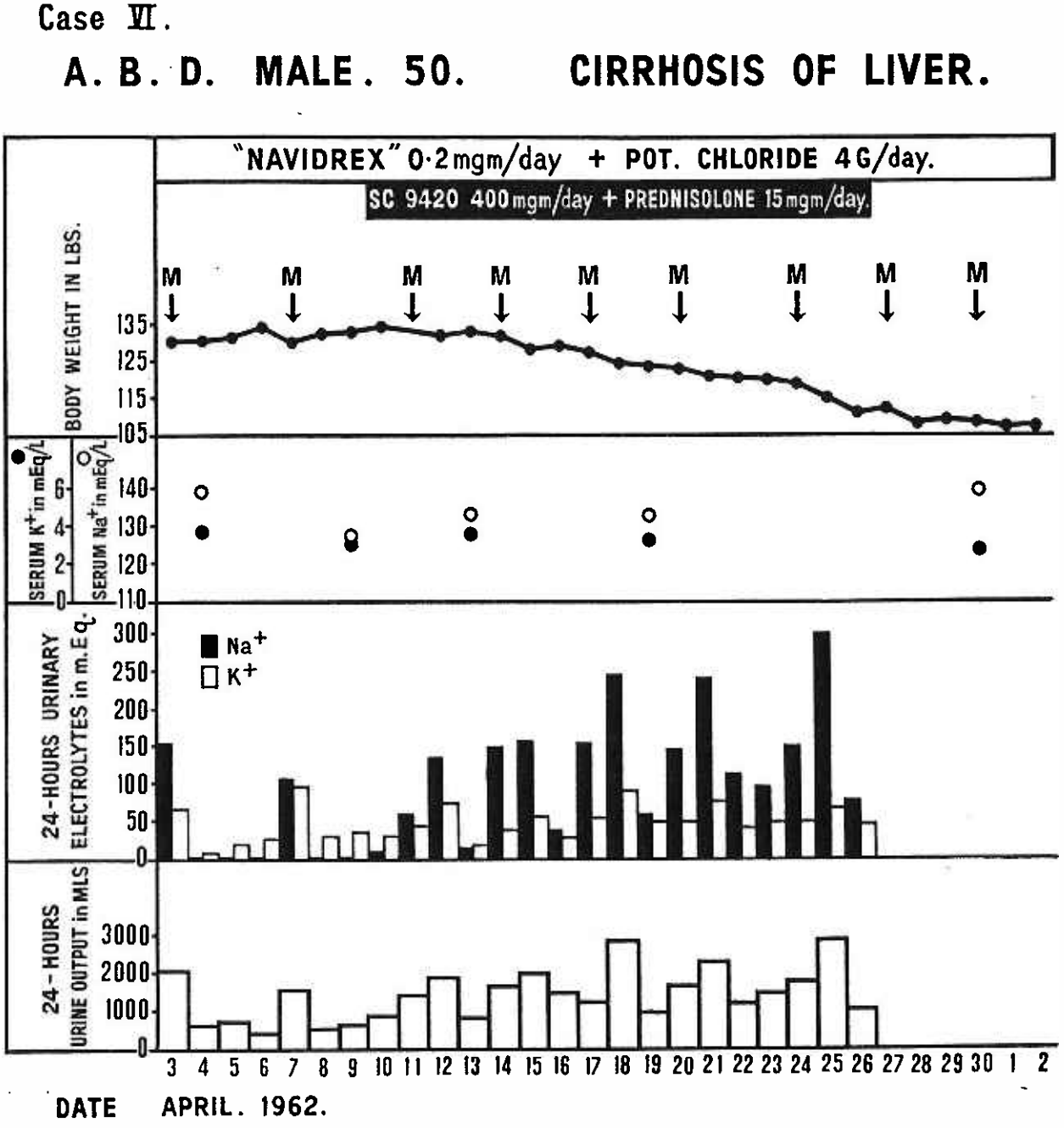


Fig. 6

Case VI.

A.B.D. MALE. AGE 50. CIRRHOSIS OF LIVER.

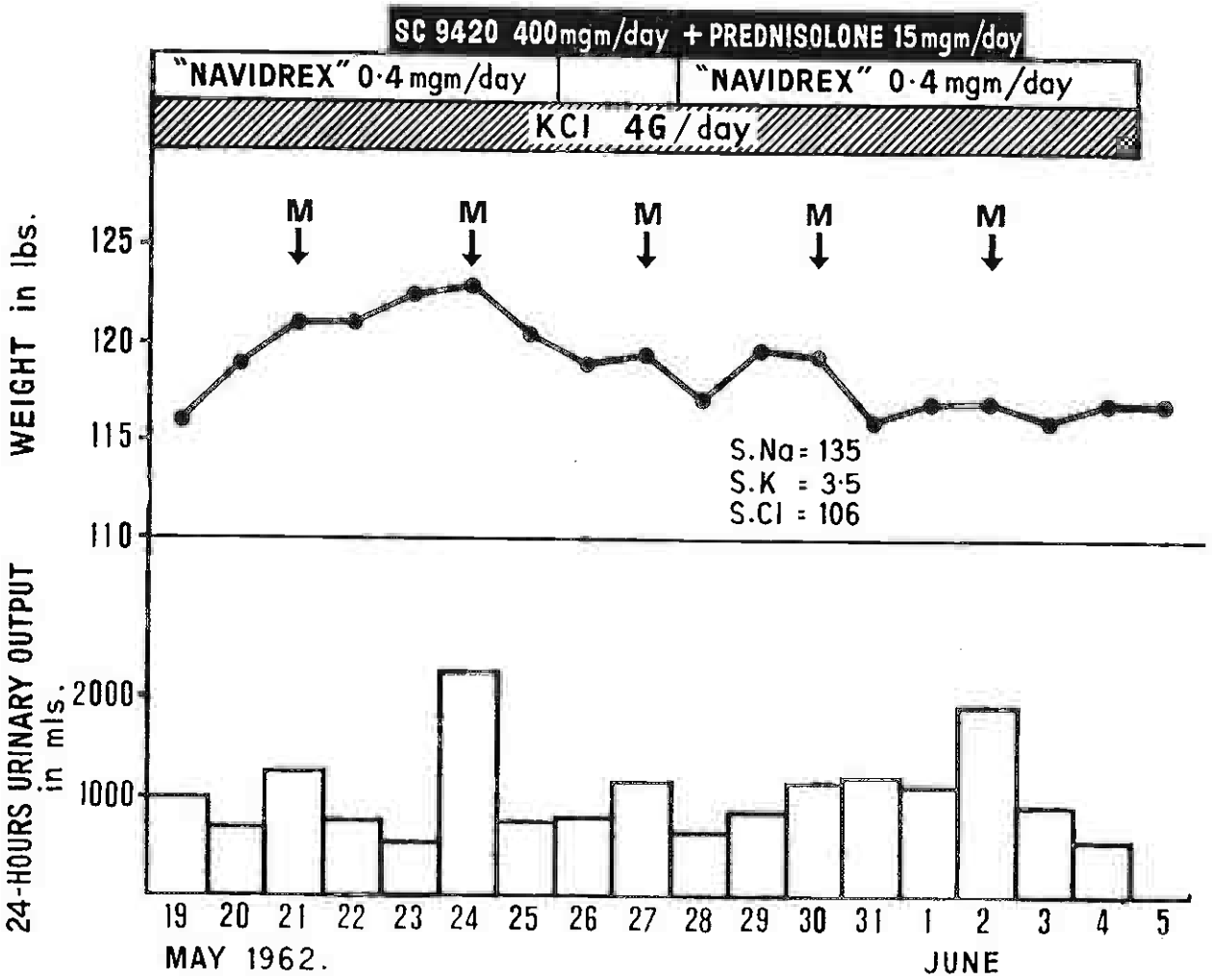
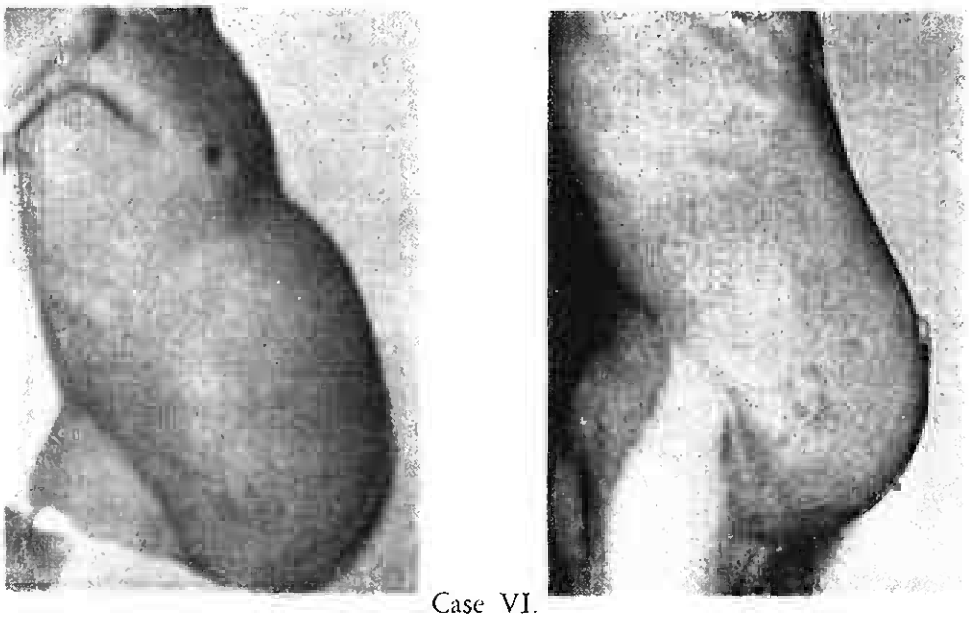


Fig. 7.



Case VI.

Before addition of Spironolactone. After first course.

DISCUSSION

Although the role of aldosterone in homeostasis is not completely understood there is sufficient evidence to believe that its production in excess in secondary hyperaldosteronism is important for the initiation and continuance of oedema states. Luetcher and Curtiss (1955) demonstrated an inverse correlation between the urinary sodium and the aldosterone secretion. Furthermore, the urinary potassium/sodium ratio correlates directly with the aldosterone secretion. These changes are reversed by Spironolactone (Shaldon 1960, Tublin 1960, Edmonds 1960) which acts as a competitive inhibitor to aldosterone at the distal tubules (Liddle, 1958).

In normal people and oedematous patients, a reduced sodium intake stimulates endogenous aldosterone secretion. This is further aggravated by sodium loss induced by a diuretic. Hence, in clinical practice, prolonged use of salt restriction and diuretics create a vicious cycle. The oedema state becomes resistant and potassium loss in the urine may be in excess of sodium loss. Edmonds and Wilson (1960) suggested that the potassium loss was related to the level of activity of the sodium retaining steroids. Hence, spironolactone is useful not only in augmenting sodium diuresis but also in preventing excessive potassium loss. In our series, the reversal of the urinary sodium/potassium during diuresis was noticeable except in Case 1.

The dose of SC 9420 used here did not exceed 400 mgm. daily. However, the dose could safely be increased to 800 mgm. daily if necessary (Clowders 1960).

The maximal response in our series occurred on the 4th or 5th day with the exception of Case 2 in whom the effect was almost immediate and maintained for some days.

There is no contra-indication to the use of spironolactone. Where the serum sodium is low initially, there is a risk of precipitating hepatic precoma by inducing hyponatremia as a result of sodium diuresis. For this reason, its use in conjunction with prednisolone is recommended (Morrison and Chalmers, 1960) (Shaldon 1960, Clowders 1960). In addition to the water diuresis induced by prednisolone, the patient's appetite and well being seem improved by this drug. In Case 3 of our series, the initial serum sodium level was normal; consequently, prednisolone was withheld. However, the level fell subsequently and hepatic flap was observed. Apart from a transient and mild erythematous rash, no side-effects directly attributable to spironolactone were observed.

The hepatic flap and drowsiness observed in Case 3 were features of hepatic encephalopathy rather than cerebellar haemorrhage from which he succumbed. Hepatic pre-coma developing as a result of massive diuresis produced by spironolactone and diuretics has been observed by others. Hypokalemia in cirrhosis induced by prolonged thiazide therapy and salt restriction is associated with hepatic encephalopathy and electroencephalographic changes (Sherlock 1957). This dangerous complication is commonly seen in cases treated in outpatients here where patients refuse to take potassium supplements because of their unpleasant taste and gastric effects. It is stated that spironolactone is effective in counteracting the excessive potassium loss and actually produces hyperpotassemia; though on theoretical grounds this is to be expected, experience does not confirm this point in every instance as shown clearly in Case 1.

In Case 6, the absolute potassium loss during spironolactone therapy was slightly increased and the serum potassium level stayed low all the way in spite of oral supplements. Ross (1958) made the similar observation in one out of every six cases treated with thiazide derivatives and spironolactone. As the total body potassium may vary widely, the actual potassium excretion in the urine is a more reliable guide of potassium loss than the serum level.

In all the six cases, there is no doubt that diuresis was initiated or enhanced by the combined therapy. Subsequent follow up of five cases showed that body weights began to show an upward trend about five days after the cessation of spironolactone therapy though in most instances the fluid retention was never as severe as before treatment with spironolactone. In some of Sherlock's cases (1958) once a massive diuresis was achieved, the ascites did not reaccumulate after the drug was stopped. In Case 6, a second course of treatment resulted in a comparatively smaller weight loss. Some tolerance due to an unknown mechanism had developed.

SUMMARY

1. Six cases of hepatic cirrhosis and resistant ascites were investigated and successfully treated with the combined regime of salt restriction, diuretics, spironolactone with or without prednisolone and oral potassium supplements.

2. All six cases showed a fair to good diuretic response when spironolactone was added, thus showing that secondary hyperaldosteronism plays an important part in the genesis or maintenance of oedema in our local cirrhotic patients.

3. In the 4 cases studied in relation to urinary electrolyte excretion, the sodium/potassium ratio was increased with the exception of Case 1.

4. One patient with hyponatremia developed hepatic precoma, and subsequently died of cerebellar haemorrhage as a result of secondary thrombocytopenia and prothrombin deficiency.

5. The benefits of administering prednisolone with spironolactone were discussed and stressed.

6. Hypokalaemia is a constant danger in cirrhotic patients. Potassium supplements should still be given with spironolactone where initial serum potassium level is low.

7. Subsequent follow-up showed that with the cessation of spironolactone therapy the ascites gradually reaccumulated though not to the extent of what they were before treatment.

8. In Case 6, a second course of treatment produced less favourable response. The reason for this is not clear.

9. In view of the expense of this drug, it is recommended only to cases which have failed to respond to the usual measures.

ACKNOWLEDGEMENT

We are indebted to our colleagues for the opportunity to study cases admitted under their care. To Dr. P. C. Leong, Biochemistry Department and Mrs. Meyer, Dietary Department, we extend our thanks and gratefulness for their help and co-operation.

The Aldactone used for this clinical trial was supplied by Dr. Venning of Searle Laboratories, to whom we are grateful.

REFERENCES

Bayliss, R. I. S., Marrack, K., Pirkis. J., Rees, J. R., Silva, J. R. (1958) "Chlorothiazide: An oral Diuretic" Lancet. 1 : 120.

Clowdus, B. F. Higgins, J. A., Rosewear, J. W., Summerskill, W. H. J., (1960) "The Treatment of Refractory Ascites with a new Aldosterone Antagonist in Patients with Cirrhosis". Proc. Mayo Clin 35:97.

Coppage, W. S., Grant, W. Liddle, (1960) "Mode of Action and Clinical Usefulness of Aldosterone Antagonists". Ann. N. Y. Acad. Sc., 88:815.

Edmonds, C. J., (1960) "An Aldosterone Antagonist and Diuretics in the Treatment of Chronic Oedema and Ascites". Lancet 1:509.

Edmonds, C. J., Wilson, G. M. (1960) "The Action of Hydroflumethiazide in Relation to Adrenal Steroids and Potassium Loss". Lancet 1:505.

Hood, G. W., Jr., S. Richardson Hill, Jr., James, A., Pittman, Jr., T. A. Farmer, Jr., (1960) "Studies on The Metabolic Effect of Spironolactone in Man". Ann. N. Y. Acad. Sc. 88:865.

Kagawa, C.m., Cella, J. A., Van Arman, C. G. (1957) "Action of New Steroids in Blocking Effects of Aldosterone and Deoxycorticosterone on Salts". Science, 126:1015.

Liddle, G. W. (1957) "Sodium Diuresis Induced by Steroidal Antagonists of Aldosterone". Science 126:1016.

Luetcher, J. A., Jr., Johnson, B. B., (1954) "Observations on the Sodium Retaining Corticoid (Aldosterone) in the Urine of Children and Adults in Relation to Sodium Balance and Oedema". J. Clin. Investig. 33:1441.

Morrison, R. S., Chalmers, T. C., (1960) "Combined Diuretic and Steroid Therapy in Cirrhosis with Ascites" Ann. N. Y. Acad. Sc. 88:907.

Misra, S. S., Teotia, S. P. S. (1960) "Hepatic Coma Precipitated by Chlorothiazide in Hepatic Cirrhosis with Ascites". Lancet 1:464.

Read, A. E., Laidlaw, J., Haslam, R. M. Sherlock, S. (1959) "Chlorothiazide In Control of Ascites in Hepatic Cirrhosis". B. M. J. 1:963.

Ross, E. J., (1959) "Aldosterone in Clinical and Experimental Medicine". Blackwell Scientific Publications.

Ross, E. J. (1961) "Importance of Potassium Supplements During the Use of Spironolactone and Thiazide Diuretics". B. M. J. 1:1508.

Shaldon, S., McLaren, J., Sherlock, S. (1960) "Resistant Ascites Treated by Combined Diuretic Therapy". Lancet, 1:609.

Sherlock, S., Read, A. E., Laidlaw, J. L., Haslam, R., (1957-1958)" "Chlorothiazide in Liver Disease". Ann. N. Y. Acad. Sc. 71:430.

Slater, J. D. H., Moxham, A., Harter, R., Nabarro, J. D. N. (1959) "Clinical and Metabolic Effects of Aldosterone Antagonism". Lancet, 2:931.

Tublin, I. N. (1960) "The Treatment of Oedema with An Orally Administered Spironolactone" J. A. M. A., 174:869.

Vander, A. J., Malvin, R. L., Wilde, W. S., Sullivan, L. P. (1959) "Localisation of the Site of Action of Chlorothiazide by Stop Flow Analysis". J. Pharmacol. & Experimental Therap., 125:19.

* Aldactone-A is now available. The therapeutic dose is approximately a quarter that of Aldactone.