SPIRONOLACTONE (ALDACTONE) THERAPY FOR ASCITES DUE TO CIRRHOSIS OF THE LIVER*

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THE DEVELOPMENT of ascites is a sign of serious liver decompensation. Control of ascites is a difficult problem in management. The life expectancy of a cirrhotic patient is short when repeated paracenteses are required for control of ascites. Repeated paracenteses cause marked protein depletion and occasionally may precipitate hepatic coma. It is generally agreed that paracentesis should be reserved for those cases in which medical management fails to control the ascites.

The relative importance of portal vein hypertension, decreased plasma osmotic pressure due to low plasma proteins, increased antidiuretic hormone activity and renal sodium retention in the development of ascites has not been established. Treatment of ascites due to cirrhosis has been variable owing to the numerous factors involved in its pathogenesis. Ascites has been decreased by medical management, consisting of abstinence of alcoholic intake and a high protein diet with vitamin supplements.[1] The effects of salt-free intravenous albumin infusions on ascites are transient. Decreasing the portal vein hypertension by surgical means is contraindicated in the presence of ascites. The development of potent agents producing renal sodium loss has been the most significant advance in the medical therapy of ascites.

Renal retention of sodium is necessary for the development of ascites in patients with hepatic cirrhosis. The decompensated cirrhotic patient retains sodium on a low sodium intake. Onen[2] has shown that the majority of decompensated cirrhotics have a markedly lowered glomerular filtration rate, which decreases the filtered load of sodium presented to the renal tubules. Increased production and increased urinary excretion of aldosterone have been demonstrated in the cirrhotic patient with ascites.[3] Farrell[4] reports that the secretion of aldosterone appears to be stimulated by a tropic factor which arises from the posterior commissure-pineal area of the brain stem. ACTH is of minor importance in the control of aldosterone secretion.[5] Recent reports[6, 7] suggest the kidney as a factor involved in control of aldosterone secretion. It appears likely that some function of intravascular volume provides the stimulus to increase aldosterone production.[8] Aldosterone increases renal sodium reabsorption, probably in the distal tubule. These two factors, the low glomerular filtration rate and the increased aldosterone production, are probably significant in producing the marked renal sodium retention in the cirrhotic patient with ascites.

Many drugs that stimulate renal sodium excretion, combined with a low sodium intake, have been used in the treatment of cirrhotic ascites. Mercurial diuretics have been effective in some cases, but the long-term results have not been impressive. The benzothiadiazine derivatives have been more effective, but they produce hypokalemia with extracellular alkalosis which is poorly tolerated by the cirrhotic patient. The increased urinary potassium loss in cirrhotics treated by the benzothiadiazines is frequently not prevented by increasing the oral intake of potassium.[9] Steroids of the 17-spirolactone group have been shown to inhibit the effects of aldosterone on the renal tubule, producing increased renal sodium excretion. Short-term studies have shown the effectiveness of the 17-spirolactones in the treatment of ascites due to cirrhosis.[10, 11] Orally effective spironolactone (Aldactone) is the most effective aldosterone-inhibiting drug at present available. This study concerns the long-term effect of spironolactone in the treatment of ascites due to cirrhosis. Spironolactone was used in three patients and combined with chlorthalidone (Hygroton) during the course of treatment in one patient. The long-term effect of spironolactone on sodium, potassium, water and acid-base balance was studied.

PLAN OF INVESTIGATION

Three cirrhotic patients with ascites were chosen for study. Prior to study on a metabolic ward the patients had demonstrated resistance to therapy directed toward decreasing the ascites. A constant sodium and potassium diet was used throughout the study. Frequent determinations of sodium and potassium were carried out on duplicate diets and the mean value of these determinations was recorded as the intake of sodium and potassium. The patients were on a constant diet at least five days before the studies. Twenty-four-hour urinary sodium, potassium and chloride determinations were performed throughout the study. Diet protein varied from 30 to 90 g. per day. The caloric intake was approximately 2000 calories daily. The oral fluid intake was recorded and was unrestricted.

Twenty-four-hour urinary creatinine clearances were determined weekly. Serum sodium, potassium, chlorides, CO_2 combining power, hematocrit, plasma proteins and blood urea values were determined weekly. Venous blood pH was estimated frequently throughout the study. Drug therapy varied, depending upon the response of each patient.

CASE HISTORIES AND RESULTS OF INVESTIGATION

CASE 1.—A 62-year-old white male was seen in 1957 with gouty arthritis and hypertensive cardiovascular disease (blood pressure was 186/100 mm. Hg). His liver and spleen were not palpable. In May

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1958, he developed weakness, anorexia and vomiting. Obstructive jaundice was present. He had marked ascites and the liver was palpable 3 cm. below the right costal margin. In July 1959, 4500 c.c. of peritoneal fluid was removed. Paracentesis was repeated in September 1959, and 6000 c.c. of fluid was obtained. A low sodium diet, 1 g. of chlorothiazide daily and intermittent administration of intravenous albumin (total dose 600 g.) from September 1959 to February 1960 did not control the ascites. The spleen was palpable in February 1960, when he was admitted to hospital with an upper gastrointestinal tract hemorrhage and hepatic coma. The blood ammonia value was 530 μg. % and the hematocrit 29%. Treatment with oral neomycin and intravenous glucose in water produced marked improvement, the blood ammonia level decreasing to 112 μg. %. The response to spironolactone therapy was studied from March 28 to June 16, 1960 (81 days). An episode of hepatic coma temporarily interrupted the study on the 37th day.

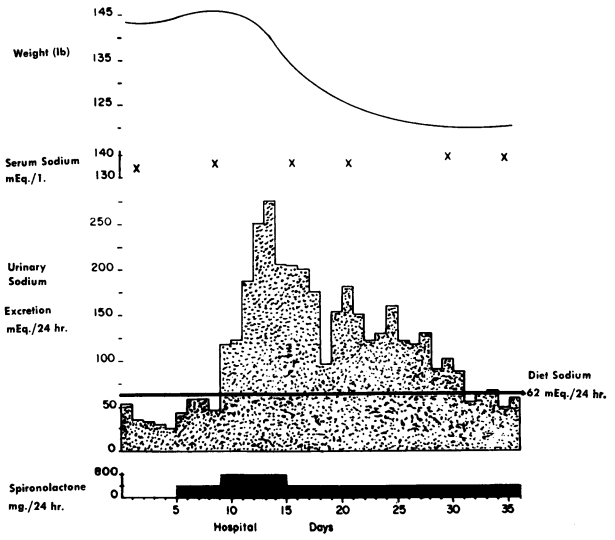

Fig. 1—Sodium balance in Case 1 prior to the episode of hepatic coma. The patient was a 62-year-old man with cirrhosis of the liver and ascites who was treated by spironolactone (Aldactone).

Fig. 1 illustrates this patient's sodium balance prior to the episode of hepatic coma. Before spironolactone therapy was begun, the patient was retaining sodium and gaining weight. Administration of spironolactone, 400 mg. per day for four days, produced a slight increase in urinary sodium excretion. The dose was increased to 800 mg. daily, and this produced a marked increase in urinary sodium excretion with concomitant fall in weight. Spironolactone was reduced to 400 mg. daily on the 15th day, and urinary sodium excretion remained greater than the dietary intake of sodium from the 15th to the 36th day. The serum sodium remained within normal limits.

Fig 2 shows the sodium balance after the episode of hepatic coma. Increased urinary excretion of sodium was maintained on a dose of 400 mg. of spironolactone a day. Reduction of the dose of spironolactone to 200 mg. daily produced a positive sodium balance. A dose of 300 mg. a day at the end of the study resulted in slight negative sodium balance. The serum sodium throughout the entire study remained within normal

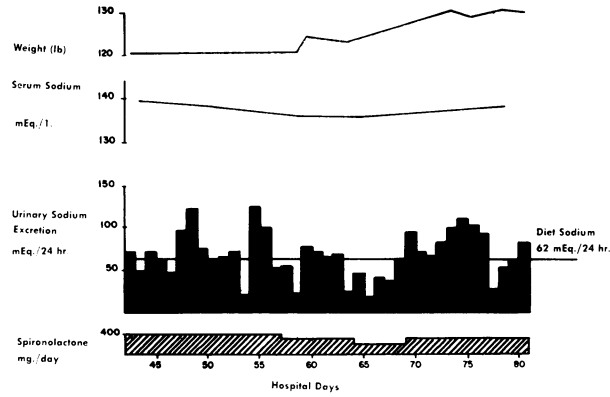

Fig. 2.—Sodium balance in Case 1 after the episode of hepatic coma.

limits. Spironolactone therapy completely controlled the ascites in this patient.

Fig. 3 shows the potassium and water balance prior to the episode of hepatic coma. The urinary potassium excretion was approximately the same as the dietary intake during spironolactone therapy. The serum potassium increased to 5.5 mEq./l. on one occasion but was otherwise within normal limits. There was a marked increase in urinary volume concomitant with the increased sodium excretion. Before therapy the mean fluid intake was 522 c.c. greater than the mean urinary output per 24-hour period. After spironolactone therapy the mean urinary output was 185 c.c. greater than the mean oral fluid intake per 24-hour period.

Fig. 4 shows the potassium balance after the episode of hepatic coma. Reduction of spironolactone therapy to 300 mg. per day produced an increased urinary potassium excretion. The serum potassium level remained within normal limits throughout the study. The CO_2 combining power decreased slightly at the termination of this study.

Fig. 5 shows the weekly hematocrit and plasma protein values in relation to the therapy and diet. There was a gradual increase in both plasma albumin and globulin. The hematocrit value increased slightly, but not to the degree that the plasma proteins increased. Hepatic coma occurred when the dietary protein reached 90 g. per day.

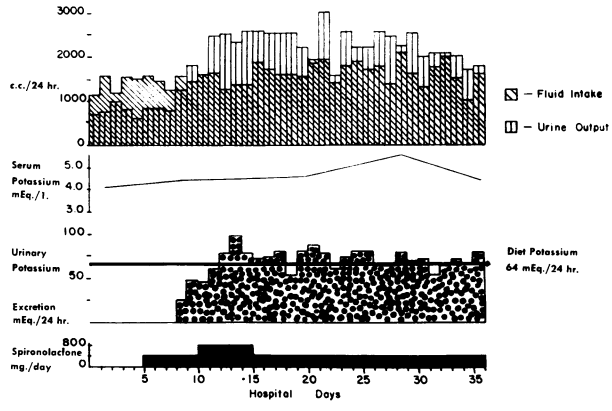

Fig. 3.—Potassium balance in Case 1 prior to the episode of hepatic coma.

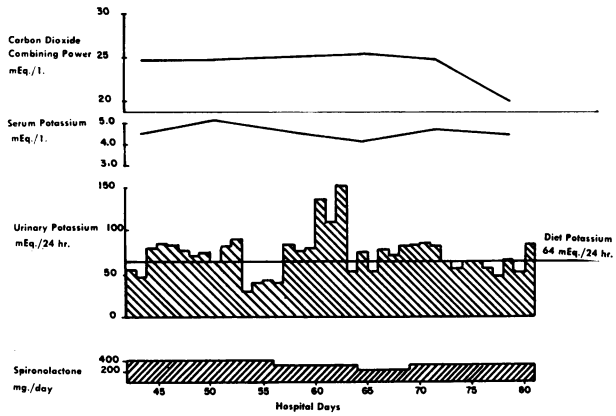

Fig. 4.—Potassium balance in Case 1 after the episode of hepatic coma.

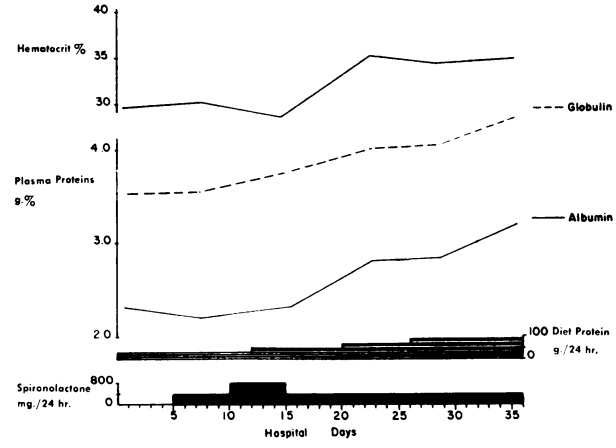

Fig. 5.—Hematocrit, plasma proteins and diet protein values in Case 1 prior to the episode of hepatic coma.

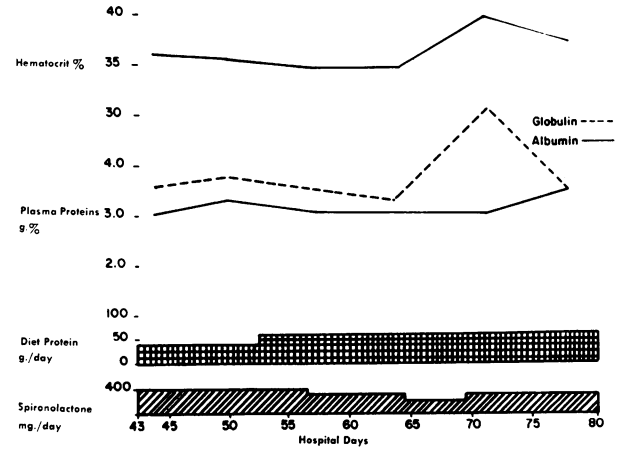

Fig. 6.—Hematocrit, plasma proteins and diet protein values in Case 1 after the episode of hepatic coma.

Fig. 6 records the weekly plasma proteins and hematocrit levels after the episode of hepatic coma. With the patient on a diet of 60 g. of protein per day, the plasma albumin continued to increase, and at the end of the study the plasma globulin and albumin values were equal. The hematocrit increased slightly.

The mean 24-hour fluid intake during the period after hepatic coma was 1788 c.c. The mean urinary output during the same period was 1735 c.c.

TABLE I.—LIVER FUNCTION TESTS IN CASE 1

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesterol flocculation (after 48 hr.)*	*Thymol turbidity (units)*
Sept. 1959	1.9	23.4	3+	4.7
Feb. 1960	2.5	28.0	4+	13.0
May 1960	0.8	13.8	4+	13.8

Table I shows the results of representative liver function tests during the period of study. The serum bilirubin gradually decreased; bromsulphthalein retention decreased; and the 48-hour cephalin-cholesterol flocculation and thymol turbidity values increased in keeping with the elevated plasma globulin.

The glomerular filtration rate, as measured by the endogenous creatinine clearance, increased slightly during spironolactone therapy.

The patient was discharged on spironolactone 100 mg. three times daily. He was readmitted eight days later in hepatic coma, produced by a high protein intake. He responded well to treatment for hepatic coma. He was discharged on a regimen of chlorothiazide, 0.5 g. daily for four days followed by four days with no medication. He has continued to take chlorothiazide intermittently, and in February 1961 was free from edema and ascites. The liver and spleen remained palpable.

CASE 2.—A 66-year-old white man had an upper gastrointestinal hemorrhage in May 1958. He recovered on conservative management. After the upper gastrointestinal bleeding he had frequent episodes of epigastric pain, before meals and at night, which were relieved by food. In January 1960, he noted swelling of his abdomen and ankles. He was admitted to hospital in May 1960, because of increased ascites and edema.

Physical examination revealed marked edema of the legs, extending into the soft tissues of the abdomen, and massive ascites. The upper extremities were thin. Palmar erythema and gynecomastia were present. The liver was palpable 4 cm. below the costal margin. The spleen was not palpable.

An upper gastrointestinal series showed deformity of the duodenal cap with no evidence of esophageal varices.

The patient responded to intitial treatment of a low sodium diet and chlorothiazide 1 g. per day, gradually losing 18 lb. in weight. Before the metabolic balance study, ascites and peripheral edema remained a problem in management. The patient's response to therapy was studied from June 8, 1960, to September 5, 1960 (93 days).

Fig. 7 records the results of the complete sodium balance study in Case 2. Before therapy there was a slight tendency to retain sodium. Institution of benzydroflumethiazide (Naturetin) therapy produced a marked intitial increase in the 24-hour urinary sodium excretion to 205 mEq. Continued therapy with benzydroflumethiazide had little effect on urinary sodium excretion. Spironolactone therapy, after the benzydroflumethiazide was discontinued, produced a prolonged increased urinary sodium excretion. Termination of spironolactone therapy resulted in a marked decrease in urinary sodium excretion. Re-institution of 200 mg.

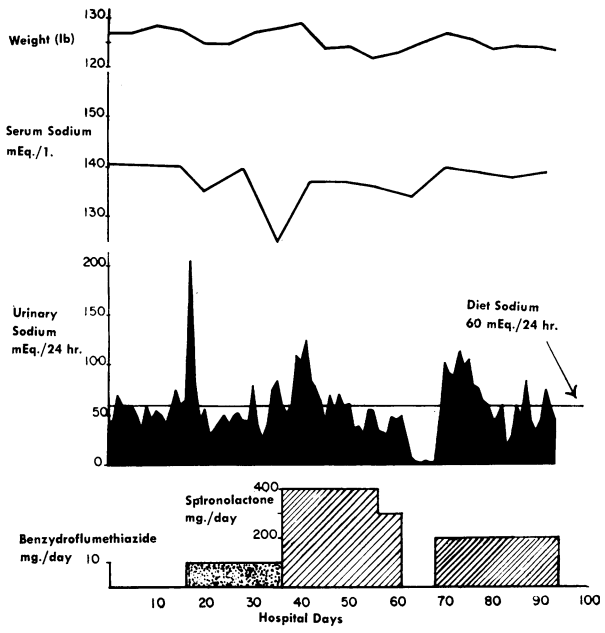

Fig. 7.—Sodium balance in Case 2. The patient was a 66-year-old man with cirrhosis of the liver and ascites.

of spironolactone per day produced an increased urinary sodium excretion. The serum sodium level decreased markedly when the patient was on benzydroflumethiazide therapy and returned to the normal range when he was on spironolactone. The patient's weight varied directly with the urinary sodium excretion. His abdomen was normal and there was no peripheral edema at the end of the 93-day study.

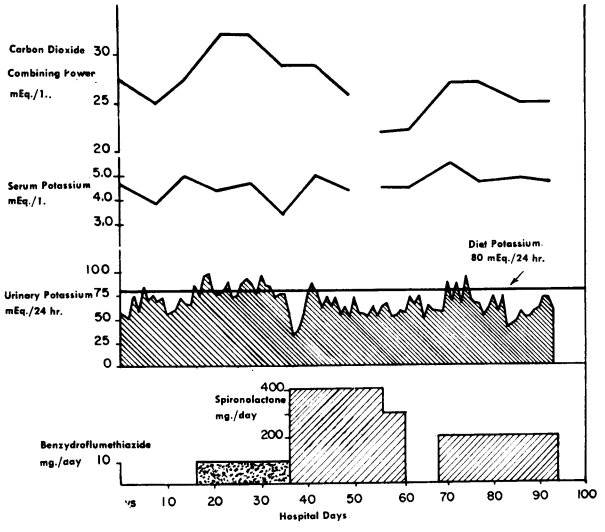

Fig. 8.—Potassium balance in Case 2.

Fig. 8 shows the potassium balance during the 93-day study period in Case 2. Before treatment the urinary excretion of potassium was slightly less than the oral intake. Benzydroflumethiazide therapy produced a urinary potassium loss in excess of the dietary intake of potassium. Termination of benzydroflumethiazide and the institution of spironolactone therapy produced a marked decrease in the urinary potassium excretion. While the patient was on long-term spironolactone therapy, the urinary potassium excretion was slightly less than the oral intake. Serum potassium decreased on benzydroflumethiazide therapy but remained normal throughout the remainder of the study during spironolactone therapy. The CO_2 combining power reflected the urinary potassium loss—increasing with benzydroflumethiazide therapy and returning to normal levels during the spironolactone therapy.

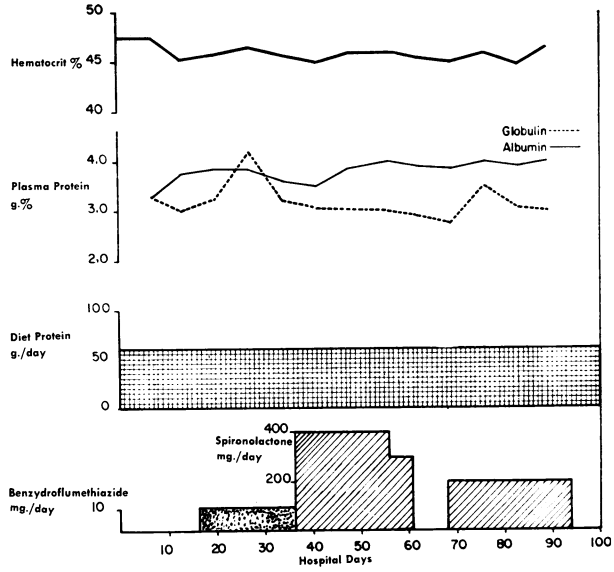

Fig. 9—Hematocrit, plasma proteins and diet protein values in Case 2.

Fig. 9 gives the hematocrit values and plasma protein levels in relation to dietary intake of protein and to therapy. During the period of study there was a gradual increase in the plasma albumin and a gradual decrease in the plasma globulin values. The hematocrit remained relatively unchanged.

TABLE II.—LIVER FUNCTION TESTS IN CASE 2

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesteral flocculation (after 48 hr.)*	*Thymol turbidity (units)*
May 1960	2.0	24.0	3+	13.8
Aug. 1960	1.0	14.0	3+	8.7
Sept. 1960	0.8	15.4	1+	7.3

Table II reveals the results of representative liver function tests during the period of study. There was improvement, as judged by the four liver function tests performed, as the ascites and edema were controlled by therapy.

The values for venous blood pH and glomerular filtration rate (endogenous creatinine clearance) showed a tendency to decrease during spironolactone therapy.

The patient was discharged from hospital free from ascites and edema in September 1960, on spironolactone, 100 mg. twice daily. He was re-admitted with an upper gastrointestinal hemorrhage in October 1960. At that time his hematocrit value was 32%. Spironolactone was discontinued, and there was a rapid accumulation of ascitic fluid. Bleeding stopped, and he recovered without transfusion. Spironolactone therapy completely cleared the ascites, and he was discharged on 400 mg. per day.

The patient was re-admitted to hospital on January 4, 1961, with a recurrence of epigastric pain. There was no ascites. He responded well to ulcer management. Spironolactone was again discontinued, to determine the necessity of this treatment. He developed ascites again and once more responded to spironolactone, the ascites disappearing completely. Epigastric pain did not recur when spironolactone therapy was re-instituted during peptic ulcer management. The spleen became palpable in February 1961.

CASE 3.—A 58-year-old white man was known to have hypertensive cardiovascular disease since 1953. During 1955, he suffered a posterior myocardial infarction complicated by an episode of complete heart block. He remained well until February 1960, when he developed dyspnea and swelling of the abdomen and feet. A low sodium diet, digitalization and intermittent use of mercurial diuretics were initially effective in controlling the fluid retention. Gradually he became refractory to mercurial diuretics and was admitted to hospital in October 1960, with massive peripheral edema and ascites. His blood pressure was 190/120 mm. Hg. He remained unresponsive to mercurial diuretics in hospital. Chlorthalidone (Hygroton) produced an increased urinary output and a loss of 10 lb. in weight. He then became refractory to chlorthalidone therapy. The patient was treated on the metabolic ward from November 11, 1960, to February 2, 1961 (84 days).

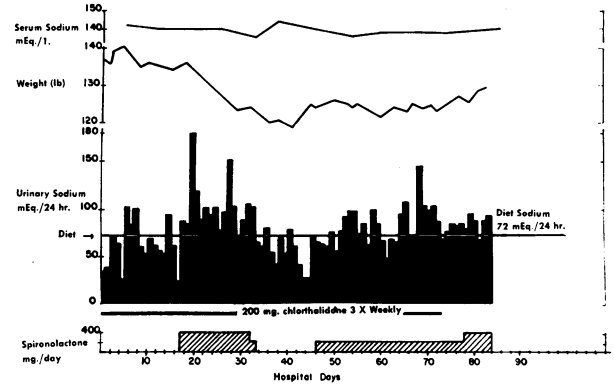

Fig. 10.—Sodium balance in Case 3. This patient was a 58-year-old man with hypertension and hepatic cirrhosis.

Fig. 10 records the results of the sodium balance study in Case 3. Chlorthalidone, 200 mg. three times weekly, produced a very slight increase in renal sodium excretion. The addition of spironolactone therapy produced a marked increase in sodium excretion. When spironolactone therapy was discontinued and the patient was maintained on chlorthalidone, sodium retention occurred. Spironolactone therapy was reinstituted on the 47th day, and increased sodium excretion again resulted. Chlorthalidone was discontinued on the 73rd day, and renal sodium excretion was maintained by use of spironolactone. The serum sodium level remained within normal limits throughout the study. His weight varied directly with the amount of renal sodium excretion.

Fig. 11 shows the potassium balance in Case 3. Renal potassium excretion exceeded the dietary intake, when chlorthalidone was the sole treatment. Spironolactone therapy in addition to chlorthalidone decreased the renal potassium excretion to levels which were much lower than the dietary intake. Hyperkalemia (6.2 mEq./l.) occurred and spironolactone was discontinued. This resulted in a marked increase in renal potassium excretion during the mid part of the study, while the patient was on chlorthalidone. Spironolactone was re-instituted on the 47th day, and decreased renal potassium excretion resulted. After chlorthalidone was discontinued on the 73rd day, there was a further reduction of renal potassium excretion.

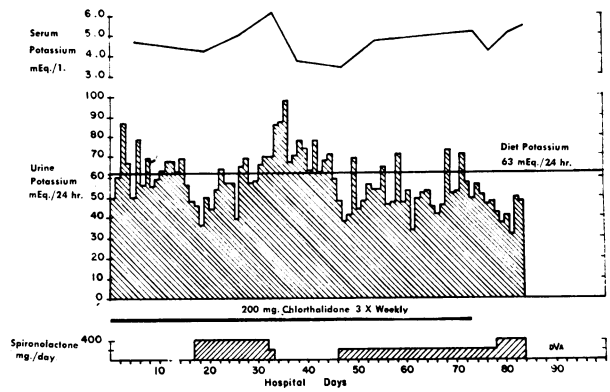

Fig. 11.—Potassium balance in Case 3.

Serum potassium decreased when chlorthalidone was used alone at the beginning of the study. The addition of spironolactone markedly increased the serum potassium, which decreased promptly when the spironolactone was discontinued. Serum potassium gradually increased when spironolactone therapy was re-instituted on the 47th day. The serum potassium increased still further when chlorthalidone was discontinued near the end of the study.

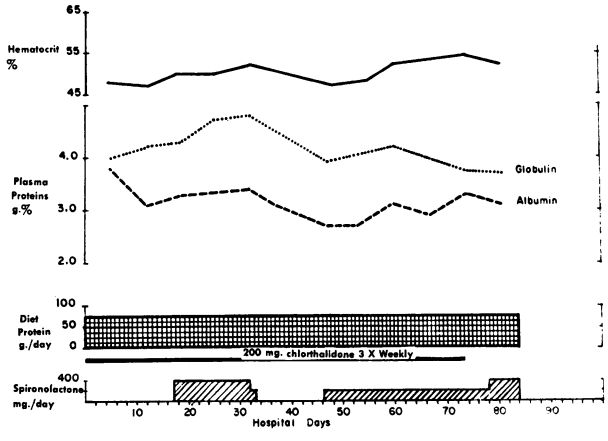

Fig. 12.—Hematocrit, plasma proteins and diet protein values in Case 3.

Fig. 12 shows the hematocrit and plasma protein values in relation to therapy in Case 3. There was a slight increase in the hematocrit during the study period. The plasma proteins remained relatively unchanged.

Fig. 13 gives the values for glomerular filtration rate (endogenous creatinine clearance), CO_2 combining power and blood pH, in relation to therapy. When the patient was on chlorthalidone therapy, the CO_2 combining power rose slightly and decreased when spirono-

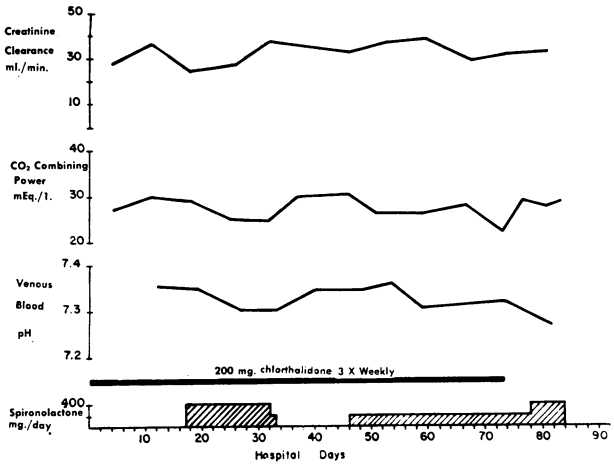

Fig. 13.—Endogenous creatinine clearance, CO_2 combining power and venous blood pH values in Case 3.

lactone therapy was added. Venous blood pH varied directly with the changes in the CO_2 combining power. The glomerular filtration rate remained low and generally unchanged throughout the study.

TABLE III.—LIVER FUNCTION TESTS IN CASE 3

Date	*Bilirubin (mg.%)*	*% BSP retention (after 45 min.)*	*Cephalin-cholesterol flocculation (after 48 hr.)*	*Thymol turbidity (units)*
Oct. 1960	2.5	—	3+	7.1
Dec. 1960	1.0	11.7	3+	14.7
Feb. 1961	0.7	10.5	4+	9.2

Table III presents the liver function tests during the period of study in Case 3. The serum bilirubin decreased, but the other liver function tests performed were little changed.

There was no clinical evidence of ascites after the initial course of spironolactone therapy in this patient. His liver and spleen became easily palpable as his ascites decreased. A liver biopsy on the 56th day of therapy revealed cirrhosis of the liver. The patient remained free from ascites during the remainder of the study. Slight edema of the feet persisted. He was discharged on February 3, 1961, on chlorothiazide 1 g. per day and spironolactone 200 mg. daily. He was re-admitted on February 7, 1961, with a complete flaccid right hemiplegia. He died 10 days later.

Postmortem examination revealed a large left cerebral infarct secondary to occlusion of the left internal carotid artery. There was a large posterior myocardial infarct and old mural thrombi in both ventricles. Laennec's cirrhosis of the liver was present. Recent thrombosis of the abdominal aorta was noted with complete obstruction at the bifurcation and left renal artery.

DISCUSSION

Spironolactone was shown to be effective in the long-term treatment (up to eight months) of ascites due to cirrhosis. Renal sodium excretion increased on the 3rd to 4th day of treatment. This response continued until the abdomen was completely free of fluid on clinical examination. The maintenance dose varied from 200 to 400 mg. daily. Spironolactone was effective in producing increased urinary sodium excretion, after a benzothiadiazine derivative and a phthalimidine derivative had previously failed. Hyponatremia did not occur. Hyponatremia has been reported with spironolactone therapy, and has been effectively treated by limiting the oral fluid intake to 1000 c.c. daily.[12] Hyponatremia is more likely to occur when a benzothiadiazine is combined with a 17-spirolactone during therapy.[10] Shaldon, McLaren and Sherlock[10] have effectively controlled the hyponatremia associated with spironolactone administration by increasing the renal osmotic load with intravenous mannitol, producing an increased renal free water clearance.

Marked renal sodium retention occurred when spironolactone was discontinued in Case 2. This suggested an increased aldosterone production when spironolactone was used to block the effect of aldosterone on the renal tubule. Walfish *et al.*[13] have reported increased urinary aldosterone excretion in cirrhotic patients with ascites treated by spironolactone. The initial abnormal liver function tests and marked response to spironolactone in Case 3 suggested that cirrhosis was the major factor in sodium retention in this case. The response to aldosterone-inhibiting drugs is greater in cirrhotic patients with edema than in patients in whom the sodium retention is secondary to congestive heart failure.[14]

Spironolactone did not produce renal potassium retention in the two patients with good renal function during long-term therapy. Renal function was poor in Case 3, and in this patient spironolactone caused potassium retention with hyperkalemia which was quickly reversed by discontinuing the drug. Potassium was retained despite the simultaneous administration of chlorthalidone, which had previously been shown to increase urinary potassium excretion. Changes in the glomerular filtration rate, estimated by endogenous creatinine clearances, were variable in the three cases. The slight decrease in the CO_2 combining power and decreased venous blood pH values during long-term spironolactone therapy suggests that the drug might inhibit renal hydrogen ion excretion. Hydrogen ion and potassium compete for excretion when sodium is reabsorbed under the influence of aldosterone in the distal renal tubule. An aldosterone-inhibiting drug would, therefore, be expected to decrease hydrogen ion excretion.

The increase in plasma albumin and the improvement in the liver function test results during therapy is in keeping with previously reported cases in which medical management decreased the ascites in patients with cirrhosis associated with alcoholism.[15] The slight changes in the hematocrit suggest that the increase in the plasma proteins was real, rather than due to the hemoconcentration that might be produced by therapy.

High protein diets frequently precipitate neuropsychiatric changes in a cirrhotic patient and

should be used cautiously. Cirrhotic patients will retain protein on a diet of less than 80 g. protein per day.[16] Cases 1 and 2 demonstrated a marked improvement in the plasma protein levels as ascites decreased while the protein intake was approximately 60 g. per day.

Tyor and Sieker[17] report that anoxemia, hyperventilation and respiratory extracellular alkalosis contribute significantly to the disordered consciousness frequently seen in cirrhotic patients. Metabolic extracellular alkalosis may also precipitate hepatic coma.[18] Frequently the metabolic extracellular alkalosis, produced by potassium loss due to benzothiadiazine therapy, cannot be prevented by potassium supplements.[9] Spironolactone is effective in preventing extracellular alkalosis in cirrhotic patients treated with benzothiadiazines and it seems advisable to prevent this complication of diuretic therapy.

It is Pitts'[19] hypothesis that there is a single mechanism for renal sodium reabsorption supplied by multiple sources of energy and that the different diuretic drugs block different sources of energy, thus explaining the varied activity of the diuretic drugs and the potentiating effect of two or more drugs on sodium excretion. Mercury probably blocks sodium reabsorption in the proximal tubule because of the increased free water clearance and the acid urine produced. The carbonic-anhydrase-inhibiting drugs block hydrogen ion excretion and therefore decrease sodium reabsorption and produce a higher urine pH than do mercurials. The benzothiadiazines are weak carbonic anhydrase inhibitors and have an action similar to that of the mercurials on the proximal tubule, as shown by free water clearance studies.[19] The 17-spironolactones by inhibiting aldosterone activity in the distal renal tubule block still another mechanism for sodium reabsorption and can potentiate renal sodium loss when given simultaneously with other diuretic agents. The varied and increased effect of the presently available diuretic drugs on renal function stresses the need for close observation of electrolyte and acid-base balance when diuretic agents are used alone or in combination.

It has become apparent that the choice of a diuretic agent in edematous and ascitic states depends on the underlying disease process and the pathological physiology producing the abnormal renal retention of sodium and water. In the decompensated cirrhotic there is good evidence[3] of a marked increase in aldosterone production, suggesting that the aldosterone-inhibiting drugs should be effective in treating the ascites of these patients. Indeed, short-term studies have shown this to be so.[10, 11] The results of a long-term study of treatment with an aldosterone antagonist, which have been described in this report, suggest that there is a definite place for the 17-spironolactone group of drugs in the treatment of ascites due to cirrhosis.

SUMMARY

Spironolactone (Aldactone) therapy was shown to be effective in the long-term treatment of ascites due to cirrhosis of the liver. Complications due to spironolactone therapy were minimal; hyperkalemia was observed in one case with poor renal function. The diuretic therapy of ascites due to cirrhosis has been discussed.

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REFERENCES

1. BROWN, C. H., MERLO, M. AND BRITTON, R. C.: *Cleveland Clin. Quart.* **27**: 67, 1960.
2. ONEN, K. H.: *Lancet*, **1**: 203, 1960.
3. PETERSON, R. E.: *Recent Progr. Hormone Res.*, **15**: 231, 1959.
4. FARRELL, G.: *Ibid.*, **15**: 275, 1959.
5. *Idem*: *Circulation*, **21**: 1009, 1960.
6. GENEST, J.: *Canad. M. A. J.*, **84**: 493, 1961.
7. BIRON, P. *et al.*: *J. Clin. Invest.*, **40**: 338, 1961.
8. BARTTER, F. C. *et al.*: *Recent Progr. Hormone Res.*, **15**: 311, 1959.
9. READ, A. E. *et al.*: *Clin. Sc.*, **18**: 409, 1959.
10. SHALDON, S., MCLAREN, J. R. AND SHERLOCK, S.: *Lancet*, **1**: 609, 1960.
11. CLOWDUS, B. F. *et al.*: *Proc. Staff Meet. Mayo Clin.*, **35**: 97, 1960.
12. HENLEY, K. S., STREETEN, D. H. P. AND POLLARD, H. M.: *Gastroenterology*, **38**: 681, 1960.
13. WALFISH, P. G. *et al.*: *Appl. Ther.*, **2**: 677, 1960.
14. FARRELLY, R. O., HOWIE, R. N. AND NORTH, J. D. K.: *Brit. M. J.*, **2**: 339, 1960.
15. SUMMERSKILL, W. H. *et al.*: *New England J. Med.*, **262**: 1, 1960.
16. GABUZDA, G. J., JR. AND DAVIDSON, C. S.: *Ann. New York Acad. Sc.*, **57**: 776, 1954.
17. TYOR, M. P. AND SIEKER, H. O.: *Am. J. Med.*, **27**: 50, 1959.
18. SHERLOCK, S.: *Ibid.*, **24**: 805, 1958.
19. PITTS, R. F.: *Ibid.*, **24**: 745, 1958.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CANCER OF THE STOMACH

Billroth did the first successful gastric resection twenty-nine years ago.

In 1839 Cruheilhier first described ulcer, distinguishing it from cancer, and suggested the possibility of the development of cancer upon the base of an ulcer. In 1840 Rokitansky also expressed the opinion that the one condition might be implanted upon the other.

In 1848 Dittrich reported six cases of cancer developing in the immediate vicinity of an active or healed ulcer, two of association of cancer and ulcer, and two of circumscribed cancer in the margin of an ulcer.

In 1878 Lebert stated that cancerous transformation occurred in 9 per cent. of ulcers, while Zenker, in 1882, believed that all cases of gastric cancer were secondary to ulceration.—Herbert A. Bruce, *Canad. M. A. J.*, 1: 805, 1911.