EXPERIMENTAL ASCITES. STUDIES OF ELECTROLYTE BALANCE IN DOGS WITH PARTIAL AND COMPLETE OCCLUSION OF THE PORTAL VEIN AND OF THE VENA CAVA ABOVE AND BELOW THE LIVER

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Previous studies (1–6) of experimental ascites primarily concerned with protein metabolism and exchange have emphasized the importance of sodium in ascitic fluid production. Recently, the importance of sodium retention in several forms of effusions and edema has been described by numerous observers (7–15) who have all directly or indirectly implicated the kidney in the causal relationships of this abnormality of sodium metabolism. This report concerns sodium, potassium, and chloride balance studies in dogs with experimentally produced ascites. Following the administration of large amounts of sodium, these ascitic animals, in contrast to the normal dog, do not excrete the excess sodium in their urine. Whereas normally in the dog there is a slightly delayed excretion of sodium with temporary retention of sodium in extracellular and intracellular spaces, these ascitic animals produce predictable amounts of ascites following an increased salt load. Potassium is promptly excreted by the kidneys and chloride is retained only when there is sodium retention. The ascites of these animals seems to resemble in some ways that of the human cirrhotic and the patient with right sided heart failure or chronic constrictive pericarditis. The *liver* seems *implicated* in this abnormality of *sodium metabolism.*

EXPERIMENTAL METHODS

Healthy mongrel dogs averaging 8 to 12 kilograms in weight were selected for these experiments following observation for several weeks under standard conditions in the animal house. Aluminum bands were used for partial and complete occlusion of the portal vein and the vena cava below and above the liver by techniques previously described (2). Two animals were studied before and after partial and complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. A third animal was studied before and after three operative procedures that first partially, then completely, occluded the portal vein and the vena cava below the liver and above the kidneys, and finally partially occluded the vena cava above the liver. The fourth and fifth animals were studied following partial occlusion of the inferior vena cava above the liver.

During these periods of observation the animals were maintained in metabolism cages with a constant daily diet of horsemeat, 200 or 250 grams, and 50 grams of a low protein mixture (16) that contained sodium, potassium, chloride, and nitrogen in amounts indicated (Table I). The daily dietary intake, therefore, was 14.5 milliequivalents of potassium, 8.5 milliequivalents of sodium, and 5.6 milliequivalents of chloride for animal 50–5, and was 17.0 milliequivalents of potassium, 9.0 milliequivalents of sodium, and 6.4 milliequivalents of chloride for the other experimental animals. Additional sodium chloride and potassium (neocurtasal) [1] were given orally in capsules in large amounts at appropriate periods indicated in the accompanying graphs. Water was allowed *ad libitum.* During these periods complete balance studies of sodium, potassium, chloride, water, and protein were carried out. The animals were carefully weighed at the same time each day. Determinations of plasma protein and ascitic fluid protein were made by methods previously described (1). A Perkin-Elmer flame photometer, model 52-A, supplied with an acetylene burner was used to determine potassium and sodium utilizing lithium as an internal standard by the method previously described (17). No significant interference was noted from neighboring bands of other elements. Chlorides were determined by the method of Van Slyke (18).

EXPERIMENTAL RESULTS

The accompanying figures summarize the balance studies carried out on our experimental animals. Nitrogen balances, though carried out, were omitted from the graphs as similar studies have been reported in detail previously (1, 3, 4, 6).

[1] The formula for this compound, kindly supplied by Winthrop-Stearns, Inc., is potassium chloride 66.0 per cent, ammonium chloride 12.0 per cent, starch 17.0 per cent, potassium formate 3.0 per cent, calcium formate 1.0 per cent, and magnesium citrate 1.0 per cent.

The daily dietary intake of sodium, potassium, and chloride was omitted for the sake of simplicity but may be determined from Table I as outlined in the experimental methods. The loads of sodium and potassium are indicated in each instance by a circle or square respectively. All values are expressed in milliequivalents per liter and are thus comparable. Dates of venous occlusive operations

TABLE I

Average electrolyte and nitrogen composition of diet given daily to each dog

	K	Na	Cl	N_2
	mEq./kg Wet wt.	*mEq./kg Wet wt.*	*mEq./kg Wet wt.*	*Gms./kg Wet wt.*
Horsemeat	49.4	25.1	13.8	44.6
Low Protein	90.5	54.3	64.7	0.12

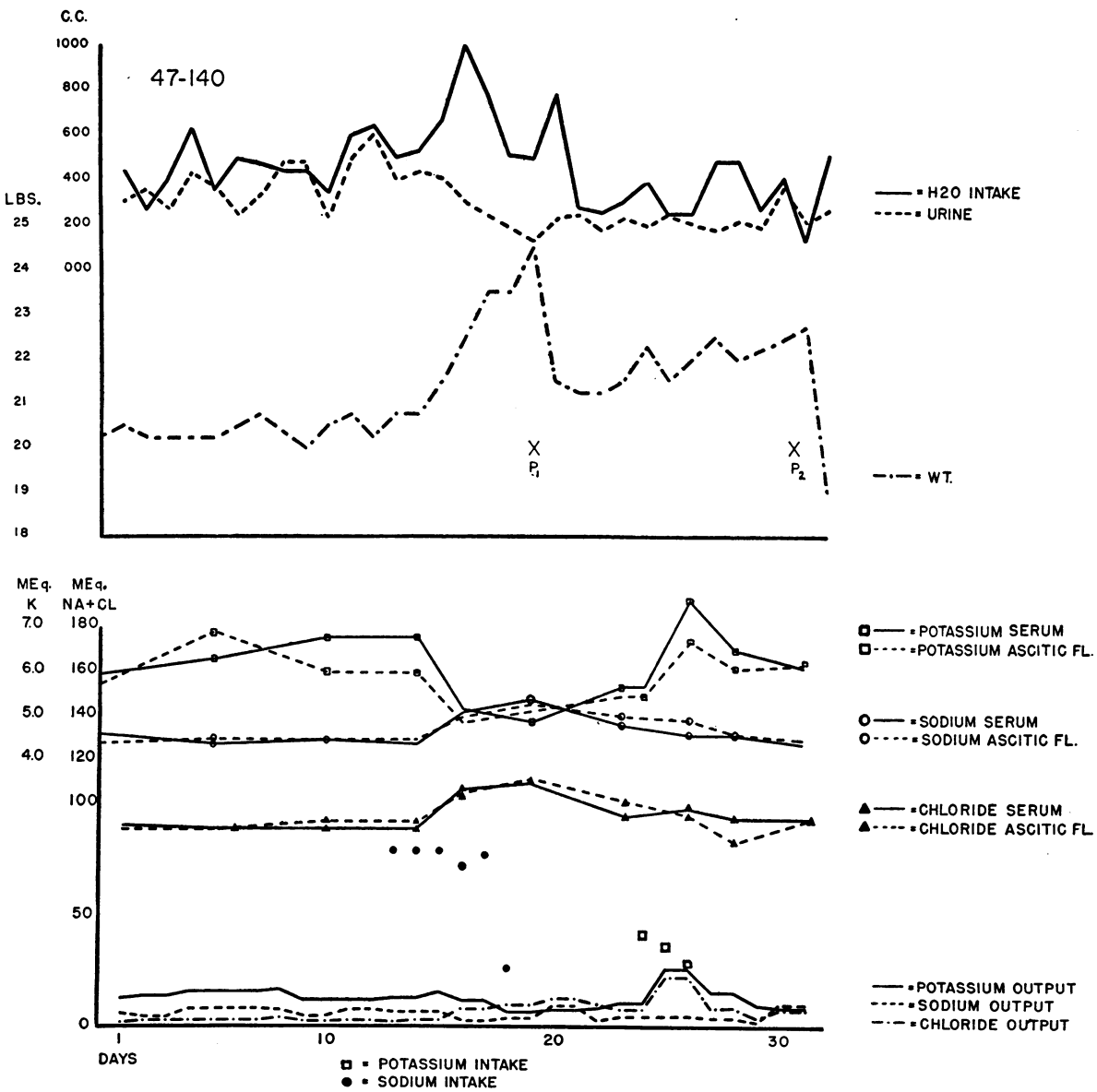

FIG. 1. ELECTROLYTE AND WATER BALANCES OF DOG 47-140, WITH PARTIAL OCCLUSION OF THE INFERIOR VENA CAVA ABOVE THE LIVER PRIOR TO METABOLIC STUDY

Twenty-one grams of sodium chloride (Na) orally during the 13th to 19th days, and 10.5 grams of neocurtasal (K) orally during the 25th to 27th days. Paracenteses (P) of 1850 cc. and 1780 cc. on the 20th and 32nd days.

where they occurred in the course of these experiments are indicated by an "O," and dates of paracenteses are shown by a "P." In two dogs, 47–140 and 50–5, the operation was performed prior to the balance studies shown in the graphs.

Administration of sodium chloride to animals 47–140 (Figure 1) and 50–5 (Figure 2) with partial occlusion of the vena cava above the liver caused a prompt predictable increase in the formation of ascitic fluid, associated with a decrease in the levels of circulating plasma proteins. The amount of sodium in the ascitic fluid recovered by paracentesis was approximately equal to that given orally and it was possible to predict the amount of

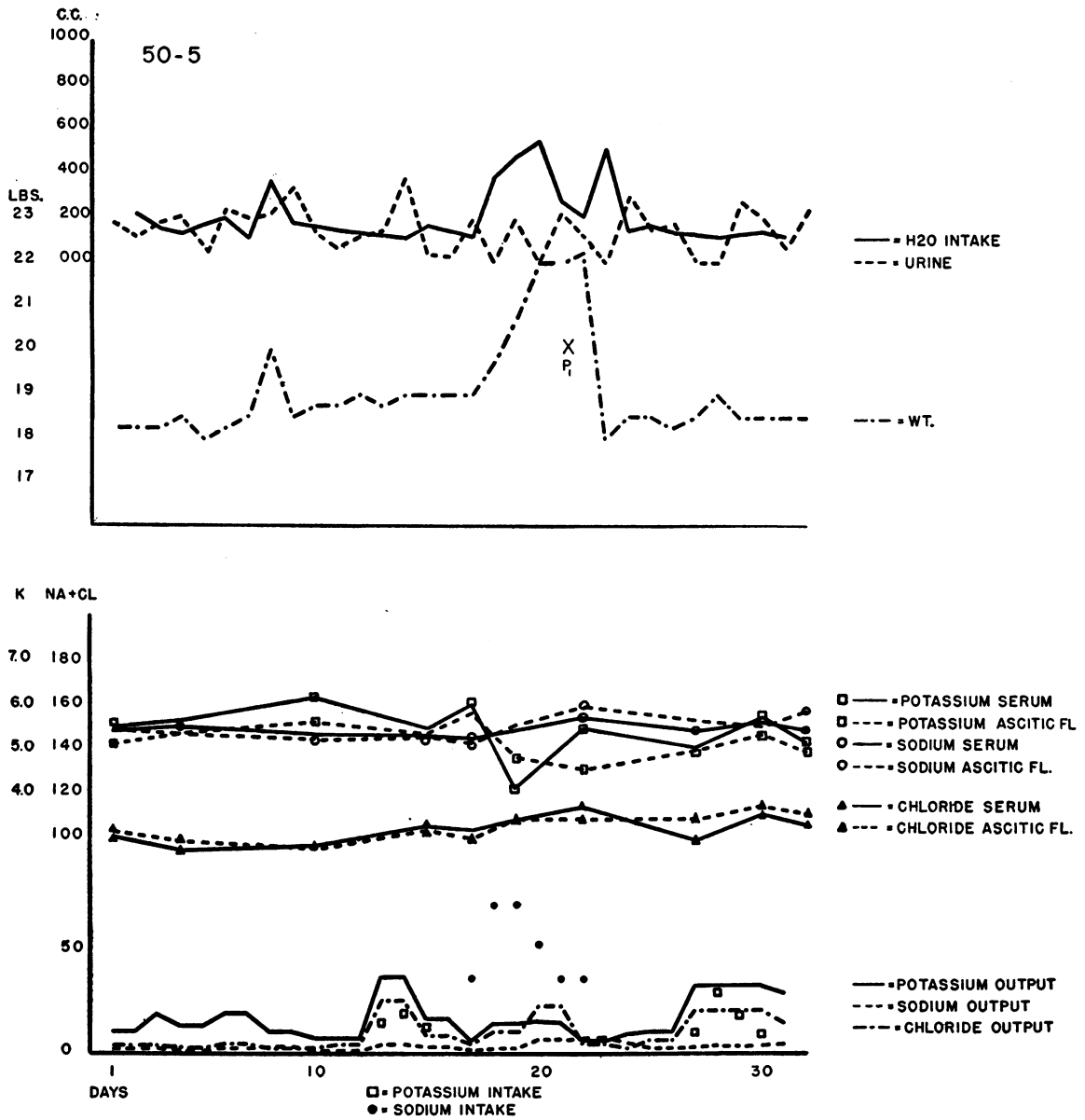

FIG. 2. ELECTROLYTE AND WATER BALANCES OF DOG 50–5, WITH PARTIAL OCCLUSION OF THE INFERIOR VENA CAVA ABOVE THE LIVER PRIOR TO METABOLIC STUDY

4.5 grams of neocurtasal (K) during the 13th to 15th days, 17 grams of sodium chloride (Na) during the 17th to 22nd days, and 6.5 grams of neocurtasal (K) during the 27th to 30th days. Paracentesis (P) of 2230 cc. on the 22nd day.

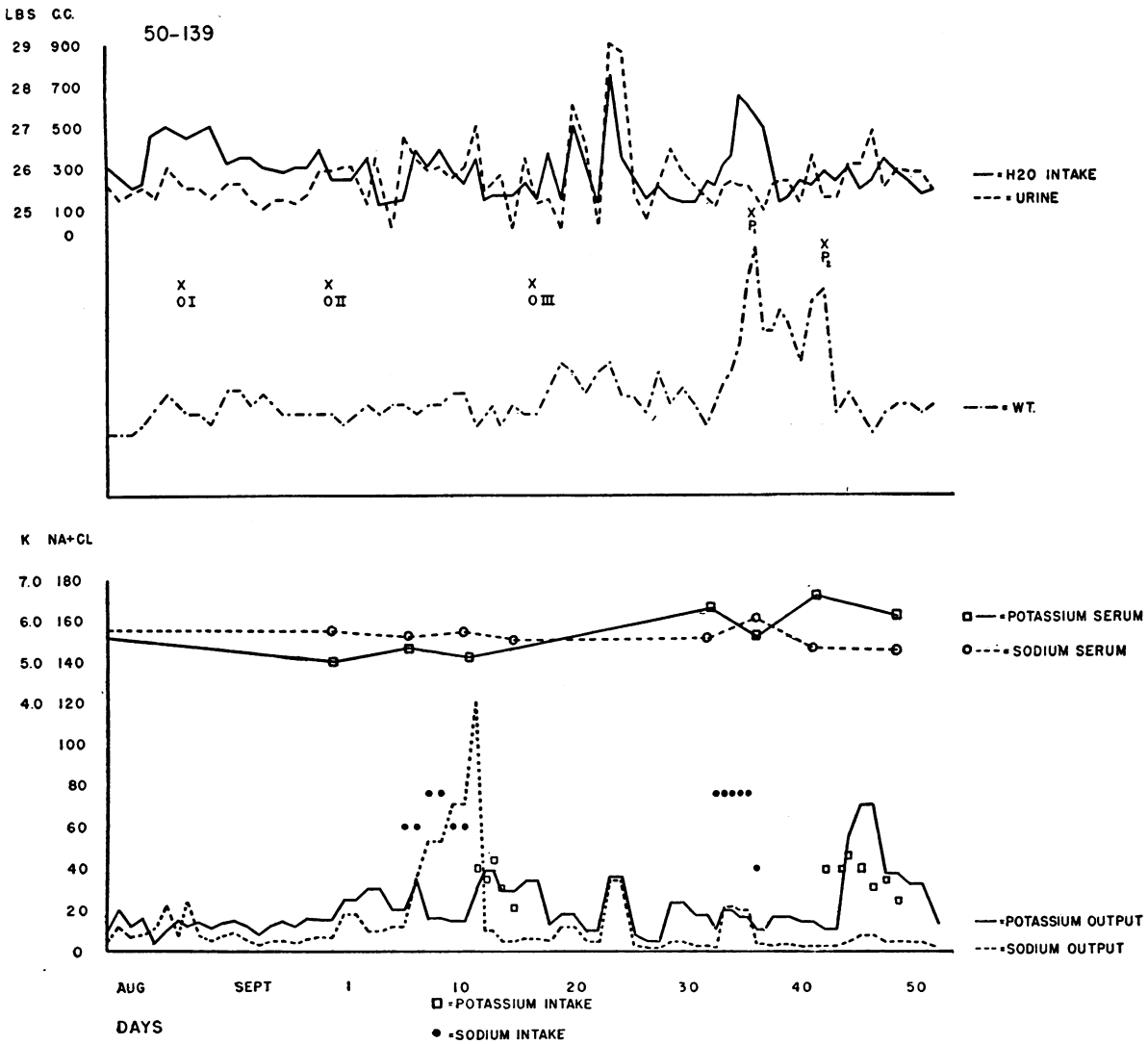

FIG. 3. ELECTROLYTE AND WATER BALANCES OF DOG 50–139

O I and O II represent partial and complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. O III represents partial occlusion of the inferior vena cava above the liver. Nineteen grams of sodium chloride (Na) and 9.5 grams of neocurtasal (K) during the sixth to 11th and 12th to 16th days respectively, and 22 grams of sodium chloride (Na) and 15 grams of neocurtasal (K) during the 33rd to 38th and 45th to 52nd days respectively. Paracenteses (P) of 1200 cc. and 1390 cc. on the 38th and 45th days respectively.

ascitic fluid that would be formed on the basis of the salt intake alone. There was no increase in sodium excretion in the urine of either animal. These observations have been confirmed repeatedly on other animals not used in these metabolic experiments (19). The amount of sodium in the ascitic fluid and urine of dog 47–140 was somewhat greater than the total sodium intake during the period of the experiment, resulting in a net depletion of the total body sodium. Administration of potassium to this animal (47–140) seemed to cause increased ascitic fluid formation presumably by displacement of intracellular sodium into the ascitic fluid. In animal 50–5 potassium was first administered resulting in a prompt, almost quantitative, excretion in the urine with no detectable increase in ascitic fluid formation. Following oral administration of 17 grams of sodium chloride and paracentesis, the loss of sodium in the ascitic fluid and urine during this period almost

exactly equalled the total amount of sodium intake. The third animal, 50–139 (Figure 3), was first studied after a two stage operative procedure that completely divided the portal vein and the vena cava above the kidneys and below the liver. Presumably the mechanical effect of these procedures on the renal circulation was more profound than partial occlusion of the inferior vena cava above the liver in the animals 47–140 and 50–5. Yet these procedures were tolerated with no detectable adverse clinical effect, edema of the extremities, or ascites. Venous pressures were not measured in these animals but in other experiments elevation of inferior caval and portal pressures after partial or complete occlusion decreased to normal ranges quite promptly with the development of collateral circulation through the azygos system (19, 20). With regard to the portal system, Hoffbauer (21) has concluded that levels of pressure in the portal vein could not be correlated with the formation of ascites and that the development of a collateral circulation occurs at relatively low levels of venous pressure. A sodium and potassium load resulted in the urinary excretion of both ions. There was a delay of approximately 36 hours in the diuresis of sodium and a very prompt excretion of potassium. There was some retention following the sodium load during the sixth to 11th days of the balance period. The third operation was performed with partial occlusion of the vena cava above the liver. Following an adequate recovery period a similar salt load was administered. This resulted in the prompt formation of large amounts of ascitic fluid (2590 cc.) with no diuresis of sodium, and the animal was clinically identical to the first two animals; namely, 47–140 and

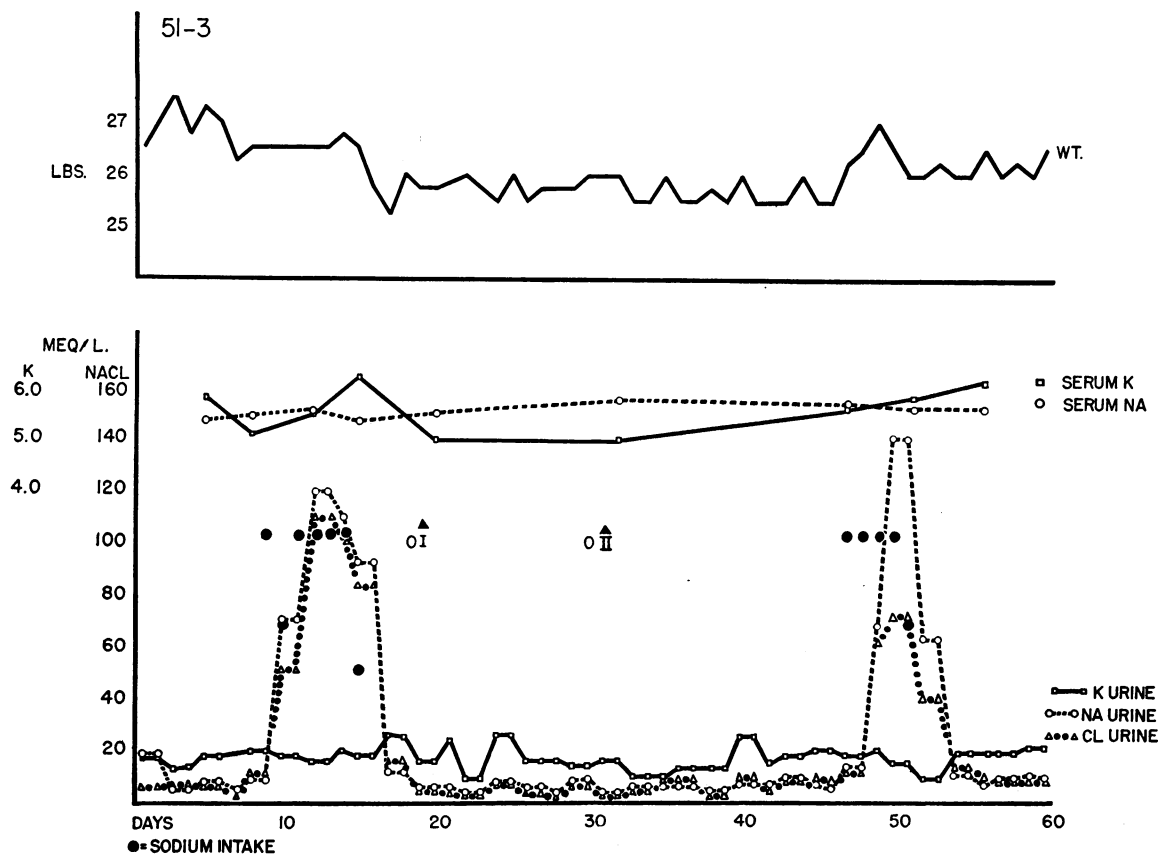

FIG. 4. ELECTROLYTE BALANCES OF DOG 51–3

O I and O II represent partial and complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. Thirty-seven and 28 grams of sodium chloride (Na) were given orally on the ninth to 15th and 47th to 51st days respectively. No ascites.

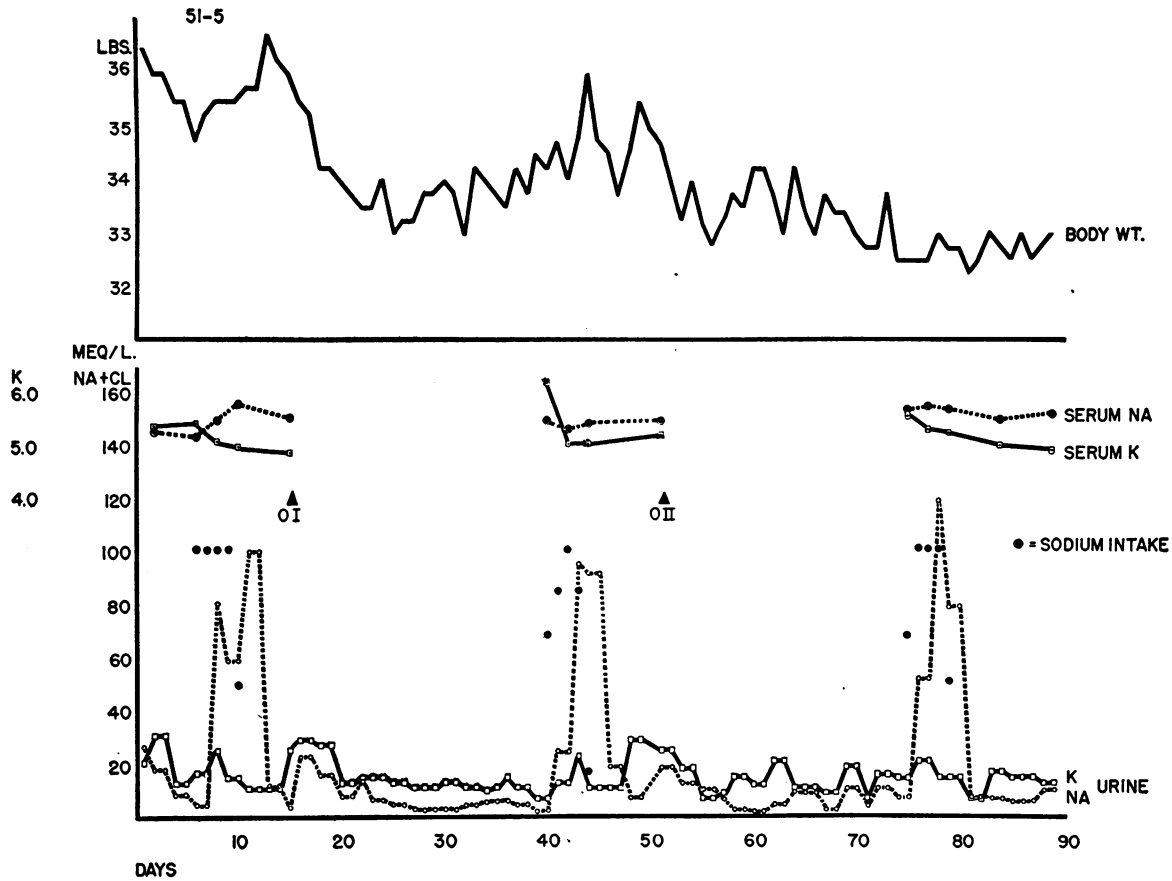

FIG. 5. ELECTROLYTE BALANCES OF DOG 51–5.

O I and O II represent partial and complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. Twenty-seven, 21, and 25 grams of sodium chloride (Na) were given orally on the sixth to tenth, 40th to 44th, and 75th to 79th days respectively. No ascites.

50–5. Similar observations have been made on four other animals with this three stage operative sequence that were not used for metabolic study. Administration of potassium resulted again in prompt excretion with no retention in intracellular fluids.

The fourth and fifth animals, 51–3 (Figure 4) and 51–5 (Figure 5), were observed before and after partial and then complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. Review of the accompanying data reveals no significant retention of sodium. Following partial and complete occlusion of the portal vein and the vena cava, there was a slightly greater delay in the urinary excretion of sodium after excessive administration with temporary retention. There was a small transient increase in the weight of these animals following a salt load, though in no way comparable to the dogs with partial occlusion of the inferior vena cava above the liver and ascites. Ascites has never been observed in our experience in any of our dogs with partial or complete occlusion of the portal vein and the vena cava below the liver.

There was in all animals a very accurate regulation of the serum levels of chloride, sodium, and potassium. The levels of non-protein-nitrogen in the serum were constant and normal. Urea clearances were normal. Sodium, potassium, and chloride were excreted by the kidneys in small constant amounts during the resting periods in the ascitic dogs with a continuous positive balance of 2 to 6 milliequivalents each day. The chloride excretion very closely paralleled the sodium excretion in all animals. In the ascitic dogs there was a remarkable similarity between the serum

and ascitic fluid electrolyte patterns, indicating a prompt and free exchange of water and electrolytes. Previously, McKee and his associates have described the similarity of the electrophoretic patterns of plasma and ascitic fluid proteins (2) and their prompt interchange utilizing lysine labeled with C^{14} (6). Serum level trends of sodium and potassium have invariably been mirror images of the other ion.

In summary, there was a slightly delayed diuresis of sodium following a salt load with temporary retention in the animals with complete occlusion of the portal vein and the vena cava below the liver and above the kidneys. In the animals with partial occlusion of the inferior vena cava above the liver, there was prompt formation of ascites containing approximately all of the sodium administered, with no increase in urinary excretion.

DISCUSSION

Recent clinical studies of edema and ascites in heart failure and cirrhosis indicate that the kidney is responsible for the retention of sodium that occurs. Our experimental findings in these ascitic dogs suggest that the liver is also involved in this abnormality. Retention of sodium, irrespective of etiology, seems to be the most important factor in the ascitic fluid formation in these animals. The lack of abnormal sodium retention with complete occlusion of the portal vein and the vena cava below the liver and above the kidneys emphasizes the lack of effect of temporary venous stasis alone. Ultimately, dogs cease to produce ascites with partial occlusion of the vena cava above the liver. These animals will again produce ascites for a short period following another operation and complete occlusion of the vena cava above the liver (19). Thus, when there is stasis of the hepatic veins in the liver there is a much greater tendency for sodium retention and ascites is formed over a long period. The reasons for this are not clear. Apparently the fluid content of the peritoneal cavity shares to a greater or lesser degree in the expansion and contraction of the interstitial fluid volume, though in an altered way when abnormal hydrostatic, osmotic, or permeability factors exist in the portal system. Rather than ascribe this to a metabolic alteration, it seems simpler, at present, to consider this due to mechanical alterations within the liver parenchyma and related to the unique anatomy of the liver lobule. There the intimate relationships of the lymphatics to the sinusoids may render them more susceptible to minor changes in venous pressure and stasis. Grindlay and his associates (22, 23) have demonstrated a marked increase in liver lymph under these circumstances. Thus, the peritoneal cavity may become an anatomical area, with little tissue pressure, trapping sodium and chloride, rather than allowing their participation in a general extracellular water expansion with subsequent renal excretion. Conversely, sodium and water retention may be a renal compensatory mechanism to offset the loss of body fluids, plasma proteins, and electrolytes into the peritoneal cavity. Stamler and his coworkers (15) have demonstrated that occlusion of the vena cava above the liver influences renal function indirectly. Here, with the formation of ascites, there is a permanent reduction of renal plasma flow, glomerular filtration rate, and sodium excretory capacity. This change seemed to occur, not in response to the elevated renal venous pressure, but to the over-all changes in the circulation and in the body fluid compartments. Hwang and his associates (24) have shown that constriction of the vena cava above the kidneys and below the liver does not cause permanent abnormalities of renal function, though there is temporary reduction in renal plasma flow, renal filtration rate, and sodium excretory capacity. Increased venous pressure *per se* does not cause ascites or a pleural effusion. In none of our animals has ascites been noted following ligation of the portal vein. It is well known clinically that extrahepatic block of the portal system does not cause ascites; that ascites when it occurs with portal hypertension is indicative of intrahepatic fibrosis and damage; and that the surgical prognosis is much more grave when ascites and portal hypertension coexist (25–27). In cirrhosis with intrahepatic portal obstruction and ascites, there is no inferior vena cava obstruction. Thus, sodium retention by the kidneys could be a compensatory mechanism from loss of fluid and electrolytes, a primary mechanism initiated by the hepatic elaboration of an antidiuretic substance, or failure of the liver to inactivate an antidiuretic substance produced elsewhere. The pulmonary veins may be constricted to the point of death without pleural effusion (28) and the superior vena cava may be tied off with im-

punity, provided the azygos system is intact (29).

Recently the diurnal variation of water and sodium excretion in patients with congestive heart failure, cirrhosis of the liver, and degenerative glomerulo-nephritis, has been emphasized (30). At night there is an increased excretion of water and sodium. This might be related to the increased flow of blood through the liver when the patient is recumbent (31, 32). Much of the clinical and experimental evidence points to an hepatic factor in sodium retention. The exact mechanism of this hepatic abnormality in the renal retention of sodium with ascites formation remains unexplained. Potassium excretion seems to be governed by a different mechanism, corroborating the findings of Baldwin, Kahana and Clarke (33). The liver seems uniquely situated with regard to the effects of venous back pressure, and may elaborate an antidiuretic substance under these circumstances. The adrenals may be implicated, though specific experiments have not been designed to include or exclude them with relation to increased venous pressure.

SUMMARY AND CONCLUSIONS

1. Sodium, potassium, chloride, and water balances were recorded in dogs before and after occlusion of the portal vein and the vena cava below the liver but above the kidneys, and following partial occlusion of the inferior vena cava above the liver.

2. Above the liver, partial occlusion of the inferior vena cava invariably caused retention of sodium and accumulation of ascitic fluid.

3. Administration of excessive amounts of sodium chloride orally caused an immediate and marked accumulation of ascites in all dogs with partial occlusion of the vena cava above the liver. This ascitic fluid contained sodium in amounts approximately equal to the administered excess.

4. Partial and complete occlusion of the portal vein and vena cava below the liver and above the kidneys failed to cause ascites. Excessive administration of sodium in these dogs was unaccompanied by clinical effect, though there was a slightly delayed diuresis of sodium compared to the normal animal.

5. Excessive amounts of potassium (such as neocurtasal) were excreted promptly in all animals with no significant changes in the tissue electrolyte patterns. In certain instances with partial occlusion of the vena cava above the liver, there seemed to be a moderate increase in the ascitic fluid production presumably by displacement of intracellular sodium which was not excreted. Potassium excretion seemed to be governed by mechanisms different from those for sodium.

6. Chloride excretion paralleled sodium excretion in the urine except in instances of high potassium output.

7. Under these experimental conditions chronic congestion of the liver, at least on an anatomical-mechanical basis, seems to be related to this type of ascites and sodium retention.

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