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THE EFFECT OF ESTROGEN ON WATER AND ELECTROLYTE METABOLISM. II. HEPATIC DISEASE

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In chronic hepatic disease, the accumulation of fluid as ascites or edema is commonly observed (1). A similar tendency can also be demonstrated in acute hepatic disease, often in the absence of clinically detectable ascites or edema (2-4), suggesting that a common fluid-retaining factor may operate in both chronic and acute diseases.

Although diminished plasma colloidal osmotic pressure, resulting from lowered plasma albumen levels, has been put forward by some observers as the chief fluid-retaining factor in chronic liver disease (5-7) others have failed to find a constant correlation between the appearance of ascites and edema on the one hand and plasma albumen levels on the other (8, 9). Furthermore, the fluid retention of acute hepatic disease is not usually associated with abnormally low plasma albumen concentrations (2).

In search for other fluid-retaining factors, the possibility was suggested that in liver disease the hepatic inactivation of fluid-retaining hormones might be impaired, and from this point of view Ralli, Robson, Clarke, and Hoagland (10), investigated the role of the pituitary anti-diuretic hormone.

However, it seemed more probable that a primarily sodium-retaining hormone might be involved. Estrogens have been shown to have a salt-retaining action in animals (11), and there is much evidence to show that in animals these hormones are normally inactivated by the liver (12). Moreover, in human liver disease there are certain clinical features which are best explained on the basis of increased estrogen activity (13-15). These observations suggest that decreased inactivation of endogenous estrogen may occur in human liver disease, which may lead in turn to sodium-retention. Under these circumstances the administration of exogenous estrogen to cases of liver disease would be expected to result in far greater retention of sodium than in normal subjects (16).

The effect of the daily administration of estrogen on water and electrolyte metabolism has been studied in cases of human hepatic disease. To elucidate further the mechanism of the changes observed, the study was extended to include cases of obstructive jaundice, ascites without hepatic disease, and portal hypertension without hepatic disease.

CLINICAL DATA

Male and female cases were selected from the wards of The London Hospital. In no case was there evidence of cardiac or renal disease. In most cases, diagnosis was established by hepatic biopsy, at laparotomy or at subsequent post-mortem examination. Of the remainder only cases presenting typical clinical features were accepted.

Group 1—Hepatic cirrhosis with ascites (9 cases). The following categories were rejected: (a) Where accumulation of ascites was so rapid as to require paracentesis during the study. Only cases where ascites was accumulating or decreasing slowly were studied. (b) Where ascites could only be controlled by a low-Na diet. Control urinary Cl and Na levels under these circumstances were too low to enable the effect of estrogen to be adequately observed. (c) Where ascites had occurred only as a temporary episode complicating hematemesis. Two cases (Nos. 33 and 62) where ascites was about to develop were accepted, together with one (No. 56) where a chronic ascites had recently disappeared with treatment in hospital. One case (No. 62) was studied twice at different stages of the disease.

Group 2—Hepatic cirrhosis without ascites (12 cases). Cases in whom there was a past history of ascites only as a temporary episode complicating hematemesis were included. Two cases were studied twice at different stages of the disease (Nos. 16 and 22). Both early and advanced cases were included.

Group 3—Infective hepatitis (4 cases). All cases in this group (except No. 48) showed signs of recovery by the time estrogen was administered. Infective hepatitis occurred rarely during the period of these studies and only one case (No. 48) in the most severe category was available.

Group 4—Obstructive jaundice (5 cases). Only cases with chronic and apparently complete obstruction of the biliary passages were accepted. Cases of gall stones were excluded.

TABLE I
The effect of estrogen administration in cirrhosis with ascites[†]

Case No.	Days in Control Period	Estrogen Period	Daily Urinary Output						Venuous			
			Water Balance (ml.)	Chloride (mEq.)	Sodium (mEq.)	Potassium (mEq.)	Phosphate (mEq.)	Total Serum Protein (g./100 ml.)	Hematocrit (%)			
(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	
1	8	12	incr [‡] (0.01)	1150 (0.08)	1380 (0.06)	50 33 (0.01)	50 20 (0.01)	-	-	-	-	
17	12	10	incr [‡] (0.7)	2080 (0.4)	1910 (0.01)	50 25 (0.01)	20 10 (0.01)	-	-	-	-	
24	10	12	incr [‡] (0.01)	940 (0.01)	1410 (0.01)	158 94 (0.01)	146 68 (0.01)	56 58 (0.6)	71 78 (0.2)	6.6	6.2	
28	9	9	incr [‡] (0.01)	385 (0.01)	1110 (0.01)	144 51 (0.01)	156 35 (0.01)	55 53 (0.7)	54 54 (0.9)	7.1	6.7	
33	8	9	55.8 (0.01)	57.5 (0.01)	930 (0.01)	1560 (0.02)	133 103 (0.02)	115 65 (0.01)	53 57 (0.2)	54 50 (0.2)	6.5	5.9
56	8	9	56.3 (0.01)	57.0 (0.01)	1180 (0.2)	1320 (0.2)	94 84 (0.2)	97 83 (0.2)	61 69 (0.01)	-	-	6.7
58	9	10	94.5 (0.01)	95.4 (0.1)	740 (0.6)	940 (0.06)	109 85 (0.05)	120 87 (0.05)	48 49 (0.7)	-	-	6.8
62	13	9	77.5 (0.6)	77.6 (0.7)	675 (0.7)	770 (0.08)	74 51 (0.02)	91 50 (0.02)	44 47 (0.4)	-	-	6.5
64	11	10	decr [‡] (0.02)	1350 (0.07)	1570 (0.01)	55 19 (0.01)	49 10 (0.01)	46 35 (0.02)	52 52 (0.2)	-	-	-
Mean difference			+0.85	+283	-36	-46	+1		+0.8	-0.57		-1.7
P			0.1	0.02	0.01		0.6		0.9	0.03		0.05

[†] Mean values for control period (a) and estrogen period (b). Figures in brackets denote values for P relating only to the two means immediately above. An asterisk (*) indicates that the P values are derived from comparison of regression lines, mean values being omitted; "incr" indicates an increased, and "decr" a decreased rate of gain. Mean differences for the whole group with P values are given at the foot of the table. Water balance = daily total water intake less urinary output.

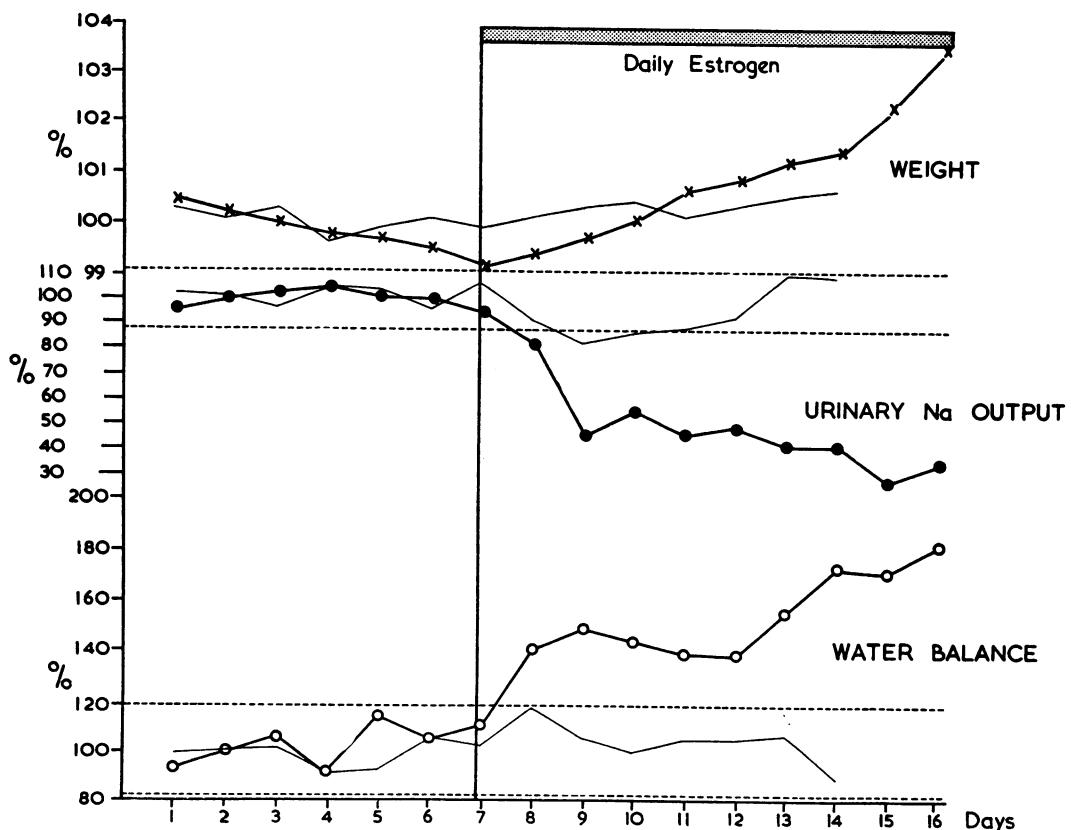


FIG. 1. THE EFFECT OF ESTROGEN ADMINISTRATION ON DAILY WEIGHT, URINARY SODIUM OUTPUT AND WATER BALANCE IN CIRRHOSIS WITH ASCITES

Control period, days 1 to 6; estrogen period, days 7 onwards. Each point represents the daily average for the group expressed as a percentage of the control period mean. Water balance = daily total water intake less urinary output. Horizontal interrupted lines denote the 95 per cent confidence limits for the control period for each class of observation. Results in the normal group are inserted for comparison (continuous line).

Group 5—Ascites without hepatic disease (3 cases). Cases were chosen where hepatic, cardiac or renal disease could be excluded. Cases were not accepted in which ascites was accumulating so rapidly that paracentesis might become necessary during the study, or in which ascites could only be controlled by a low Na diet. Two cases had carcinomatous peritonei and one had tuberculous peritonitis.

Group 6—Portal hypertension without hepatic disease (2 cases). In the two cases in this group portal hypertension was due to splenic vein thrombosis. Liver function tests were normal, hepatic biopsy showed normal histology, and the liver appeared normal at laparotomy. There was no ascites.

The balance study, estradiol dosage, estimations, methods and presentation of results are as described in the previous paper (16) with the following exceptions. The "thiocyanate space" was not determined in cases with ascites, due to difficulty in obtaining an equilibrium CNS concentration between plasma and ascitic fluid. In statistical analysis an extended use was made of regres-

sion line comparisons, particularly in the analysis of weight trends. Values for P (derived from the t test) of between 0.03 and 0.05 were regarded as of "borderline significance." In calculating group mean differences for weight, cases where there was an obvious trend during the control period (marked by an asterisk in Tables I to IV) were omitted.

RESULTS

Cirrhosis with ascites (Table I)

Weight. The group mean difference between control and estrogen periods was calculated only from the four cases (Nos. 33, 56, 58, and 62) in which there was no obvious trend during the control period. In the remaining cases, regression lines were calculated for both periods. In all these subjects (except No. 17) a highly significant difference between control and estrogen regres-

sion lines was observed, the difference indicating an increased rate of weight gain during the estrogen period in case 1, and a slightly decreased rate of gain in case 64. In cases 24, and 28 there was a complete reversal of a downward trend following estrogen administration. In cases 33, 56, 58, and 62, the significance of differences between means could be tested. There was a significant increase of weight in cases 33, 56, and 58.

Water balance. There was a group mean difference between periods of + 283 ml. which was significant. In individual cases an increased mean figure was observed in all cases, except in No. 17, but the difference was of a magnitude to attain significance only in cases 24, 28, and 33.

Daily urinary outputs. Cl and Na. There was a group mean difference between periods of - 36 mEq. Cl and - 46 mEq. Na, each difference being highly significant. A significantly decreased mean output of Cl and Na during the estrogen period was observed in each subject, except in Nos. 56, 58, and 62. In No. 58 the decrease in both Cl and Na was of borderline significance, and in case 62 the decrease in Na was significant, but that in Cl was not. In case 56 no significant variation in either Cl or Na occurred during the estrogen period.

K. This estimation was performed in seven cases. There was no significant difference between periods as a group. In case 56, there was

a small but significant increase in average output of K, and in case 64 a small but significant decrease.

PO₄. Phosphate output was studied in four cases. The group mean difference was not significant and there was no significant difference between period means in any individual case.

Total serum protein. There was a mean decrease of 0.57 g. per 100 ml., which was of borderline significance. This represents a mean decrease of 8 per cent of control values.

Venous hematocrit. A mean decrease of 1.7 per cent was observed in the seven cases in which this observation was made. The significance was borderline. This represents a mean decrease of 4 per cent of control values.

Plasma Cl and Na. No significant variation in concentration was observed following the administration of estrogen ($\bar{d} = -0.3$ mEq. per L. [$P = 0.8$] and + 0.7 mEq. per L. [$P = 0.8$], respectively).

Water tolerance test. Mean results for the five cases studied are given in Table IV. The hourly differences were either non-significant or of borderline significance, but the mean difference for all hours and all cases (- 67 ml.) was highly significant ($P = 0.01$).

In contrast to the normal findings there was a marked and sustained fall in daily average urinary Na output (Figure 1), accompanied by an



FIG. 2. THE EFFECT OF ESTROGEN ADMINISTRATION ON THE DAILY URINARY Na/Cl RATIO IN CIRRHOSIS WITH ASCITES

Control period, days 1 to 6; estrogen period, days 7 onwards. Each point represents the daily average for the group. Results in the normal group are inserted for comparison (continuous line).

TABLE II
The effect of estrogen administration in cirrhosis without ascites †

Case No.	Control Period	Days in Estrogen Period	Water Balance (ml.)		Daily Urinary Output		Total Serum Protein (g./100 ml.)		Venous Hematocrit (%)		"Thiocyanate Space" (l.)	
			(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
16	7	10	45.3 (0.8)	45.3 (0.8)	880 (0.08)	980 (0.08)	105 (0.08)	90 (0.02)	111 (0.02)	92 (0.02)	6.7	6.7
18	6	12	47.4 (0.01)	48.6 (0.03)	860 (0.05)	1050 (0.02)	69 (0.02)	50 (0.02)	62 (0.02)	49 (0.02)	6.3	5.5
19	8	12	68.1 (0.01)	68.4 (0.1)	960 (0.01)	1090 (0.1)	74 (0.2)	60 (0.2)	57 (0.2)	44 (0.2)	7.3	6.3
22	6	10	65.7 (0.01)	66.3 (0.06)	1150 (0.06)	890 (0.04)	90 (0.04)	99 (0.9)	79 (0.9)	80 (0.9)	51 (0.6)	7.2
39	8	10	56.7 (0.2)	57.0 (0.09)	1470 (0.09)	1110 (0.06)	130 (0.06)	115 (0.02)	125 (0.02)	110 (0.02)	63 (0.8)	7.2
50	7	7	52.0 (0.06)	52.0 (0.05)	860 (0.05)	1130 (0.04)	106 (0.04)	90 (0.05)	105 (0.05)	84 (0.05)	41 (0.5)	7.0
63	8	8	41.6 (0.03)	41.2 (0.4)	710 (0.4)	805 (0.4)	108 (0.7)	105 (0.7)	120 (0.6)	114 (0.6)	71 (0.03)	6.7
65	12	9	62.5 (0.7)	62.5 (0.7)	790 (0.2)	680 (0.2)	110 (0.9)	111 (0.9)	106 (0.7)	110 (0.7)	64 (0.5)	6.1
70	10	9	49.7 (0.02)	50.4 (0.2)	730 (0.2)	870 (0.2)	88 (0.1)	69 (0.1)	89 (0.1)	67 (0.1)	63 (0.4)	6.8
71	7	10	64.8 (0.01)	66.2 (0.9)	1030 (0.9)	1030 (0.9)	93 (0.1)	82 (0.1)	89 (0.1)	77 (0.1)	56 (0.1)	5.6
72	8	8	50.1 (0.01)	49.7 (0.01)	655 (0.8)	675 (0.8)	106 (0.7)	102 (0.7)	117 (0.7)	106 (0.7)	28 (0.5)	6.5
73	10	10	58.5 (0.01)	58.1 (0.3)	925 (0.3)	1060 (0.2)	131 (0.2)	117 (0.05)	145 (0.05)	113 (0.05)	68 (0.05)	9.2
Mean difference			40.3	+28	-10	-14.1	-1.6	-0.4	-1.6	-0.4	-0.4	-1.2
P			0.1	0.7	0.01	0.01	0.9	0.01	0.9	0.01	0.2	0.03

† See footnote, Table I.

equally sustained rise in water balance and in weight during the estrogen period. The extent of the 95 per cent confidence limits for the cirrhotic group indicates the high degree of significance of these findings. The figures for weight are necessarily cumulative, and, since there was a steady fall during the control period, the increase following estrogen administration should be measured from the last day of the control period and not

from the control mean. The extent of weight gain is then seen to be far greater than in the normal.

Daily average urinary Na/Cl output ratios (Figure 2) decreased from a control mean of 0.94 to a sustained level of approximately 0.67 during estrogen administration, in contrast to normal values.

There was an average apparent retention during the estrogen period of 325 mEq. Na, 218 mEq. Cl,

TABLE III
The effect of estrogen administration in obstructive jaundice, infective hepatitis, ascites without hepatic disease and portal hypertension without hepatic disease †

Case No.	Days in		Weight (kg.)	Water Balance (ml.)	Daily Urinary Output						Total Serum Protein (g./100 ml.)	Venous Hematocrit (%)		
	Control Period	Estrogen Period			(a)	(b)	(a)	(b)	(a)	(b)				
<u>OBSTRUCTIVE JAUNDICE</u>														
3	7	7	51.2 (0.01)	49.4 (0.4)	650 (0.4)	820	155 (0.01)	114 (0.1)	165 (0.1)	147	-	-	-	39 41
23	5	8	45.6 (0.7)	45.2 (0.6)	840 (0.6)	880	75 (0.1)	61 (0.03)	69 (0.4)	43	60 (0.2)	55 (0.7)	6.6 5.2	44 39
29	6	10	43.4 (0.01)	42.6 (0.1)	600 (0.1)	715	77 (0.2)	70 (0.4)	70 (0.4)	62	51 (0.04)	46 (0.9)	7.2 6.5	42 39
40	10	10	57.2 (0.6)	57.1 (0.5)	1450 (0.5)	1570	151 (0.2)	131 (0.03)	139 (0.03)	107	85 (0.05)	74 (0.7)	5.5 5.3	38 36
42	6	10	57.9 (0.3)	57.4 (0.09)	1165 (0.09)	1460	102 (0.01)	80 (0.1)	51 (0.1)	41	39 (0.06)	33 (0.2)	5.9 5.8	32 30
Mean difference P			-0.7 0.08	+148 0.08			-18.8 0.02		-20.8 0.02		-9.2 0.04	-3.8 0.3	-0.48 0.2	-3 0.01
<u>INFECTIVE HEPATITIS</u>														
2	6	13	54.7 (0.01)	57.7 (0.2)	1085 (0.2)	1280	217 (0.4)	206 (0.2)	195 (0.2)	184	-	-	-	6.1 6.4
10	10	11	42.8 (0.01)	43.4 (0.01)	1230 (0.01)	1380	96 (0.3)	110 (0.3)	108 (0.7)	106	-	-	-	7.5 7.7
48	6	9	incr. (0.01)	incr. (0.02)	215 (0.02)	995	249 (0.01)	167 (0.01)	260 (0.01)	168	70 (0.4)	76 (0.4)	-	6.2 5.8
75	7	9	61.6 (0.1)	61.8 (0.05)	1210 (0.05)	1555	92 (0.8)	91 (0.8)	96 (0.2)	87	66 (0.5)	68 (0.5)	-	8.3 7.7
Mean difference P				+4.18 0.04			-25.4 0.3		-20 0.9				-0.18 0.5	-3.7 0.2
<u>ASCITES WITHOUT HEPATIC DISEASE</u>														
25	10	10	incr. (0.01)	incr. (0.01)	1200 (0.5)	1270	incr. (0.01)	incr. (0.01)	incr. (0.01)	124	62 (0.9)	62 (0.9)	50 (0.01)	57 (0.01)
35	14	10	incr. (0.01)	incr. (0.01)	1040 (0.4)	970	128 (0.09)	107 (0.09)	127 (0.06)	105	50 (0.6)	48 (0.6)	44 (0.7)	42 (0.7)
66	8	9	60.5 (0.01)	57.6 (0.01)	171 (0.01)	504	170 (0.01)	115 (0.01)	188 (0.01)	123	64 (0.03)	55 (0.03)	-	-
<u>PORTAL HYPERTENSION WITHOUT HEPATIC DISEASE</u>														
14	8	10	57.4 (0.03)	58.0 (0.3)	830 (0.3)	980	158 (0.04)	125 (0.04)	153 (0.2)	133	-	-	-	6.0 6.0
49	8	9	65.9 (0.01)	66.5 (0.1)	890 (0.1)	1100	175 (0.4)	168 (0.4)	186 (0.2)	166	56 (0.5)	60 (0.5)	60 (0.1)	66 (0.1)

† See footnote, Table I.

and 1950 ml. water. There was an average gain of weight of 2.06 kg. These values are in approximately the expected proportion, if the changes observed were due to an increase in the volume of extracellular fluid (ECF). Since intake remained constant and there were no abnormal losses, these findings taken together indicate that the retention of Cl, Na, and water was in fact due to an increase in ECF volume.

Cirrhosis without ascites (Table II)

Weight. There was no significant difference between periods in the group as a whole. There was, however, a significant increase in weight in five individual cases (Nos. 18, 19, 22, 70, and 71), and a significant decrease in two (Nos. 72 and 73).

Water balance. The group mean difference of + 28 ml. was not significant. There was no significant difference between period means in any case, but in No. 18 a difference of + 190 ml. was of borderline significance.

Daily urinary outputs. Cl and Na. There was a small but significant difference between control and estrogen periods in both Cl and Na outputs, group mean differences being - 10.0 mEq. Cl and - 14.1 mEq. Na.

No significant difference was observed in in-

TABLE IV
Water tolerance tests *

No. of subjects	Urinary volume (ml.)				
	1st hour	2nd hour	3rd hour	4th hour	All four hours
Cirrhosis with ascites					
5	-80 (0.2)	-113 (0.04)	-51 (0.03)	-25 (0.06)	-67 (0.01)
Cirrhosis without ascites					
5	-25 (0.7)	-100 (0.01)	-22 (0.6)	-9 (0.8)	-39 (0.06)
Obstructive jaundice					
5	+3 (0.3)	+58 (0.6)	-20 (0.7)	-58 (0.1)	-16 (0.6)

* Figures represent the group mean differences between control period and estrogen period tests (P figures are in parentheses).

dividual cases, except in Nos. 16, 18, and 39. In cases 16 and 39 there was a small but significant decrease in Na output alone during the estrogen period; in No. 18 a significant decrease was observed in both Cl and Na.

K. There was no significant difference between periods as a group nor in any of the nine cases in which the estimation was done.

Total serum protein. There was a significant decrease, mean difference being - 0.4 g. per 100

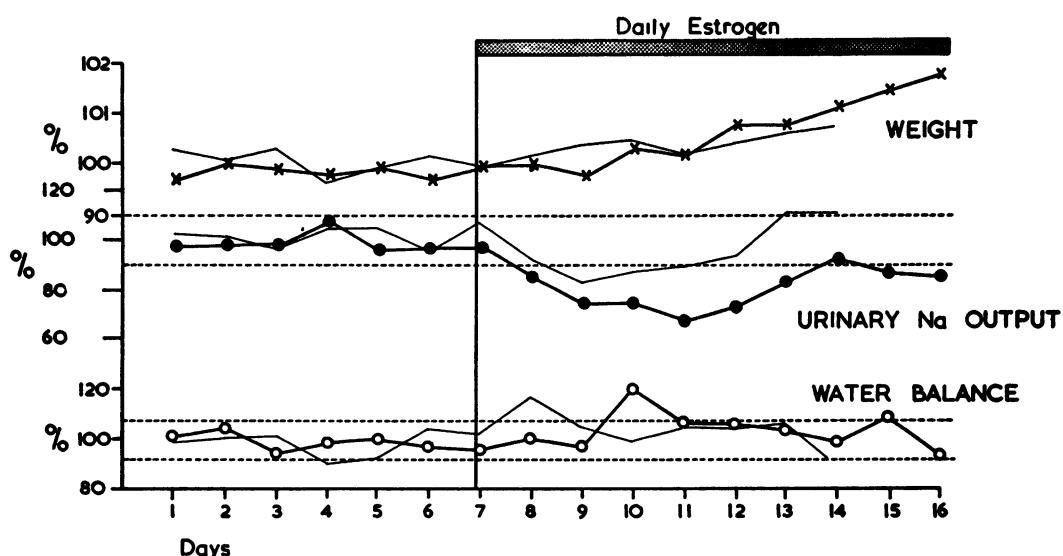


FIG. 3. THE EFFECT OF ESTROGEN ADMINISTRATION ON DAILY WEIGHT, URINARY SODIUM OUTPUT AND WATER BALANCE IN CIRRHOSIS WITHOUT ASCITES

See footnote, Figure 1.

ml. This represents a decrease of 5.5 per cent of control values.

Venous hematocrit. A mean decrease of 1.2 per cent was not significant. This estimation was done on seven cases. It represents a decrease of 3.0 per cent of control values.

"Thiocyanate space." This observation was made in five cases only. There was a mean increase of 1.16 L. which was of borderline significance.

Plasma Cl and Na levels. No significant change was observed in the level of either ion (group mean differences, + 0.2 mEq. per L. Cl and + 0.6 mEq. per L. Na, $P = 0.8$ in each case).

Water tolerance test (Table IV). This test was performed in five cases. The group mean difference between periods for all hours and all cases of - 39 ml. was not significant. Analysis of results by hours shows that there was a significant difference following estrogen administration only in the second hour ($\bar{d} = - 100$ ml., $P = 0.01$).

Figure 3 indicates that there was no marked difference between the cirrhotic group and the normal in respect of average daily weight or water balance, but average daily Na outputs in the cirrhotic group were somewhat lower during the estrogen period. In addition, the Na output failed to return to the control mean in nine days, whereas in the normal group, values rose above the control mean in seven days. Daily average urinary Na/Cl ratios did not differ significantly from the normal.

There was an average apparent retention of 126 mEq. Na, 99 mEq. Cl, and 266 ml. water and an average weight gain of 0.74 kg. during the estrogen period. Na and Cl were retained in approximately the proportion expected, if retention were solely due to increased extracellular fluid volume, but the apparent retention of water and the increase in weight were not in the expected proportions.

Obstructive jaundice (Table III)

Weight. There was, as a group, no significant change during the estrogen period. Individual records show either no significant change (Nos. 23, 40, 42), or a small but significant decrease of weight during the estrogen period (Nos. 3 and 29). However, inspection of the individual records in these two cases indicated that a decreasing

tendency was already evident during the last days of the control period, although there was no systematic tendency throughout the period as a whole.

Water balance. No significant variation occurred as a group during the estrogen period nor was there any significant variation in any individual case.

Daily urinary outputs. Cl and Na. There was a significant decrease in Cl and Na (group mean differences, - 18.8 mEq. Cl, and - 20.8 mEq. Na, $P = 0.02$ in each case).

In individual cases, there was a significant decrease in Cl output alone in cases 3 and 42, and a decrease in Na output alone of borderline significance in cases 23 and 40 ($P = 0.03$).

K. This estimation was done in four cases. A group mean difference of - 9.2 mEq. was of borderline significance ($P = 0.04$). A decrease of borderline significance also occurred in two individual subjects (Nos. 29 and 40).

PO₄. There was no significant variation as a group nor was there any significant difference in any of the four individual cases.

Venous hematocrit. There was a highly significant mean decrease in packed cell volume of 3 per cent ($P = 0.01$). This represents a decrease compared with control values of 7.5 per cent.

There was no significant change in either total serum protein levels or in thiocyanate space (mean difference for thiocyanate space + 1.9 L., $P = 0.1$).

Plasma Cl and Na. There was no significant change following estrogen administration (group mean difference + 0.2 mEq. per L. Cl and + 0.4 mEq. per L. Na, $P = 0.9$ in each case).

Water tolerance test (Table IV). The mean difference between control and estrogen periods for all cases and all hours was not significant. Analysis of hourly results indicated no significant difference between periods for any hour.

Figure 4 shows that Na output decreased well below the normal range, but rose above control levels by the end of the estrogen period. Water balance rose above the 95 per cent confidence limits, then returned to control values, the variation corresponding to that of Na output. Weight which had been falling steadily during the control period, rose during the estrogen period. Average daily urinary Na/Cl ratios did not however vary significantly between periods.

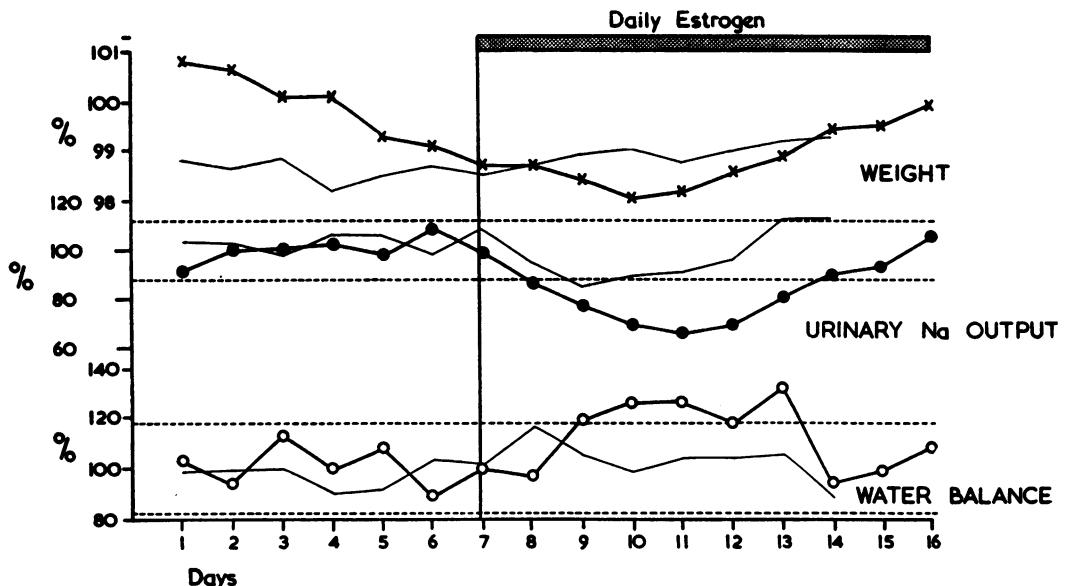


FIG. 4. THE EFFECT OF ESTROGEN ADMINISTRATION ON DAILY WEIGHT, URINARY SODIUM OUTPUT AND WATER BALANCE IN OBSTRUCTIVE JAUNDICE

See footnote, Figure 1.

There was an average apparent retention of 178 mEq. Cl and 167 mEq. Na, and 1360 ml. H_2O during the estrogen period. There was an average increase in weight (estimated from the last day of the control period) of 0.25 kg. These figures are not in the proportion expected if retention were due solely to an increase in ECF volume.

Infective hepatitis (Table III).

Weight. (Group analysis was not attempted.) There was a significant increase in weight during the estrogen period in cases 2, 10, and 48, being particularly marked in No. 2. In No. 48, the falling tendency during the control period was reversed following estrogen administration.

Water balance. There was a group mean difference of +418 ml. between periods, which was of borderline significance ($P = 0.04$). In cases 10 and 48, there was a significant increase in water balance during the estrogen period. In case 75 the increase was of borderline significance ($P = 0.05$), and in case 2 non-significant.

Daily urinary outputs. Cl and Na. There was no significant group mean variation between periods in the output of either ion. In case 48, there was a significant fall in urinary Cl and Na output during the estrogen period. In the remaining cases there was no significant change.

No significant change was observed in urinary K output, nor in total serum protein, venous hematocrit and plasma Cl and Na levels. Water tolerance tests were carried out in three cases; there was no significant difference between periods.

In the four cases of infective hepatitis estrogen administration had no significant effect as a group on water balance or on urinary Cl and Na output. However, a significant decrease in urinary Na and Cl output, accompanied by a significant increase in weight and water balance, did occur in case 48. Here an NaCl and water diuresis was temporarily reversed on estrogen administration. The individual record showed that a second diuresis occurred when estrogen was discontinued.

Ascites without hepatic disease (Table III)

Group analysis was not carried out in these three cases. In case 25, there was a steady increase in weight during the control period due to the accumulation of ascites. Estrogen administration was accompanied by a slight but significant increase in the rate of weight gain. There was a progressive decrease in urinary Na and Cl output during the control period, comparison of regression lines indicating that the rate of decrease became significantly less during the estrogen period. A

significant mean decrease in urinary PO_4 output was observed during the estrogen period, and there was a reduction in venous hematocrit of 2 per cent.

In case 35, there was a steady decrease in weight during the control period, which was significantly reversed during the estrogen period ($P = 0.01$). No significant change was observed in urinary output of Cl, Na, K, or PO_4 , but total serum protein decreased by 0.9 g. per 100 ml., and the venous hematocrit by 4 per cent. Case 66 was undergoing a slow spontaneous diuresis during the control period. The significant decrease in weight during the estrogen period was attributable to this factor, which also accounted for the significant diminution in water balance, and urinary Na and Cl output. A slight decrease in K output was of borderline significance.

Plasma Cl and Na levels were not significantly affected by estrogen administration in any of these cases. Water tolerance tests performed in cases 25 and 35 showed a mean difference between periods for both cases and all hours of -131 ml., which was of borderline significance ($P = 0.03$).

There was no indication in any of the three cases that estrogen caused any significant alteration in NaCl and water metabolism.

Portal hypertension without hepatic disease (Table III)

Group analyses were not carried out. In both cases studied there was an increase of weight following estrogen administration, significant in case 49 and of borderline significance in case 14. This was not reflected in any significant decrease in water balance or urinary output of Cl or Na. A mean difference of Cl only (-33 mEq.) in case 14 was of borderline significance. Urinary K and PO_4 outputs in case 49 were not significantly affected. Plasma Cl and Na and total serum protein levels were not significantly changed. A decrease in hematocrit of 2 per cent in case 14 was observed. The water tolerance test showed no significant change between periods in either case.

There was no indication that estrogen caused any significant retention of water or NaCl in either case.

DISCUSSION

The considerable and sustained retention of Cl, Na, and water observed in the group of cirrhosis with ascites following the administration of estrogen

is in marked contrast with the effect of the same dosage in the normal (16). The changes in the cirrhotic group were apparent not only in the group as a whole (Table I, Figure 1 and 2) but also in each individual case, save one (No. 56) in which ascites had already disappeared following six weeks' hospital treatment.

In the group of cirrhosis without ascites, on the other hand, the effect of estrogen on NaCl and water metabolism did not differ markedly from the normal. However, although no significant change occurred in any individual case, save one (No. 18), a small but significant retention of Cl and Na was detected on group analysis (Table II, Figure 4), indicating that the difference between the two cirrhotic groups of the effect of estrogen administration is quantitative rather than qualitative.

The effect of estrogen on the group of infective hepatitis did not differ from the normal in three cases, but in the fourth (No. 48) estrogen administration was associated with a marked reversal of an existing NaCl and water diuresis similar to that observed in two cases (Nos. 24 and 28) in the group of cirrhosis with ascites. It is of interest that this (No. 48) was the only case of infective hepatitis in which recovery was not already evident by the time estrogen was administered, suggesting that NaCl and water retention might have been observed more often if more severe cases had been available.

The prominent increases in weight in the absence of NaCl retention, observed in some cases of infective hepatitis and cirrhosis without ascites after estrogen, may be attributable to increased tissue formation, as in the normal group (16).

The evidence (12) that, in sub-primates, the liver is the main site of estrogen inactivation is convincing. Although somewhat more controversial (17), the balance of evidence indicates that in humans also estrogens are chiefly inactivated in the liver (18, 19).

The marked NaCl and water storage observed in the present series of cirrhotics with ascites after estrogen administration might be accounted for by failure of a diseased liver to inactivate the hormone. However, the quantitative difference in NaCl and water retention observed between the two cirrhotic groups would then imply differing rates of hepatic estrogen inactivation. Before

this thesis can be accepted, various extrahepatic factors, which could account for the findings in the cirrhotics with ascites, must be excluded.

Increased abdominal tension (20) or congestion of the inferior vena cava (21) can cause, at least acutely, a decrease in renal clearance rates. Although the mechanism of renal excretion of estrogens is not known (22), it is possible that the presence of ascites might, by reducing renal clearances through one of the above mechanisms, delay the renal excretion of the estrogen. However, this possibility appears unlikely. No impairment of renal function was demonstrated in this group of cirrhotics with ascites by conventional renal function tests, and glomerular filtration rate and renal plasma flow have been shown to be in general normal in cirrhosis with ascites (23, 24) except possibly where ascites is accumulating rapidly (25). (Cases in the latter category were excluded from this study.) Furthermore, in this series marked NaCl and water retention following estrogen occurred before ascites had developed in case 33, and when ascites was absent in cases 18 and 48. Finally, no alteration in NaCl and water metabolism attributable to estrogen was observed when the hormone was administered to the group of ascites without hepatic disease.

It is also unlikely that portal hypertension was by itself an important factor in the differing response of the two cirrhotic groups, since firstly, portal hypertension, as judged by the demonstration of esophageal varices on barium swallow, was present in several of the group without ascites (notably Nos. 58 and 70, in whom the effect of estrogen administration did not differ significantly from normal), and secondly the response to estrogen administration in the group of portal hypertension without hepatic disease was within the normal range.

It appears therefore, that the differences observed between the two cirrhotic groups could reasonably be accounted for by differing rates of estrogen inactivation. This process may in turn be dependent on three intrahepatic factors.

There is good evidence that in animals estrogens are excreted in the bile (26, 27) and there is some evidence that biliary excretion may also occur in the human (28). If this pathway were important in the human, either for excretion in

the feces, or as part of the process of hepatic inactivation, then either extrahepatic biliary obstruction or intrahepatic disorganization of the biliary tree would presumably result in high blood estrogen levels following estrogen administration. However, in the group of extrahepatic biliary obstruction (obstructive jaundice) in this series, although some significant retention of NaCl and water did occur (Table III) after estrogen administration, this was only of the same order as in the group of cirrhosis without ascites, and was moreover, transient (Figure 4). These observations indicate that failure of biliary excretion of estrogen due to a disorganization of the intrahepatic biliary tree is not mainly responsible for the NaCl and water retention observed in the group of cirrhosis with ascites following estrogen administration.

Although the process of hepatic inactivation must eventually depend on hepatocellular activity, an adequate hepatic circulation must also be essential. Since evidence from clinical observation, hepatic function studies and hepatic biopsy suggested that hepatocellular damage was rather more severe in our group of cirrhosis without ascites, it appears possible that the factor deciding the rate of hepatic inactivation of administered estrogen in this series, and so the degree of NaCl and water retention, may be an impairment of the hepatic circulation. Estimated hepatic blood flow is known to be reduced in cirrhosis of the liver (29), but the discrete effects of ascites have not been studied.

Our observations support the view that the action of estrogens may be a factor in the fluid retention of liver disease, since if exogenous estrogen can produce NaCl and water retention, then endogenous estrogen would be expected to have the same effect, provided that adequate quantities of the hormone were being produced. The findings of increased urinary estrogenic material on bioassay in both chronic (30, 31) and acute (32) hepatic disease indicates that estrogen production in these conditions is in fact substantial.

SUMMARY

1. Daily administration of 10 mg. estradiol benzoate caused sustained retention of NaCl and water in eight of nine cases of hepatic cirrhosis with ascites.

2. In hepatic cirrhosis without ascites the same dose of estradiol caused NaCl and water retention only slightly greater than in the normal, in eleven of twelve cases.

3. The effect of estradiol in five cases of jaundice due to extrahepatic biliary obstruction was similar to that in cirrhosis without ascites.

4. In a group of four cases of infective hepatitis estradiol caused significant NaCl and water retention in one only.

5. In three cases of ascites without hepatic disease and two cases of portal hypertension without hepatic disease, no significant NaCl and water retention attributable to estradiol administration was demonstrated.

6. Evidence is put forward suggesting that the NaCl-retaining effect of estradiol in the group of cirrhosis with ascites is due to decreased hepatic inactivation of the hormone. This decreased inactivation may in turn be dependent mainly on a disturbance of the hepatic circulation, rather than on hepatocellular damage.

7. The above findings indicate that increased estrogen activity may be a factor in the fluid retention of liver disease.

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