Hemodynamic Changes Associated with Fluid Retention Induced in Noncardiac Subjects by Corticotropin (ACTH) and Cortisone; Comparison with the Hemodynamic Changes of Congestive Heart Failure

By ROY E. ALBERT, M.D., WARREN W. SMITH, M.D. AND LUDWIG W. EICHNA, M.D.

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This study proposed to determine whether marked fluid retention, induced by ACTH and cortisone, produces hemodynamic alterations similar to those of clinical congestive heart failure. Of 20 noncardiac subjects, four gained marked amounts of fluid, became edematous and three developed symptoms and signs consistent with congestive heart failure. The associated hemodynamic changes were similar to those of congestive heart failure in that the heart enlarged, "blood volume" increased and right heart and venous pressure rose, but differed in that cardiac ouput and A-V oxygen difference remained normal. It is suggested that the hemodynamic state associated with marked fluid retention is a noncardiac circulatory congestion which simulates congestive heart failure in several non-specific hemodynamic functions but differs in that primary cardiodynamic functions remain normal and the heart does not fail as a pump.

CONGESTIVE heart failure is characterized clinically by the presence of circulatory congestion in the vessels leading to either the right heart, the left heart or both; it is this congestion which gives rise to most of the symptoms and physical signs considered diagnostic of congestive heart failure. One of the hypotheses advanced to explain the genesis of this circulatory congestion holds that a primary failure to excrete salt and water leads to the retention of fluid in the vascular system, which in turn produces the characteristic congestion and manifestations of congestive heart failure.[1, 2, 3] In recent years, there has been increasing evidence that clinical manifestations similar to those observed in congestive heart failure may occur in association with fluid retention of noncardiac origin, for example, after daily intravenous infusions of serum albumin,[4] during the oliguria of acute glomerulonephritis,[5, 6] following excessive fluid intake in lower nephron nephrosis[7, 8, 9] and during the administration of the salt and water retaining substances, desoxycorticosterone acetate (DCA), corticotropin (ACTH) and cortisone.

It was the purpose of the present study to determine whether marked accumulation of fluid, produced in noncardiac subjects by the administration of salt and water retaining substances, could induce cardiovascular hemodynamic alterations similar to the changes observed in naturally developing congestive heart failure. Such determinations should bear directly upon the various hypotheses of the genesis of congestive heart failure.

From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

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METHODS

Cardiovascular dynamic functions were determined in the same subjects in the control state and again when maximal fluid accumulation had been produced by the administration of corticotropin or cortisone. In approximately one-half of the subjects the control determinations were made before administration of the drug, in the other half after completion of the diuresis and weight loss which followed discontinuation of the drug. The following hemodynamic functions were measured: cardiac output by cardiac catheterization and the direct Fick method;[11] oxygen consumption by the open method with analysis of exhaled air for oxygen and carbon dioxide by the Beckman oxygen analyzer;[12] pressures in the right heart and peripheral systemic artery by direct recording with Hamilton manometers; peripheral systemic venous pressure by saline manometer; oxygen content of arterial and right heart blood by manometric analysis;[13] "blood volume"* by the Evans Blue dye (T-1824)† dilution method[14] and electrocardiogram by string galvanometer. Body weight was determined daily. Plasma potassium and serum sodium concentrations, measured by flame photometer, were determined on the day of the hemodynamic measurements and once weekly during the period of administration of the drugs. Heart size was estimated by teleoroentgenograms of the chest taken on the day of the hemodynamic measurements.

Hemodynamic determinations were made in the morning after an overnight fast. Three successive sets of measurements were carried out with the subjects supine and at rest. The samples of exhaled air, arterial and mixed venous blood were collected over a three-minute period; the various pressures were recorded during the immediately preceding two-minute "washout" of the Tissot gasometer. The concentration of the dye T-1824 in serum was extrapolated to the time of injection from measurements on samples taken 10, 20, and 30 minutes after injection of the dye. The data presented are the averages of the three individual measurements, except in occasional instances where technical difficulties resulted in fewer determinations. Standard procedures were used in the calculations. The values for surface area were always based on the patient's edema-free weight.

Of the 14 subjects who received corticotropin, seven were convalescing from some intercurrent disease, three had rheumatoid arthritis, one had arthritis other than rheumatoid, one had lupus erythematosus disseminata and two were patients with heart disease who had just recovered from congestive heart failure with bed rest and mercurial diuretics, but without digitalis (table 1). Of the eight subjects who received cortisone, six were convalescing from an intercurrent disease, one was being treated for sarcoidosis and one for rheumatoid arthritis (table 3). Except for the two known cardiac patients, no subject had evidence of heart disease as judged from the history, physical examination, electrocardiogram or roentgenographically determined heart size. No subject was febrile during the period of study and all partook of the usual hospital ward activity. Cortisone was given orally as Cortone acetate and corticotropin as Acthar intramuscularly. The duration of administration was two to six weeks. The subjects ate the regular hospital diet, without restriction or addition of salt and received 2 Gm. of potassium chloride daily.

* The shortcomings of the dye dilution technic for measurement of blood volume are keenly appreciated, but the method does give results in the same direction as more precise methods and serves, therefore, to indicate changes in blood volume.

† Generous supplies of Evans Blue dye were supplied by the Warner-Chilcott Laboratories.

Results

Almost every subject gained some weight presumably as flesh and this weight was not lost during the diuresis which followed discontinuation of corticotropin or cortisone. Since the study was focused on the effects of fluid retention, the values for fluid gain in tables 1 and 3 exclude weight gained as flesh and were derived by obtaining the difference between the maximum weight while receiving the drugs and the weight after completion of the diuresis induced by withdrawal of the drugs. Most of the subjects (10 of 14 receiving corticotropin and 3 of the 8 receiving cortisone) gained no fluid, or less than five pounds. In this category are the two undigitalized cardiac subjects who received corticotropin shortly after recovering from congestive heart failure. Five subjects, one receiving corticotropin and four cortisone, gained moderate amounts of fluid, from 9 to 14 pounds. Four subjects, three receiving corticotropin and one cortisone, gained considerable amounts of fluid, 16 to 23 pounds. Only these subjects presented clinical manifestations in any way suggesting congestive heart failure. Serum sodium and plasma potassium concentrations remained essentially unchanged in all subjects. Since the hemodynamic alterations produced by corticotropin and cortisone were largely similar, the changes produced by the two substances will be considered together.

Minimal Fluid Retention. When fluid gain was absent or small, less than 5 pounds, alterations in hemodynamic functions were likewise absent or small (tables 1, 2, 3, 4 and fig. 1). The most frequent change was a small increase in the residual pressures in the right heart, greater in right ventricular end diastolic pressure than in

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TABLE 1.—*Effect of ACTH on Cardiac Output and Blood Oxygen Extraction*

Subject Sex, Age, Surface Area yrs. $M.^2$	Diagnosis	Total* Dose	Duration Days	Fluid Gain pds.	Oxygen Consum. ml./$M.^2$/min.	Arterial Oxygen vol. %	Mixed Venous Oxygen vol. %	A-V O_2 Diff. vol. %	Cardiac Index L./$M.^2$/min.
J.S.: M, 52, 1.70	Recovered Coryza	1.8	13	0	125	17.7	12.9	4.8	2.6
					124	17.1	12.3	4.8	2.6
G.T.: M, 56, 1.85	Recovered Pneumonia	3.7	27	0	106	15.4	11.7	3.7	2.9
					137	15.3	10.9	4.4	3.1
L.G.: M, 46, 1.82	Alcoholism Phlebitis	2.1	18	0	157	13.4	9.7	3.7	4.2
					149	14.4	10.6	3.8	3.9
C.M.: M, 14, 1.60	Rheumatoid Arthritis	1.6	20	0	140	18.3	14.0	4.3	3.3
					134	17.8	13.5	4.3	3.1
P.P.: M, 30, 1.77	No Diagnosis	4.1	21	0	110	20.3	16.1	4.2	2.6
					145	18.4	14.5	3.8	3.8
J.R.: M, 50, 1.87	Bronchial Asthma	3.0	22	0	132	16.4	11.9	4.5	2.9
					122	16.6	12.4	4.2	2.9
R.S.: M, 23, 2.00	Arthritis Undiagnosed	2.0	16	2	172	15.8	12.0	3.8	4.5
	Type				136	15.2	11.4	3.9	3.5
F.K.: M, 67, 1.89	Arterioscler. Heart	4.1	26	3.5	124	18.6	13.1	5.5	2.3
	Disease				127	18.4	13.1	5.3	2.4
M.M.: M, 52, 1.75	Recovered Pneumonia	1.5	15	4	127	15.7	11.9	3.8	3.3
					128	14.2	10.8	3.4	3.8
A.H.: M, 61, 1.57	Arterioscler. Heart	3.2	16	4	116	17.2	13.2	4.0	2.9
	Disease				167	15.5	11.7	3.8	4.4
E.R.: M, 49, 1.48	Pulmonary Fibrosis	1.8	23	9.5	160	9.7	6.0	3.7	4.3
					156	8.8	5.3	3.4	4.6
F.R.: M, 53, 1.64	Rheumatoid Arthritis	2.3	19	16	131	11.5	7.7	3.8	3.4
					127	10.3	6.8	3.5	3.6
C.R.: F, 48, 1.49	Lupus Erythematosus	3.9	39	19	150	15.9	12.1	3.8	4.0
					158	13.8	9.9	3.9	4.1
W.C.: F, 42, 1.53	Rheumatoid Arthritis	3.0	25	19	—	—	—	—	—
					—	—	—	—	—

For each subject the first set of determinations are control, the second set at peak of ACTH effect.
* Doses in thousands of units.

right atrial pressure. Femoral arterial pressure also tended to rise. Both pressure changes were more frequent in subjects receiving cortisone and largely absent in subjects receiving corticotropin. No consistent changes occurred in the other hemodynamic functions and indeed the data of these subjects served largely to indicate the satisfactory reproducibility of the measurements in the same subjects, under the conditions of the study. None of these subjects developed changes in the electrocardiogram or in heart size.

Marked Fluid Retention. The four subjects who gained more than 15 pounds of fluid all developed edema, rated as moderate in degree. Three of the subjects (F. R., W. C., T. M.) who gained 16, 19 and 23 pounds of fluid developed, in addition, slight venous congestion, mild dyspnea on exertion and orthopnea of sufficient degree to make sleep at night a little difficult. The clinical manifestations were consistent with mild congestive heart failure. In these three subjects the heart size increased appreciably and congestive changes (rales) appeared in the lungs (fig. 2). The electrocardiogram remained unchanged, except for occasional ventricular premature contractions in subject T. M. for several days at the height of the fluid gain. All of the above manifestations disappeared and the control state returned after completion of the diuresis which followed discontinuation of corticotropin or cortisone.

The marked fluid retention in these three subjects was associated with increases in vascular pressures and "blood volume" but without change in cardiac output. The in-

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TABLE 2.—*Effect of ACTH on "Blood Volume" and Vascular Pressures*

Subject	Plasma Vol. L./M.²	Arterial Hct. %	"Blood Vol." L./M.²	Pressures mm. Hg FA	PA	RV	RA	Vein	Systemic Vascular Resistance mm.Hg/L./min./M.²
J.S.	1.70	37.0	2.65	122/65 (82)	—	15/3	4	2	10.3
	2.09	38.0	3.36	140/71 (90)	—	25/7	5	2	11.4
G.T.	1.81	35.5	2.93	136/74 (94)	—	20/3	5	—	9.1
	1.98	37.0	3.15	141/75 (94)	21/10 (15)	21/7	5	10	8.3
L.G.	2.29	38.0	3.70	150/86 (104)	—	—	4	8	7.1
	—	—	—	148/83 (104)	—	—	2	6	7.9
C.M.	1.57	36.0	2.45	119/75 (88)	—	25/8	2	—	10.2
	—	—	—	117/75 (88)	—	—	0	10	11.0
P.P.	1.79	41.0	3.04	125/73 (90)	19/10 (12)	18/5	6	5	10.1
	1.93	40.0	3.22	150/84 (104)	20/11 (16)	22/8	6	8	8.3
J.R.	2.49	37.5	3.99	123/76 (90)	—	16/4	−3	3	9.0
	2.40	37.0	3.81	126/76 (89)	—	20/6	2	4	8.5
R.S.	—	—	—	160/90 (116)	32/10 (21)	30/4	−1	—	6.5
	1.75	39.0	2.88	160/80 (102)	28/15 (24)	27/6	5	—	7.0
F.K.	2.35	38.0	3.80	121/78 (88)	—	22/4	3	2	10.6
	2.38	35.0	3.60	152/84 (104)	—	21/2	2	2	11.9
M.M.	1.90	42.0	3.28	128/67 (88)	23/7 (15)	22/3	2	11	8.4
	2.22	38.0	3.58	141/72 (92)	21/6 (11)	24/5	2	3	7.8
A.H.	1.98	42.0	3.38	141/72 (92)	—	33/3	−2	0	12.9
	2.24	40.0	3.74	159/75 (103)	—	32/3	1	1	9.4
E.R.	2.37	31.0	3.44	113/62 (72)	56/26 (32)	57/5	−3	−4	7.8
	—	—	—	150/81 (99)	—	55/8	1	4	9.9
F.R.	2.03	30.0	2.95	125/58 (77)	—	19/3	2	11	8.0
	2.44	27.0	3.34	159/76 (96)	—	37/15	10	17	8.6
C.R.	1.85	34.0	2.80	127/74 (92)	13/3 (6)	12/1	0	0	10.5
	2.49	33.0	3.72	130/59 (82)	—	21/7	2	2	8.9
W.C.	1.72	36.0	2.69	120/70	—	—	—	5	—
	2.52	26.0	3.40	146/70	—	—	—	13	—

For each subject the first set of determinations are control, the second set at peak of ACTH effect.
Pressures in parentheses are mean pressures.
FA—femoral artery; PA—pulmonary artery; RV—right ventricle; RA—right atrium; Vein—axillary.

creases in pressure occurred in all parts of the circulatory system: (1) residual pressures in the right heart, i.e. right atrial pressure and right ventricular end diastolic pressure; (2) right ventricular systolic pressure and presumably pulmonary artery pressure; (3) systemic venous pressure and (4) systemic arterial pressure (tables 2, 4 and figs. 3 and 4). The increases in right ventricular end diastolic pressure were proportionately the most marked. "Blood volume" increased by 0.6 to 1.3 liters (tables 2 and 4). There were no changes in cardiac output or in arterial-mixed venous oxygen extraction (tables 1, 3 and figs. 3 and 4).

Subject C. R., who gained 19 pounds of fluid while receiving corticotropin, differed from the above three subjects in that she remained asymptomatic, developed smaller increases in right heart pressures and no rise in femoral artery pressure. However her "blood volume" increased by 1.3 liters. The hemodynamic changes in this patient indicate the lack of correlation between increases in vascular pressures and increases in "blood volume", a result which occurred not only in the subjects with marked fluid retention, but in all subjects studied (tables 2, 4). Increases in vascular pressures appeared more consistently related to the degree of water (and presumably salt) retention (table 5).

As expected, when the fluid gain was of

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TABLE 3.—*Effect of Cortisone on Cardiac Output and Blood Oxygen Extraction*

Subject Sex, Age, Surface Area yrs. M.²	Diagnosis	Total Dose Gm.	Duration Days	Fluid Gain pds.	Oxygen Consum. ml./M.²/min.	Arterial Oxygen vol. %	Mixed Venous Oxygen vol. %	A-V O_2 Diff. vol. %	Cardiac Index L./M.²/min.
W.P.: M, 14, 1.59	Sarcoidosis	2.0	20	0	142	15.7	11.8	3.8	3.7
					143	17.2	12.6	4.6	3.1
S.N.: M, 46, 2.08	Alcoholism	4.5	29	0	—	—	—	—	—
					124	16.8	12.6	4.3	2.9
R.R.: M, 38, 1.88	Hepatic Cirrhosis	3.4	16	4	—	—	—	—	—
					150	16.7	12.6	4.1	3.7
G.A.: M, 45, 1.80	Alcoholism Neuritis	6.1	27	9	—	—	—	—	—
					128	13.6	9.2	4.4	2.9
J.Ph.: M, 38, 2.10	Recovered Pneumonia	4.2	21	10	125	16.9	13.6	3.3	3.8
					142	17.1	13.2	4.0	3.6
M.S.: M, 62, 1.89	Recovered Pneumonia	5.4	27	12	97	17.6	13.7	3.9	2.5
					120	15.5	11.2	4.3	2.8
J.Pa.: M, 53, 1.58	Recovered Pneumonia	3.8	19	14	138	15.2	10.3	4.8	2.9
					139	12.2	8.6	3.7	3.8
T.M.: M, 62, 1.71	Rheumatoid Arthritis	3.4	17	23	128	18.6	14.4	4.2	3.0
					136	15.0	10.4	4.7	2.9

For each subject the first set of determinations are control, the second set at peak of cortisone effect.

TABLE 4.—*Effect of Cortisone on "Blood Volume" and Vascular Pressures*

Subject	Plasma Vol. L./M.²	Arterial Hct. %	"Blood Vol." L./M.²	Pressures mm. Hg					Systemic Vascular Resistance mm.Hg/L./min./M.²
				FA	PA	RV	RA	Vein	
W.P.	1.58	39.5	2.61	137/92 (109)	22/10 (16)	22/3	1	—	11.6
	1.71	42.5	2.97	150/100 (117)	21/11 (15)	21/4	2	9	14.6
S.N.	—	—	—	194/110 (138)	—	—	8	—	—
	1.96	44.0	3.49	173/92 (120)	—	—	5	5	9.2
R.R.	—	—	—	—	—	—	—	—	—
	2.20	40.0	3.66	140/75 (102)	35/22 (27)	37/17	13	11	6.9
G.A.	—	—	—	—	—	—	—	—	—
	2.02	37.0	3.21	168/88 (116)	33/17 (24)	32/13	9	7	11.0
J.Ph.	2.14	39.0	3.50	140/82 (102)	21/8 (16)	21/5	3	4	6.2
	2.24	40.0	3.74	166/88 (111)	—	24/10	5	7	7.0
M.S.	1.90	43.0	3.33	137/64 (91)	—	21/4	0	—	10.3
	2.18	38.5	3.46	206/88 (123)	—	40/15	7	—	11.7
J.Pa.	1.74	40.0	2.91	122/64 (88)	24/7 (16)	20/0	−3	−4	12.8
	2.22	34.0	3.35	156/80 (109)	27/10 (18)	31/7	4	—	11.2
T.M.	1.51	40.0	2.52	145/73 (89)	—	21/6	3	5	9.7
	2.00	39.0	3.26	156/87 (104)	—	39/19	14	16	10.6

For each subject the first set of determinations are control, the second set at peak of cortisone effect.
Pressures in parentheses are mean pressures.
FA—femoral artery; PA—pulmonary artery; RV—right ventricle; RA—right atrium; Vein—axillary.

intermediate degree, 10 to 15 pounds, the hemodynamic alterations were intermediate in varying degrees between those observed in subjects with marked and minimal fluid accumulation.

Digitalis. In congestive heart failure, Digoxin administered intravenously in single therapeutic doses induces characteristically prompt falls in right heart and peripheral venous pressures and a concomitant increase in cardiac output.[15] These events have their onset approximately 15 minutes after administration of

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the glycoside and their peak effect one to two hours later. When subject W. C. had gained 19 pounds of fluid as a result of corticotropin medication and was experiencing some dyspnea on exertion and orthopnea at night, she was given

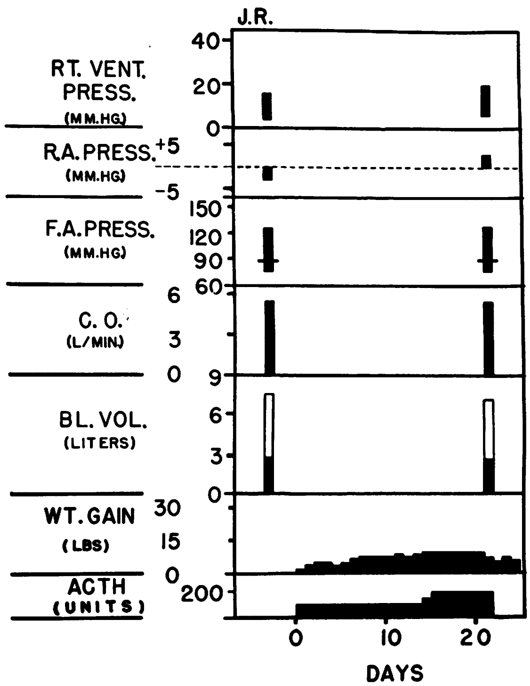

FIG. 1. Absence of significant hemodynamic alterations when corticotropin failed to induce fluid retention.

Details of plotting from top down: *right ventricular pressure*, top of column systolic pressure, bottom of column diastolic pressure; *right atrial pressure*, maximum deviation of column from zero; *femoral artery pressure*, top of column systolic pressure, bottom of column diastolic pressure, cross bar mean pressure; *cardiac output*, top of column; *blood volume*, total blood volume top of column, plasma volume open column, red cell volume solid column; *weight gain*, total gain in pounds above control weight.

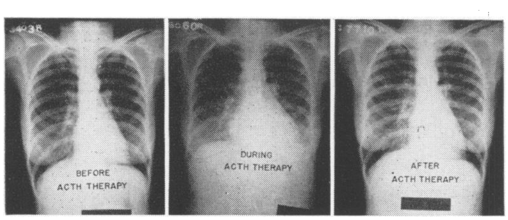

FIG. 2. Patient W. C. Note increase in heart size and development of pulmonary congestion associated with a fluid gain of 19 pounds during administration of corticotropin.

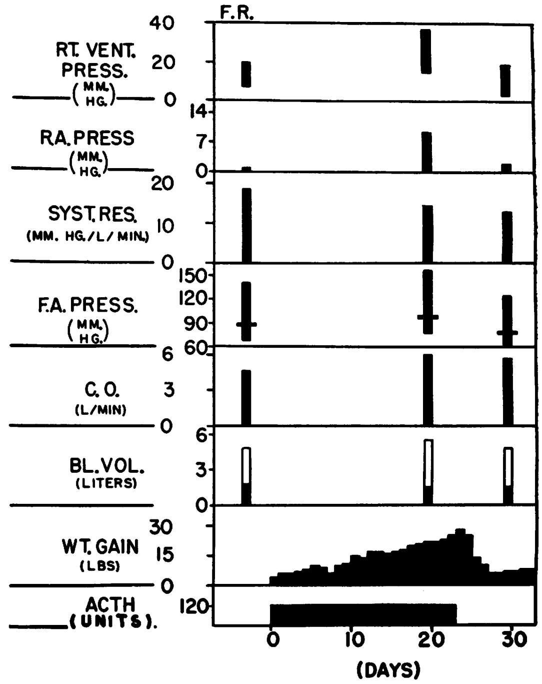

FIG. 3. Hemodynamic alterations associated with a fluid gain of 16 lb induced by administration of corticotropin. For details of plotting see legend of figure 1.

Because the hematocrit fell during administration of corticotropin, the third set of determinations was made after the diuresis which followed discontinuation of the drug. This set of determinations constitutes the preferred control for the changes induced by the corticotropin.

0.8 mg. of Digoxin intravenously without effect upon the elevated venous pressure of 170 to 180 mm. saline. Starting three hours later, 1.0 Gm. of digitalis leaf was given orally in 24 hours without reduction in the still elevated venous pressure and without initiation of diuresis or relief of symptoms, events which would have been expected in a patient with congestive heart failure. Only after corticotropin was discontinued did a diuresis with a concomitant fall in venous pressure and relief of symptoms ensue.

DISCUSSION

The observations presented suggest three points for discussion: (1) the disparity in fluid accumulation by different subjects, (2) the increase in pressure in the right heart and systemic arteries when fluid accumulation occurred and (3) the circulatory dynamics in

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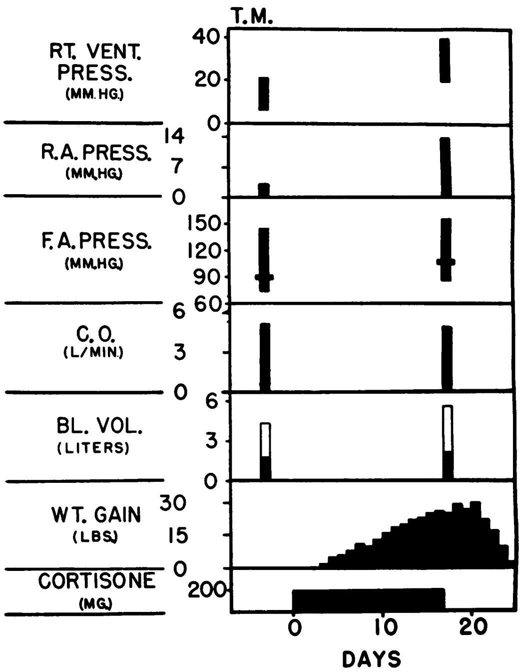

FIG. 4. Hemodynamic alterations associated with a fluid gain of 23 pounds induced by administration of cortisone. For details of plotting see legend of figure 1.

the three subjects with marked fluid accumulation and symptoms simulating mild congestive heart failure.

No explanation is apparent for the disparity in fluid gains by the different subjects. The degree of fluid retention appeared not to be related to the primary illness of the subjects, their state of convalescence, or whether corticotropin or cortisone was given. Although observations were not made in completely normal subjects, it seems unlikely that the subjects who retained large amounts of fluid had "hidden" or potential heart disease. In no subject, except the two known cardiac patients, was there evidence of heart disease. Furthermore, the failure of the two undigitalized cardiac patients, recently recovered from congestive heart failure, to retain more than minimal amounts of fluid suggests that some form of heart disease is not essential for the fluid retention. Apparently, homeostatic mechanisms promoting salt and water excretion are so potent that few subjects receiving these salt and water retaining drugs, in the doses used, retain sufficient fluid to become so edematous that congestive changes simulating congestive heart failure develop.

The most consistent hemodynamic change induced by both corticotropin and cortisone was the increase in pressure in all parts of the vascular tree. A first consideration would suggest that the pressure elevations resulted from an increase in blood volume with subsequent overdistension of the venous reservoir and right heart. However, the failure of correlation between increases in vascular pressures and changes in "blood volume" (table 5) suggests that "blood volume" is not the sole determinant of changes in pressure and that an additional factor is probably operating. A possible and attractive explanation would be that corticotropin and cortisone increased the vascular tone of the entire vascular system from arteries to veins and right heart. Such an increase in tonus could produce two effects: (1) raise the pressure in all parts of the vascular system and (2) redistribute the blood from the higher toned arterial and arteriolar side to the lesser toned, and more distensible venous side. These

TABLE 5.—*Correlation of Changes in Vascular Pressures with Changes in Fluid Gain and "Blood Volume" During Administration of ACTH and Cortisone*

The data for the two drugs have been combined

Functions Correlated*	Number of Subjects N	Correlation Coefficient r	t	p
Δ RA_m and Δ Wt.	18	0.71	2.92	0.01
Δ RA_m and Δ B.V.	14	0.26	0.92	0.38
Δ RV_d and Δ Wt.	16	0.78	2.96	0.01
Δ RV_d and Δ B.V.	14	0.45	1.62	0.14
Δ RV_s and Δ Wt.	16	0.69	2.60	0.02
Δ RV_s and Δ B.V.	14	0.41	1.47	0.2
Δ FA_m and Δ Wt.	19	0.35	1.46	0.15
Δ FA_m and Δ B.V.	14	−0.41	1.46	0.2

* The analysis is for the *changes* between control values and values at peak of drug administration for the several functions: Wt. = weight; B.V. = "blood volume"; RA_m = mean right atrial pressure; RV_d = right ventricular end diastolic pressure; RV_s = right ventricular systolic pressure; FA_m = mean femoral artery pressure.

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changes could then account, in part and perhaps in full, for the observed increases in arterial, venous and residual right heart pressures.

No explanation is offered for the mechanism by which cortisone or corticotropin might increase vascular tone. The first observations were made with corticotropin and the possibility was entertained that contaminating Pitressin may have been responsible for the observed pressor effects. When cortisone produced similar increments in pressure it seemed unlikely that a contaminating known vasopressor agent was responsible for the increases in pressures. Since the rises in residual pressures in the right heart seemed to correlate better with the degree of fluid gain than with the increase in "blood volume" (table 5), the possibility should be considered that salt itself may have been the pressor agent. Neither cortisone nor corticotropin in themselves appear to possess vasopressor activity, for equally large doses, when they failed to induce fluid retention, failed also to produce rises in vascular pressures.

Since it was the purpose of this study to determine whether induced fluid retention in noncardiac subjects was associated with hemodynamic changes similar to, or different from, the hemodynamic alterations of spontaneously developing congestive heart failure, the changes in cardiovascular dynamics in the subjects with marked fluid retention deserve particular attention. In three respects the changes noted in these subjects were similar to the manifestations of naturally occurring congestive heart failure: (1) there developed the symptoms of edema, exertional dyspnea and orthopnea, (2) the "blood volume" was increased and (3) the residual pressures (atrial and ventricular end diastolic) in the right heart were elevated. The increase in right ventricular end diastolic pressure assumes particular significance since elevation of this pressure has been considered to be the criterion of congestive heart failure.[16] However, each of the above three manifestations may be considered to be nonspecific, or secondary in origin, in that they are the resultants of some other more primary physiologic change or changes. Therefore, the presence of these manifestations in two states does not necessarily indicate that both states are similarly derived.

The hemodynamic alterations associated with induced fluid retention differed markedly from the hemodynamic changes in congestive heart failure in several important, primary, cardiodynamic functions. Thus, in both the corticotropin- and cortisone-induced congestion, cardiac output remained normal and arterial-mixed venous oxygen extraction, relating as it does blood supply (cardiac output) to the demand for it (oxygen consumption), also remained normal. In congestive heart failure the changes in these functions are diametrically different: cardiac output is reduced and arteriovenous oxygen difference is abnormally high. Furthermore, the failure of intravenously administered Digoxin to lower the elevated venous pressure in one patient with corticotropin-induced vascular congestion also suggests an essential difference between this type of vascular congestion and congestive heart failure, where similarly administered Digoxin promptly reduces venous and intracardiac pressures.[15] In view of these primary and more specific differences, it is difficult to consider that the vascular congestion associated with hormonally-induced fluid retention is the same entity as congestive heart failure. Both types of congested states have similar nonspecific manifestations but different specific cardiodynamic functions.

These observations suggest that the clinical manifestations and some of the hemodynamic alterations (elevation in right heart and venous pressures) traditionally considered characteristic of congestive heart failure may occur under circumstances in which cardiac output remains normal and the heart does not fail as a pump. Such noncardiac circulatory congestion simulating congestive heart failure was here produced in three subjects by inducing fluid retention with corticotropin and cortisone. The question has been raised whether the circulatory congestion present in several diseases and generally considered to be congestive heart failure may, in fact, represent other instances of noncardiac circulatory congestion simulating congestive heart failure.[17] In this category

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have been placed the circulatory congestions which occur in severe, "pinch-cock", mitral stenosis,[17] acute diffuse glomerulonephritis,[5] anuria with excess fluid intake,[8] beri-beri,[18] arteriovenous fistula[18] and severe anemia.[17] In all of these instances the essential difference from congestive heart failure, as it typically occurs in a patient with heart disease, is the hemodynamic competence of the myocardium to maintain an adequate cardiac output. Such a differentiation based on primary physiologic hemodynamic functions appears warranted and seems more tenable than the traditional view which assumes that all vascular congested states are the result of myocardial insufficiency, simply because these congested states have clinical manifestations similar to congestive heart failure.

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Summary

The purpose of this study was to determine whether fluid retention, induced in noncardiac subjects by means of salt and water retaining substances, produces alterations in cardiovascular dynamics similar to the changes observed in naturally occurring congestive heart failure.

In 20 noncardiac subjects, corticotropin (ACTH) was administered to 12 patients and cortisone to eight patients. Essentially similar effects were produced by the two drugs.

When fluid retention was absent or less than 5 pounds, hemodynamic changes were absent or limited to slight increases in right ventricular, right atrial and systemic arterial pressures. These pressure changes were somewhat more marked when fluid retention was more moderate, 6 to 15 pounds. In neither group did cardiac output or arteriovenous oxygen difference change.

Three subjects gained 16, 19 and 23 pounds of fluid, respectively, became edematous, developed slight cardiac enlargement and manifested in a mild form the symptoms of congestive heart failure. The associated hemodynamic changes of elevation of pressures in the right heart and systemic arteries and increases in "blood volume" were similar to the changes in these functions in congestive heart failure; however, unlike congestive heart failure, cardiac output and arteriovenous oxygen difference remained normal.

Two cardiac subjects, recently "compensated" from congestive heart failure by mercurial diuretics and rest, failed to gain fluid when given corticotropin.

In discussion, the hypothesis is explored that the circulatory congestion associated with marked fluid retention in noncardiac subjects represents not congestive heart failure, but a type of noncardiac circulatory congestion which simulates congestive heart failure. The distinction between the two states is here based on hemodynamic differences in contrast to the traditional view which assumes, on the basis of similarity of clinical manifestations, that all vascular congested states are congestive heart failure.

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Summario in Interlingua

Le objectivo del presente studio esseva determinar si retention de fluido, inducite in individuos non-cardiac per medio de substantias retenitori de sal e aqua, produce alterationes del dynamica cardiovascular simile al alterationes observate in occurrentias natural de congestive disfallimento cardiac.

In un serie de 20 individuos non-cardiac, corticotropina (ACTH) esseva administrate a 12 patientes e cortisona a 8 patientes. Le effectos producite per le duo drogas esseva essentialmente simile.

Quando le retention de fluido esseva absente o infra 2,25 kg, le alterationes hemodynamic esseva absente o restringite a leve augmentos del pressiones dextero-ventricular, dextero-atrial, e arterio-systemic. Iste alterationes del pression esseva alique plus pronunciate quando le retention de fluido esseva inter 2,7 e 6,75 kg. Ni le un ni le altere del gruppos monstrava un alteration del ejection cardiac o del differentia atrio-ventricular de oxygeno.

Tres individuos ganiava respectivemente 7,2, 8,55, e 10,35 kg de fluido. Illes deveniva

edematose e disveloppava un leve allargamento cardiac. Illes manifestava in un forma innocue le symptomas de congestive disfallimento cardiac. In lor casos le associate alterationes hemodynamic—augmento de pression in le corde dextere e le arterias systemic e augmento del "volumine de sanguine"—esseva simile al alterationes hemodynamic in congestive disfallimento cardiac. Del altere latere, le ejection cardiac e le differentia atrio-ventricular de oxygeno remaneva normal, in contrasto con lo que se observa in congestive disfallimento cardiac.

Duo individuos cardiac, recentemente "compensate" ab congestive disfallimento cardiac per diureticos mercurial e reposo, non ganiava fluido post administrationes de corticotropina.

Nos discute le hypothese que le congestion circulatori associate con marcate retention de fluido in individuos non-cardiac representa non un forma de congestive disfallimento cardiac sed un typo de congestion circulatori non-cardiac que simula congestive disfallimento cardiac. Nostre distinction del duo statos es basate super differentias hemodynamic, in contrasto con le conception traditional que conclude super le base de simile manifestationes clinic que omne statos de congestion vascular es congestive disfallimento cardiac.

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Circulation

Hemodynamic Changes Associated with Fluid Retention Induced in Noncardiac Subjects by Corticotropin (ACTH) and Cortisone; Comparison with the Heinodynamic Changes of Congestive Heart Failure

ROY E. ALBERT, WARREN W. SMITH and LUDWIG W. EICHNA

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