hormone (ACTH) or cortisone. Such observations suggest that a relative or absolute hypo- or dysfunction of the secretory activity of the adrenal cortex, or of the responsiveness of peripheral tissues, may exist in these conditions.

The increased intake of NaCl produced by ligation of the inferior vena cava in the rat is reminiscent of the similar chain of events in animals treated with desoxycorticosterone (DOC)(14). Insofar as it is possible, on the basis of the gross observations reported here, to hazard an explanation of the role of the adrenal cortex in the edema of congestive failure, it may be remarked that in this condition, as the result of changes in venous pressure, in electrolyte balance, and in protein and volume regulation, changes which in themselves may not seem grossly exaggerated, that a relative disproportion may occur in the secretion and/or peripheral effects and/or excretory rates of adrenal salt retaining steroids (DOC-like) as contrasted with the 11-17 oxycorticosteroids [see reviews by Burch and Ray(10), Stead(15), and Smith (16).] In this connection, comment must be made on a possible relationship between the diurnal rhythm of congestive failure (nocturnal dyspnea, etc.) and a similar rhythmic cycle in the secretory activity of the adrenal cortex.

Summary. The edema produced in the rat by ligation of the inferior vena cava and voluntary intake of 1% NaCl solution is studied as altered by adrenalectomy and nephrectomy. (1) The obligatory role of NaCl in the formation of edema fluid is reemphasized. (2) The venous congestion produced by ligation of the inferior vena cava is not a sufficient stimulus to cause edema formation in the nephrectomized rat, but does cause edema if the animal is nephrectomized and adrenalectomized. (3) Under these conditions, it is demonstrated that the kidney does not play an obligatory role in the formation of the edematous state in the adrenalectomized rat. (4) The evidence supplied by these experiments is discussed in relationship to the role of the adrenal cortex in conditions exhibiting generalized edema (congestive heart failure, nephrotic syndrome).

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Effect of ACTH Upon Gastric Secretion.* (19067)

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The two principal physiological pathways by which the stomach may be stimulated to secrete hydrochloric acid and pepsin are mediated (a) by way of the vagus nerve and (b) by the release of a hormone, gastrin, produced by the gastric mucosa. Evidence will be presented indicating that the adrenal gland and the adrenal corticoids constitute a third mechanism by which gastric secretion may be stimulated. The vagal phase of secretion is activated by sight, smell, and ingestion of food, insulin induced hypoglycemia, and

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psychic stimuli. Emotional stimuli are expressed under cortical control through the hypothalamus and relayed to the vagal centers. Stimulation or excitation along the course of the fiber tracts from the anterior hypothalamus to the vagal centers may produce gastric erosions, perforations or ulcer accompanied by hypersecretion and hyperchlorhydria(1). Although the gastric response to stress is undoubtedly mediated in part at least through the vagus nerve there is evidence suggesting that an additional hormonal mechanism is involved which may be associated with the general adaptation syndrome. The production of gastric and duodenal ulcerations associated with hemorrhage or perforation is an integral and prominent part of the alarm reaction in response to a number of physical and emotional stress factors, which lead to the release of ACTH by the pituitary gland(2) resulting in the secretion of a variety of adrenal steroid hormones including cortisone and closely related compounds. The hypothalamus which plays a key role in this response to stress may be independent of nervous pathways. Recent studies indicate that in response to emotional and systemic stress the cells of the anterior hypothalamus secrete a humeral substance which stimulates the pituitary to release ACTH(3). Keller has shown, moreover, that section of the vagus nerves still leaves open a pathway over which abnormal or excessive impulses from the hypothalamic centers can exert an effect upon the stomach. After bilateral vagotomy experimental lesions in the hypothalamus and brain stem produced focal hemorrhages in the stomach identical in all respects with those observed with the vagi intact(4).

In an effort to investigate the hormonal role of chronic stress upon the stomach ACTH was administered to human subjects daily for 3-4 weeks to determine its effect upon gastric secretion. The repeated administration of ACTH over a period of time simulates chronic stress since it elicits many of the same responses as those of sustained alarm(5) such as a decrease in the number of circulating eosinophiles in the peripheral blood and an increase in the urinary excretion of 17-ketosteroids.

Methods. ACTH was administered intramuscularly in doses of 100-160 mg daily for a period of 3 to 4 weeks to 6 patients with essentially normal stomachs, one patient with a healed duodenal ulcer and one patient with a gastric ulcer. The basal gastric secretion was obtained by inserting a Levine tube into the stomach in the morning, following a 10 to 12 hour overnight period of fasting, and aspirating the stomach for a period of 60 to 90 minutes by continuous manual suction, following the method of Bloomfield *et al.*(6). The first specimen was discarded and then 3 to 5 consecutive 15-minute aspirations were obtained with constant suction. Consistent and reproducible volumes of gastric secretion were observed during these serial aspirations. The diet was kept constant, and whenever possible the aspirations were performed by the same operator. During the study the fasting patient received nothing by mouth; no belladonna alkaloids or sedatives were administered. The end of the tube was positioned roughly in the lower fundus. The collected juice was immediately placed in an ice bath. Studies were restricted to patients who tolerated intubation well. Basal morning fasting secretions were obtained on at least two occasions before ACTH was administered in order to establish a baseline control. The studies were repeated at 3 to 7 day intervals during the administration of ACTH, and were again carried out several weeks after ACTH had been discontinued in order to establish a level of secretion during the recovery period.

The adrenal response to stimulation was confirmed by eosinophile counts and 17-ketosteroid excretion studies. The volume, consistency, blood, and bile content of each specimen were recorded. The pH was determined

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TABLE I. Effect of ACTH Upon Gastric Acidity. Continuous 15 min serial aspirations for one hr (basal secretion).

Patient	Avg values	Control period		ACTH, days administered			Recovery period		% increase
		1	2	7	14	21	1	2	
A.	15 min vol (cc)	17		20	18				
E.		22	14	27	18	18			
D.		20	22	21	30	31	32	32	
I.		21		20					
N.		21	27		25	27	17		
U.		17	20	32	33	35	30	27	
F.		10	15		24		27		
A.	Free HCl	18		55	30				206
E.	(clinical units)	20	32	60	78	70			144
D.		20	15	28	18	73	15	15	265
I.		28		80					186
N.		20	32		59	86	21		169
U.		30	47	48	58	60	45	17	27
F.		0	7		70		0		
A.	Free HCl se-	44		162	79				268
E.	creted/hr (mg)	65	65	236	204	183			263
D.		59	48	85	79	330	70	48	460
I.		35		234					175
N.		61	126		220	332	51		164
U.		74	136	221	280	300	197	64	121
F.		0	15		242		0		

with a glass electrode and the free hydrochloric acid and total acidity were determined by titration with 10th normal sodium hydroxide, using Topfer's reagent and phenolphthalein as indicators. Pepsin was determined by the method of Bucher, Grossman, and Ivy(7). The 24-hour excretion of uropepsin was determined coincidentally with the basal gastric secretion at frequent intervals during the period of ACTH administration and for approximately one week prior to and following ACTH administration. Uropepsin excretion was determined by a modification of the method described by Bucher, Mirsky, and Anson(8).

Results. The continuous administration of 100-160 mg of ACTH daily for periods of 7-21 days resulted in a significant increase in the basal gastric secretion of hydrochloric acid (Table I), demonstrated by an increase in the average free acidity in clinical units and an increase in the secretion of free hydrochloric acid in mg per hour, accompanied by a decrease in the pH of the gastric juice.

A mean increase of 166% in the clinical units of free acid was observed within 7-21 days of ACTH administration in the basal fasting gastric secretion. The total hourly secretion of free hydrochloric acid (expressed as mg per hour) increased an average of 241% during the administration of the hormone (Table III). In some instances the acidity rose within the first week of ACTH administration but in others the gastric acidity was not affected until 14-21 days of ACTH administration. Upon discontinuation of ACTH the gastric acidity returned to the control level usually within a period of 7 days.

A similarly marked increase in the concentration of gastric juice pepsin was observed in the serial 15-minute basal aspirations during 7-21 days of continuous ACTH administration (Table II). The mean pepsin concentration rose 182% in 5 of the 7 patients studied and the pepsin output per hour increased 169%. After the discontinuation of ACTH the pepsin concentration and output per hour returned to the pre-ACTH control levels. The increase in uropepsin excretion paralleled the

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TABLE II. Effect of ACTH Upon Gastric Pepsin and Urinary Uropepsin.

Patient	Avg values	Control period 1	Control period 2	ACTH, No. days administered 7	14	21	Recovery period	% increase
A.	Gastric pepsin,	272		472	779			187
E.	units/cc	512		581	482	471		
I.		572	639	1500			813	135
D.		150	177	847	577	458	170	390
N.		466	274		997	716	444	114
F.		0	232		431		0	86
U.		341	319	339	264	235	267	
A.	Gastric pepsin,	18500		37760	56000			202
E.	units/hr	36800		63000	34800	39400		71
I.		48000	53500	120000			65040	124
D.		12000	15600	71000	69300	57000	21800	354
N.		39200	29600		99700	77500	30000	154
F.		0	13900		41500		0	200
U.		23100	25520	43100	35000	33000	28760	77
A.	Urinary uropep-	2507		4416	11234		2100	348
E.	sin, units/24 hr	2713		5234	9936	9860	2400	266
I.		4889	4920	10270			4795	109
D.		3900	4450	7400	7300	14000	4500	236
N.		2406	2632		4816	5798	2200	130
F.		3186	3104		5486		2737	74.5

TABLE III. Average Increase in Acid, Pepsin and Uropepsin During ACTH Administration.

Gastric pepsin (units/cc)	182%
(units/hr)	169
Urinary uropepsin (units/24 hr)	194
Free HCl (clinical units)	166
(mg/hr)	241

rise in gastric juice pepsin (Table II). The mean uropepsin increase was 194% compared to an average rise of 182% in pepsin concentration. In general the increase in uropepsin excretion may be demonstrated within 48 to 72 hours of ACTH administration, and precedes the increase in gastric juice pepsin, which usually requires 7-21 days of continuous ACTH administration.

The oral or parenteral administration of 200-250 mg of cortisone daily resulted within 24 to 72 hours in an increase in uropepsin excretion similar to that observed with ACTH. The average increase was 88%.

Discussion. These studies indicate that the stomach is capable of responding to hormonal stimulation by the adrenal cortical steroids, as evidenced by a significant increase in the hydrochloric acid and pepsin content of the gastric juice and a rise in the uropepsin excretion in the urine, following prolonged ACTH administration. The site of action of these hormones upon the gastric glands has not as yet been elucidated. Whether they act upon the vagal nerve endings or whether there is a direct cellular action upon the gland itself or an interrelationship with other hormones such as gastrin remains to be determined. The fact that atropine does not inhibit the effect of ACTH upon uropepsin excretion and that 14-21 days of ACTH administration are necessary to increase the gastric secretion of acid and pepsin suggest a direct hormonal effect rather than vagal mediation. Moreover, the appearance of focal hemorrhages in the stomach following hypothalamic and brain stem lesions in vagotomized animals could result from a hormonal effect through the hypothalamic-pituitary-adrenal-gastric pathway. This mechanism could also explain, in part, the gastroduodenal ulcerations characteristic of the adaptation syndrome.

The effect of ACTH upon the stomach is mediated through the secondary outpouring of adrenal cortical steroids rather than to the direct pharmacological action of ACTH upon the stomach. No gastric response to ACTH can be elicited in patients with adrenal insufficiency but a definite effect can be demonstrated, however, by the administration of cortisone. Both cortisone and ACTH elicit a gastric response in patients with normal ad-

renal function although the effect of ACTH is more pronounced than that of cortisone.

The uropepsin excretion in the urine reflects the peptic activity of the stomach. It is derived from the secretion of pepsinogen directly into the blood stream by the peptic cells of the stomach. Pepsinogen is then transported to the kidneys and is excreted in the urine as uropepsin(8). That uropepsin has its origin in the stomach is evidenced by the disappearance of the enzyme following total gastrectomy and by its absence in the urine of patients with pernicious anemia(9).

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Summary. ACTH administered intramuscularly to normal subjects in doses of 100-160 mg daily for periods of 3-4 weeks produced a marked increase in the basal gastric secretion of hydrochloric acid and pepsin associated with an equally significant rise in the urinary uropepsin excretion. In every instance these values were increased to the levels usually observed in patients with active peptic ulcer. These studies indicate that an endocrine relationship exists between the stomach and the adrenal gland and that a hormonal phase of gastric secretion may be mediated by the adrenal corticoids. The pathway by which chronic emotional and physical stress may affect the stomach by a hypothalamus-pituitary-adrenal-gastric pathway is discussed.

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Pathogenic Properties, and "Vertical"* Transmission of the Mouse Leukemia Agent.† (19068)

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It has been recently observed in this laboratory that "spontaneous" leukemia could be prompted to develop in middle aged mice of a foster nursed C3H subline, designated by the symbol C3H(f), and known to be essentially free from this disease, by inoculating such animals within the first 12 hours after birth with centrifugated extracts prepared from leukemic mice of the Ak line, or with normal Ak embryo cell suspensions. Generalized leukemia developed in some of the inoculated animals after they had reached 8 to 11 months of age(2).

This report deals with the inoculations of the centrifugated leukemic extracts into infant mice 12 hours to 6 days old, with the results of preliminary experiments on the filtration of the leukemic agent, and with the transmission of the leukemic agent from parents to their offspring.

Materials and methods. Centrifugated leukemic extracts. Mice of the Ak line that developed leukemia either spontaneously, or as a result of inoculation with a transplanted strain of Ak leukemia(3), were used as donors

* Vertical transmission designates the passage of a parasitic agent from one generation to another(1), such as rickettsia through eggs in ticks, mosaic virus through seeds in plants, or mammary carcinoma virus through milk in mice. In contrast, horizontal transmission occurs from one individual to another within the same generation, as in smallpox, typhoid fever, or malaria, through contact, carriers, food, or insects, respectively.

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