present in the dog liver are important in producing the fatal toxemia of liver autolysis(6).

If it is assumed that the bacteria normally present in the dog pancreas arise from the intestine, reduction of the intestinal bacterial count following oral streptomycin or sulfasuxidine should in time reduce the number of pancreatic bacteria. Effective pancreatic sterilization should then reduce the toxicity of experimental pancreatitis. The failure of these methods to reduce the mortality may be due to an inadequate pancreatic sterilization, for the two animals in the group in which pancreatic cultures were taken before pancreatitis was produced both had gram positive bacteria in the pancreas.

We have no evidence that antibiotics are effective in treating acute hemorrhagic pancreatitis in humans.

Conclusions. 1. Treatment with penicillin G in oil and wax has been effective in lowering the fatality rate of experimental hemorrhagic pancreatitis in dogs. 2. Total pancreatectomy as a treatment or preoperative oral streptomycin or sulfasuxidine as prophylaxis have been ineffective.

5. Lewis, F. J., and Wangensteen, O. H., PROC. SOC. EXP. BIOL. AND MED., 1950, v73, 533.

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Pituitary Basophile Hyperplasia and Crooke's Hyaline Changes in Man After ACTH Therapy. (17938)

ABNER GOLDEN, PHILIP K. BONDY AND WALTER H. SHELDON
(Introduced by P. B. Beeson)

From the Departments of Pathology and Medicine, Emory University School of Medicine, Emory University Hospital and Grady Memorial Hospital, Atlanta, Ga.

A significant increase in the basophilic cells associated with Crooke's hyaline cytoplasmic changes was found in the anterior pituitary of two patients following adrenocorticotropic hormone therapy. To our knowledge these findings have not previously been reported in man.

Material. The first patient was a 43-year-old white man with chronic glomerulonephritis who was given a course of ACTH therapy. He died in uremia on the fifth day of treatment having received a total dose of 400 mg intramuscularly. Autopsy confirmed the diagnosis of chronic glomerulonephritis. The combined weight of the adrenal glands was 18.5 g. Histologic examination of the pituitary suggested a distinct increase in basophilic cells, which displayed striking hyaline cytoplasmic changes as described by Crooke in Cushing's syndrome(1). Many of the chromophobe cells showed definite basophilic stippling, suggesting a transition between these and the basophilic cells. Both chromophobes and basophiles were most prominent in the anterior portion of the lobe. No increase in basophiles was noted in the pars intermedia and there was no basophilic infiltration of the posterior lobe.

The second patient was a 19-year-old white nullipara with chronic glomerulonephritis who received 490 mg of ACTH intramuscularly over a period of 8 days, terminating 7 days prior to death in uremia. Autopsy showed chronic glomerulonephritis. The combined weight of the adrenal glands was 18.5 g. Gross examination of the pituitary gland revealed a speckled yellowish gray appearance of the anterior lobe.

Histologic examination suggested a diffuse increase in basophilic cells with a concentration in the anterior and central portions. A minimal basophile infiltration of the posterior lobe was noted. Hyaline cytoplasmic changes of the basophiles were present in only a few scattered cells. Many chromophobes in both

1. Crooke, A. C., *J. Path. and Bact.*, 1935, v41, 339.

TABLE I.
Differential Counts of Pituitaries from 2 Patients Receiving ACTH and from 2 Control Patients.

Patient	Age	Sex	Disease	Total No. cells counted	Acidophile, %	Basophile, %	Chromophobe, %
1 ACTH, 400 mg	43	M	Chron. glom. nephr.	24229	37.9	23.9	38.2
			χ^2		2.75	3582	1484
			p*		>.10	<.01	<.01
Control	46	M	Chron. glom. nephr.	21672	37.8	11.6	50.5
2 ACTH, 490 mg	19	F	Chron. glom. nephr.	21088	44.5	24.5	31.0
			χ^2		.19	9586	2560
			p*		>.50	<.01	<.01
Control	21	F	Acoustic neuroma	21272	44.4	7.2	48.4
Comparison of counts with mean percentages obtained by Rasmussen(2).							
Mean for adult males					37.0	11.0	52.0
Compared with Patient 1				χ^2	61.6	4095	1838
				p*	<.01	<.01	<.01
Mean for nulliparous females					43.0	7.0	50.0
Compared with Patient 2				χ^2	19.6	9895	3042
				p*	<.01	<.01	<.01

* p from the tables of Snedecor, G. S., Statistical Methods, The Iowa State College Press, 1946.

the anterior and intermediate portions revealed basophilic stippling.

Method. Differential counts of the three cell types of the anterior pituitary were performed following the method of Rasmussen (2). The glands were fixed in 10% solution of USP formaldehyde and divided into three blocks by horizontal cuts. In addition to the routine hematoxylin and eosin stain, sections from each block were stained for differential counting by Mallory's 1% acid fuscin, orange G, aniline blue stain(3). A minimum number of 20,000 cells was counted from each gland. Pituitaries from two patients of the same sex, parity and approximate age who had not received ACTH were processed in the same manner and employed as controls. Further details of these cases and the results are shown in Table I.

Results. The basophilic cells in the patients treated with ACTH were increased to 23.9% and 24.5%. This change is statistically significant not only in relation to our controls but also when applied to the large series reported by Rasmussen(2). The increase is associated with a corresponding decrease in the number of chromophobes. These figures, moreover, do not adequately reflect the magnitude of the basophilic change since the many chromophobes with basophilic stippling were not counted as basophiles.

Discussion. These findings cannot be satisfactorily explained at present but a tentative interpretation of their meaning seems warranted. Experimental observations have shown that the administration of exogenous

2. Rasmussen, A. T., *Am. J. Path.*, 1929, v5, 263; *ibid.*, 1933, v9, 459.

3. Mallory, F. B., Pathological Technique, W. B. Saunders Co., Philadelphia, 1938, p. 153.

TABLE II.
Differential Counts of 5 Pituitaries from Hypertensive Patients With or Without Uremia.

Age	Sex	Disease	Total No. cells counted	Acidophile, %	Basophile, %	Chromophobe, %
46	M	Uremia, chronic glomerular nephritis; hypertension	21672	37.8	11.6	50.5
48	F	Essential hypertension, cerebral hemorrhage (nullipara)	23996	45.8	13.5	40.8
84	M	Essential hypertension, nephrosclerosis, bacteremia	20492	46.5	13.0	40.5
58	M	Chronic pyelonephritis, uremia, hypertension	26741	36.4	10.7	53.0
72	M	Essential hypertension, tubular nephritis, uremia	9170	37.6	9.1	53.3
Mean				40.8	11.6	47.6
Stand. dev.				4.9	1.8	6.5

adrenal steroids suppresses the release of ACTH from the pituitary(4). In a patient with unilateral functional carcinoma of the adrenal cortex, atrophy of the other adrenal indicated a similar effect(5). Crooke's changes, which are a constant finding in Cushing's disease, were also present in the pituitary of this patient. The administration of ACTH to our patients may have produced the same effect by increasing the concentration of endogenous adrenocortical hormones. This suggests that basophilism and Crooke's change in our cases may reflect an inhibition of the normal release of ACTH from the pituitary.

It must be considered that the changes which we have described could be related to chronic glomerulonephritis and uremia rather than to the administration of ACTH. Berblinger(6) reports an increase in the basophiles of the anterior pituitary in cases of hypertension, either essential or associated with chronic progressive nephritis and uremia. For this reason we performed differential counts on the pituitaries of five patients who had either longstanding hypertension or chronic progressive nephritis with uremia (Table II). This control series revealed a maximum basophile percentage of 13.5% and a mean of 11.6% which is not significantly different from Rasmussen's mean value of 11%. Rasmussen investigated the pituitaries of 90 patients with hypertension and found no correlation between arterial pressure and the number of pituitary basophiles(7). We wish to reemphasize the need for differential counts in estimating the distribution of cell types in the pituitary since preliminary histologic examination of two cases suggested a definite increase in basophiles which was not confirmed on actual count.

The absence of marked Crooke's changes in the second patient who had not received ACTH during the last 7 days of life, suggests that this change may be readily reversible. In this connection another patient whom we have studied may be of interest. This was

4. Cheng, C.-P., Sayers, M. A., and Sayers, G., *Fed. Proc.*, 1949, v8, 24.

5. Kepler, E. J., Sprague, R. G., Clagett, O. T., Power, M. H., Mason, H. L., and Rogers, H. M., *J. Clin. Endocrinol.*, 1948, v8, 499.

6. Berblinger, W., *Endokr.*, 1935, v16, 19.

7. Rasmussen, A. T., *Endocrinol.*, 1936, v20, 673.

a 19-year-old white nullipara who died of myasthenia gravis. She had received 975 mg and 500 mg of ACTH 9 and 6 months respectively before death. The pituitary showed a focal increase of basophiles, resembling an adenoma. Differential counts done in a similar manner as described revealed 13.9% of basophiles, a few of which showed Crooke's changes. This focal adenomatoid accumulation of basophiles might represent a residual effect of ACTH therapy.

The therapeutic administration of ACTH may stimulate the adrenal cortex which then produces storage of endogenous ACTH in the anterior pituitary. The morphologic expression of this storage appears to be pituitary basophilism and Crooke's changes. Conversely a decrease in basophiles might be expected when the circulating adrenal cortical hormones are reduced and when the pituitary is released from their inhibiting effect. This occurs in Addison's disease where a decrease in the basophiles of the pituitary has been reported(8).

Our findings seem to indicate that morphologic changes are associated with alterations of the functional balance between the anterior pituitary and the adrenal cortex. Such morphologic changes might be useful in the experimental investigation of the relationship between these glands. The advent of ACTH and cortisone makes such an experiment quite feasible.

Summary. The administration of ACTH appears to have produced morphologic changes in the anterior pituitary of two patients. These changes consisted of an increase in the total number of basophiles, Crooke's hyaline cytoplasmic changes in these cells and basophilic stippling of many of the chromophobes. It is possible that these changes reflect the storage of endogenous ACTH following stimulation of the adrenal cortex by the therapeutic administration of this hormone.

8. Crooke, A. C., and Russell, D. S., *J. Path. and Bact.*, 1935, v40, 255.

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Experimental Nephrotoxic Nephritis in the Rat Treated with ACTH or Cortisone. (17939)

DONALD B. HACKEL, ALMERINDO G. PORTFOLIO AND THOMAS D. KINNEY

From the Department of Pathology, Cleveland City Hospital, and Western Reserve University School of Medicine.

Recent studies have demonstrated the marked effects of ACTH and cortisone on diseases involving hypersensitivity(1,2). The present work was carried out to determine whether experimental nephrotoxic nephritis, which is thought to involve a hypersensitivity reaction, could be prevented by the administration of these two agents.

Methods. Nephrotoxic serum was prepared according to the method used by Smadel (3). Nineteen black and white hooded rats of a specially inbred strain and averaging 250 g in weight, were studied. Weights, eosinophile counts, and white blood cell counts were determined. The urinary sediment was examined and the urinary albumin content was estimated, using both the heat and acetic acid and sulfosalicylic acid methods. Fourteen of these 19 rats received 1 cc of nephrotoxic serum per 100 g of body weight divided into 2 doses intravenously administered on successive days. Six rats

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2. Berthrong, M., Rich, A. R., and Griffith, P. C., *Bull. Johns Hopkins Hosp.*, 1950, v86, 131.

3. Smadel, J. E., *J. Exp. Med.*, 1936, v64, 921.