

High titers of pituitary ACTH having been found in coexistence with a large-scale depletion of the acidophilic, the beta(1), and, as the results of this paper show, the delta granulation, none of the 3 types of secretory granules in the hypophysis of the rat can be regarded as the morphological equivalent or even the site of ACTH storage. Since, on the other hand, the secretory granulation is the only reliable distinguishing mark between pituitary cell types, it is hard to conceive how the exclusive role of any given class of cells in the production and storage of ACTH could be convincingly established with our present histophysiological technics. Theoretically, two possibilities exist: (a) ACTH is produced by only one type of cell, or (b) it is elaborated by several or all classes of adenohypophysial cells, possibly including the chromophobes. In either case its storage does not appear to take place in the form of microscopic particles. The connection between ACTH and the uniform microsomes observed by Fernández-Morán and Luft(6) in basophil, acidophil and chromophobe cells of the rat pituitary remains to be explored.

The reduction in the amount of pituitary ACTH in both the castrates and the estrogen-treated rats of this study seems to have been due to an accelerated release rather than a block of formation, since the adrenals were

found to be enlarged in both conditions. The lowered ACTH level in the castrate pituitaries might explain why Szego and White(7) observed a diminished adrenocorticotrophic response to the stress of starvation in castrated rats.

Emery and Winter(8), in contradiction to our observations, found no difference between the adrenal-stimulating potency of the pituitaries of castrated and intact male rats. As these authors did not use hypophysectomized recipients, the reliability of their assay method is open to serious doubt.

Summary. (1) The ACTH content of the pituitaries of estrogen-treated and castrated male rats was assayed against that of controls by the adrenal ascorbic acid-depletion method. (2) The estrogen-hypophyses were found to contain 75% and those of the castrates 63% of the amount of ACTH encountered in the controls. (3) Since no parallelism was observed between the ACTH content and the amount of delta granules present in these pituitaries, it is concluded that adenohypophysial ACTH is not associated with the delta granules. (4) Further histophysiological and physiological implications of these findings are discussed.

7. Szego, C. M., and White, A., *Endocrinology*, 1951, v48, 576.

8. Emery, F. E., and Winter, C. A., *Anat. Rec.*, 1934, v60, 381.

6. Fernández-Morán, H., and Luft, R., *Acta endocrinol.*, 1949, v2, 199.

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Sinusoidal Dilatation in Liver and Adrenal Cortex of Tumor-Bearing Rats.* (18986)

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The weights of the liver, spleen, adrenals and other organs of tumor-bearing rats and mice are reported as significantly increased over that of normals(1,2). In some in-

stances this increase in total weight of the organ is associated with increased water con-

1. Annau, E., Manginelli, A., and Roth, A., *Cancer Res.*, 1951, v11, 304.

2. McEwen, H. D., and Haven, F. L., *Cancer Res.*, 1941, v1, 148.

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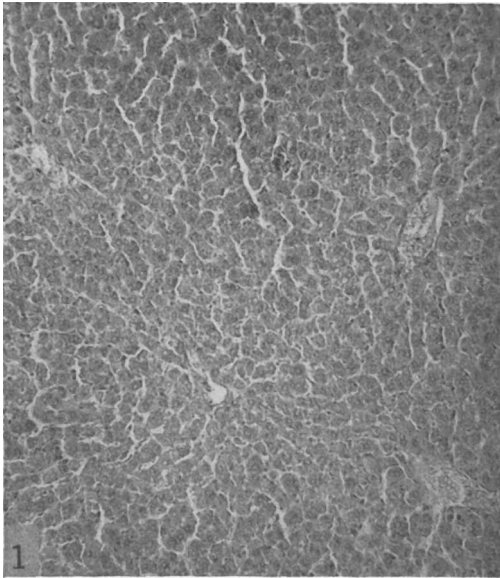


FIG. 1. Liver, tumor-bearing rat No. 247 ROLV, showing small degree of sinusoidal dilatation. Tumor wt 107 g. Haematoxylin and eosin. $\times 165$.

tent, but to what extent the increase in weight can be accounted for by the presence of additional water or of dry residue is not clear in every case. Also the vastly dilated sinusoids of the liver and other organs in the case of tumor-bearing mice(1,3), suggests this as a possible site of the excess water in tumor-bearing rats.

In studies on rats bearing the Walker rat tumor 256, a series of 15 animals bearing tumors ranging in size from 10 g to 121 g was sacrificed by decapitation and the adrenals and liver removed and fixed in Bouin's solution or in 10% formalin. Controls were 5 animals that were uninoculated or in which the inoculum did not take. Paraffin sections of livers and adrenals were stained in hematoxylin and eosin or in iron hematoxylin. While no differences were found with respect to sinusoidal conditions in various regions of the liver, for purposes of comparison we used only sections taken from the anterior edge of the left lobe. Water content of the livers of tumor-bearing and control animals was determined from tissue samples by a method previously described(2), and found to average

73.3% and 69.3%, respectively. The adrenals were sectioned sagittally and sections through the middle of the gland saved for study.

On examining the livers and adrenals of these rats we were not able to find sinusoidal conditions that corresponded to those described for mice. In none of the livers of tumor-bearing rats could we find very marked morphological sinusoidal changes (Fig. 1). Measurements of sinusoidal diameters in 50 random fields of liver sections from an animal with a 121 g tumor gave an average value of 17.6μ , while a similar count of a control gave 17.3μ . With respect to the adrenal cortex, an essentially similar condition was found, except that dilatation of the sinusoids was somewhat more pronounced (Fig. 2). No detectable sinusoidal dilatation was seen in the spleen or kidney.

Although the increased water content of the liver may be determined when the transplanted tumor is as small as 10 g(2), there is no accompanying histological change. The slight sinusoidal changes that are occasionally seen, usually in rats bearing large tumors, are inconstant and of doubtful importance. It seems to us unlikely, on the basis of these

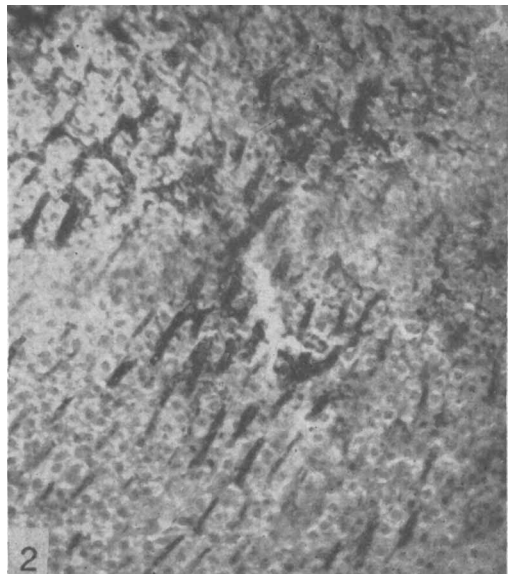


FIG. 2. Adrenal cortex, tumor-bearing rat No. 408 RV. The black areas are mildly dilated sinusoids occluded by erythrocytes. Tumor wt 121 g. Iron haematoxylin. $\times 195$.

observations, that any significant amount of additional free water in the livers of tumor-bearing rats is present in the sinusoids. This must be sought, rather, in the cells, the intercellular spaces, and the blood. In the adrenal cortex, the sinusoidal dilatation is relatively greater than in the liver though hardly

enough to assume this as the only site of a greatly increased water content for this organ.

Summary. The increased water content of the livers and adrenal glands of tumor-bearing rats is not correlated with an increase in caliber of liver or adrenal cortex sinusoids.

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In vitro Antibacterial Activity of Dimethylaminoethyl Substituted Compounds. (18987)

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In the course of systematic investigations* of alkyl-substituted dimethylaminoethyl ethers and dimethylaminoethyl amines we have surveyed their antimicrobial activity *in vitro*. The results of preliminary screening tests are presented below.

Experimental. Tests were performed against *Staph. aureus* 209, *B. mycoides* ATCC 6462, *Klebsiella pneumoniae* Type A ATCC 6450, *E. coli* ATCC R 5190, *Vibrio metchnikovi* and *Sh. sonnei* ATCC grown in Difco nutrient broth, *Diplococcus pneumoniae* A 5 grown in blood broth, *Cl. welchii* ATCC 460 grown in thioglycollate broth, and *Mycobacterium tuberculosis* H 37 RV and B 1, both grown in Dubos' liquid medium. The inoculum of non-acid fast organisms was 0.1 ml of a 1-500 dilution of an 18-hour culture. The inoculum of tubercle bacilli was 0.1 ml of a 14-day culture in Dubos' medium which had been diluted to an optical density of 0.2 as measured in Lumetron colorimeter. Final readings were taken after 3 days incubation with non-acid fast bacteria, and after 2 weeks incubation with tubercle bacilli. In addition, some of the compounds were assayed against *Trichophyton mentogrophytes*† grown in 4% dextrose, 1% peptone broth. The inoculum was 0.1 ml of a suspension, containing 15,000-25,000 spores, prepared from a 10-day culture

on Sabouraud's dextrose agar. Cultures were incubated at room temperature (20-22°C), and final readings were taken after 15 days incubation. The compounds were dissolved in the medium used for each organism at a starting concentration of 64 mg % (w/v). A 2-fold serial dilution method was used throughout. Controls were included in every series and each test was run in duplicate. Some of the more active compounds were tested against a wider spectrum of pathogenic fungi, including *Trichophyton rubrum* ATCC 671, *Sporotrichum schenckii* ATCC 10213, *Sporotrichum floccosum* ATCC 10227, *Microsporum canis* ATCC 10214, *Microsporum audouinii*, and *Candida albicans* ATCC 2091, using the method outlined above.

Results. Using the compound R-O-CH₂-CH₂-N (CH₃)₂, and replacing R in the aliphatic series, no activity was found against any organism until R = heptyl (8 mg% against *M. tuberculosis* B 1). When R = octyl slight activity appeared (64 mg %) which gradually increased as R increased to dodecyl (0.5-4 mg %). In general *V. metchnikovi* was slightly more sensitive to these compounds than were the other organisms tested. Of the cyclic ethers tested, B-pyridyl, phenyl, cyclohexyl, and benzyl were inactive, thymyl and methyl were weakly active (64 mg %), while tetrahydro furfural was moderately active (4-8 mg %).

Using the compound R₁ R₂ N-CH₂-CH₂-N (CH₃)₂, and replacing R₁ and R₂ by ali-

* To be published from these laboratories.

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