than those used in the present experiments and were probably inadequate for the production of sustained eosinopenia(4).

The failure of ACTH to reduce the acute toxic effect of influenza virus and of rickettsiae as well as the failure of the hormone to increase the survival rate of mice with pneumococcal and influenza viral infections(11,17,18) leaves unexplained the mechanism by which the dramatic changes in the clinical course of pneumococcal and viral pneumonias have been produced. It is possible that such changes represent relatively secondary phenomena reflecting such effects of ACTH as its antipyretic action(19). It appears unlikely that the clinical improvement which follows the administration of ACTH to patients with infectious diseases is due to stimulation of the capacity of the host to resist the acute toxic action of the infectious agent.

Adrenal cortical hormones are not essential to the metabolism of cells and it is conceivable, therefore, that the toxic agents tested in these experiments interfere with cellular metabolism at levels of enzymic activity which are not directly under regulation by adrenal cortical hormones.

Summary. ACTH did not reduce the acute toxic effect of influenza virus in mice or rats nor the similar action of the rickettsiae of murine and epidemic typhus in mice.

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Development of Thyroid Neoplasms in the Rat Following a Single Injection of Radioactive Iodine.* (18558)

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In recent reports(1,2) we called attention to the presence of atypical epithelial cells in the thyroid glands of rats 8 months after they had been injected with single large doses of I^{131}. These cells resembled the so-called Hürthle cells found in both neoplastic and non-neoplastic thyroid glands of man. These cytological changes led us to extend our studies to later intervals.

The present report deals with 10 rats that were sacrificed 18 months after I^{131} treatment. Neoplastic changes were observed in the thyroids of two animals. In addition, Hürthle-like elements were prominent in all thyroid glands.

Experimental. Ten male rats of the Long-Evans strain, which had received a single intraperitoneal injection of 400 μc of I^{131} 18 months earlier, were anesthetized with ether and exsanguinated. The tracheas with attached thyroid glands were removed and fixed in 10% neutral formalin, embedded in paraffin, and sectioned serially at 10 μ. Representative sections of liver and kidney were sectioned at 6 μ. All tissues were stained with hematoxylin and eosin. Wilder's stain was employed for the demonstration of reticulum.

Thyroids of rats 1-8. Microscopic examination of the thyroid glands of 8 of the rats revealed the typical post-radiation picture of fibrosis, fibrosed and hyalinized vascular channels, and glandular atrophy. These changes were similar to those described in our earlier

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communication(1). Large areas containing follicles filled with pale colloid were found in all thyroid glands. The lining cells of the follicles were, for the most part, squamous or low cuboidal, and their nuclei showed no abnormalities. The cytoplasm of some of the epithelial cells contained a yellow granular material, identification of which was not attempted. Abundant fibrous tissue pervaded the glands, effecting wide follicular separation and appearing to compress the glandular and vascular elements. Many scattered, single epithelial cells were observed in this intracinar fibrous tissue. These cells contained a pale cytoplasm, and were quite irregular in shape. Many of their nuclei were extremely large and exhibited marked pleimorphism. The chromatin content of the nuclei was meager. In some areas a slight, chronic inflammatory condition persisted. This consisted of large and small lymphocytes, macrophages, plasma cells, and many tissue eosinophils. A constant feature in the parenchyma of all glands was the widespread occurrence of large, irregular epithelial cells (Hürthle-like) containing intensely eosinophilic, granular cytoplasm, and large, pleiomorphic nuclei which varied greatly in chromatin content and intensity of staining. These cells were scattered throughout the gland either singly or in groups; occasionally they formed small follicles with deep eosinophilic colloid. Collections of these cells, arranged in clusters or cords, were found principally at the poles of the glands.

Thyroids of rats 9 and 10. The thyroid glands of these 2 rats were composed of altered parenchyma, nodular areas, and, in addition, normal appearing tissue. The parenchymatous changes described for rats 1-8 were also observed in rats 9 and 10. In the former three neoplastic thyroid foci were noted; in rat 10, four foci were found in one lobe and 3 in the other lobe. Surprisingly enough, all tumors present in a single lobe were not of the same type. Multiple adenomata, consisting of large and small follicles lined by epithelium, ranging from cuboidal to high columnar, and containing a thin, pale, granular eosinophilic colloid, were found in both animals (Fig. 1, 2). The nuclei were quite regular and hyperchromatic. Cystic and hemorrhagic changes had occurred. A

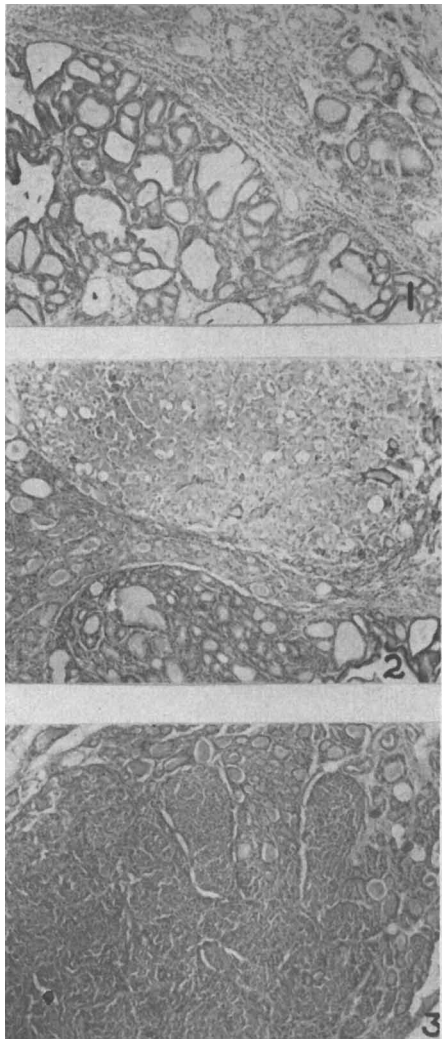

FIG. 1. Benign adenoma found in thyroid of rat No. 10. Note slight encapsulation and lack of colloid in follicles of adenoma. Normal thyroid tissue is seen in lower left corner. Hematoxylin and eosin ×34.

FIG. 2. Two tumors found in lobe of thyroid of rat No. 9. Normal tissue is present between the tumors. The tumor at upper right is that designated type A in the text. Note the poor encapsulation of this tumor and only occasional acini are seen in an almost solid sheet of cells. The tumor at lower center is a benign adenoma. Hematoxylin and eosin ×34.

FIG. 3. Portion of another tumor (type B) found in the thyroid of rat No. 10. Hematoxylin and eosin ×34.

thin, fibrous capsule separated these tumors from the surrounding tissue, although in some areas the encapsulation was not complete. These adenomata, which exerted marked compression on the adjacent normal tissue, did not appear malignant as judged by morphologic criteria. Two distinct types of thyroid tumors (A and B) that bore no resemblance to the adenomata described above were also observed in these rats.

Type A. This tumor which is shown in Fig. 2, was found in both rats. It was composed of sheets of large, irregular polyhedral cells that stained weakly eosinophilic and that contained a granular cytoplasm. Only occasionally were these cells arranged in acini. The nuclei were chromatin-poor and stained quite weakly. Mitotic figures were noted. This tumor was only partly encapsulated by a few strands of fibrous tissue.

Type B. This type of tumor, which is shown in Fig. 3, was found only in rat 10. It was composed of small, tightly packed cells containing pleiomorphic and hyperchromatic nuclei. *This neoplasm was invading adjacent tissue and showed no evidence of encapsulation.* Mitotic figures were frequent. A reticular stain revealed sparse argyrophilic fibers. The amount and distribution of reticulum left no doubt that this lesion was not of a sarcomatous nature.

Examination of the livers and kidneys revealed no evidence of metastases. No pathologic alterations were observed in the livers of any of the animals. The kidneys in 2 of the animals revealed some glomerulosclerosis, interstitial scarring, and chronic interstitial nephritis.

Discussion. It is necessary to call attention to the 2 types of tumors designated here A and B. Although we recognize that a diagnosis of malignancy is difficult to make—particularly in the case of the thyroid—without evidence of metastatic invasion, the possibility that these tumors may be malignant should be tentatively entertained for the following reasons: (1) their morphological resemblance to malignant thyroid lesions (type A to adenocarcinoma and B to small cell carcinoma) seen in man; (2) their lack of encapsulation; and (3) their invasion of neighboring thyroid tissue (Fig. 3). Further studies directed, in particular, to the question of their malignancy are in progress in this laboratory.

A review of the literature shows that spontaneous thyroid carcinomata rarely occur in the rat. Bullock and Curtis(3) state "of the many thousands of rats which have been examined post mortem only two developed thyroid tumors." One was a benign adenoma; the other, a malignant growth, was found in a rat 948 days old. Van Dyke(4) found benign thyroid adenomata only in a group of very old rats (801-906 days old). In this laboratory, examination of well over 1,000 rats of various ages up to 2.5 years failed to reveal thyroid malignancy(5). Moreover, in rats that were fed a diet containing 0.2% propylthiouracil for various periods up to 28 months, we found only occasional adenomata. Moon examined serial sections of thyroids of 14 rats, 615 to 723 days old, of the same strain as that used in the present study(6). He found no evidence of malignancy but he did observe 6 small adenomata. Thus, there can be little doubt that the 2 malignant-like thyroid neoplasms found among the first 10 rats we sacrificed 18 months after I^{131} treatment were not of spontaneous origin but were related to the administration of radioactive iodine.

The mechanism underlying the production of the tumors described here is, as yet, not clear. Two possibilities will be considered. Overstimulation of the thyroid epithelium by excess thyrotrophic hormone is believed to be a factor in the genesis of thyroid tumors. For example, malignant thyroid disease in man, according to Joll(7), is common in endemic goiter areas. Experimental work on the rat also indicates that the major etiological factor in the genesis of thyroid tumors is chronic overstimulation of the gland by thyrotrophic hormone(8,9). The Hürthle-like cells found

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throughout the thyroid parenchyma of all rats may also be indicative of exhaustion from excessive thyrotrophic stimulation.

The possibility that the trapped I^{131} might initiate neoplastic changes in the thyroid gland has been recognized by many clinical investigators(10-13) who have expressed the need for caution in the use of radioiodine for diagnosis and treatment of Grave's disease. The discovery of 2 highly suspicious tumors among the 10 rats that were treated with radioactive iodine further emphasizes the need for caution.

Summary. Examination of 10 rats sacrificed 18 months after a single injection of 400 μc of radioactive iodine revealed the following changes in the thyroid gland: 1. Hürthle-like elements (previously reported by us in thyroids of rats sacrificed 8 months after a single I^{131} injection) were evident in the parenchyma of all glands. 2. Multiple adenomata, apparently benign in nature, were found in the thyroids of 2 rats. 3. Two types of anaplastic, nonencapsulated neoplasms, one of which was invading adjacent thyroid tissue, were also found in the thyroids of these 2 rats.

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Japanese B Encephalitis in the Rat. (18559)

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It has been reported that the rat can be infected with the virus of Japanese B encephalitis if the virus is injected intratesticularly (1). However, this finding has not been confirmed and it is generally believed that the rat is resistant to infection with Japanese B encephalitis virus(2). The observation that 7- and 8-day-old albino rats are uniformly susceptible to St. Louis encephalitis virus whereas 21-day-old rats fail to develop a clinically apparent infection even though the virus is injected directly into the brain(3,4) suggested that experiments be conducted to determine whether rats of different ages behave toward the related Japanese B encephalitis virus in a similar manner.

The purpose of the present report is to record the data obtained from a study designed to determine the behavior of rats of different ages following injection of Japanese B encephalitis virus.

Materials and methods. Virus and animals. The Nakayama strain of Japanese B encephalitis virus which had been maintained by mouse-brain passage was used.† Mouse brains infected with the virus were ground in a mortar with sand and sufficient of a mixture composed of equal parts of rabbit serum and

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