

Experimental Production of Struma Lymphomatosa.* (20509)

H. J. CLAUSEN.

From the Department of Anatomy, University of South Dakota School of Medicine, Vermillion,

In a series of experimental investigations dealing with the effects of the prolonged administration of thiouracil to rats(1), it was noted that some of the animals developed a thyroid condition similar to that which has often been reported under the general heading of chronic thyroiditis in man(2-5).

As far as the author has been able to determine, only one report(6) of the experimental production of chronic degenerative thyroiditis, namely struma lymphomatosa (Hashimoto), has been reported to date. In view of this, it was thought of sufficient importance to report the following findings.

Material and methods. A series of 21-day-old Sprague-Dawley rats were given a .1% thiouracil† solution as a substitute for their drinking water. The food consisted of Purina laboratory chow. Littermate control animals were carried along with the above experimental rats on a similar diet without the thiouracil in their drinking water. All animals in both groups were sacrificed 600 days following the initiation of the experiment. Various tissues, including the thyroid glands, were removed at this time. Tissues were fixed in formalin, Bouin's or Zenker's fixative. The thyroid glands were stained with hematoxylin and eosin for the most part. Some sections were stained with Mallory's connective tissue stains.

Results. Adenomatous formations of various types were found in the thyroid glands of the majority of the experimental animals. Various changes in the parathyroid glands were also noted. The above findings are being further investigated and will be reported at a later date.

In 6 of the animals within the experimental series (25%), the thyroid glands were found to exhibit a characteristic chronic thyroiditis of the Hashimoto type. Upon removal of each

of the thyroid glands, prior to their fixation, it was noted that the gland was very much increased in size. The tissue was white and very firm and little or no lobulation was in evidence. No cysts were recognized grossly.

Microscopically, it was apparent that the capsule was increased in thickness. When compared to the controls, it could be noted that there was a diffuse and uniform degeneration of the acini with a general flattening of the epithelium and an absence of colloid in the treated glands (Fig. 1, 2). The epithelial elements were reduced in size and many eccentrically placed nuclei were present. Extensive interlobular and intralobular lymphocytic infiltration was an outstanding characteristic in most of the cases. A consistent increase in fibrous tissue (Fig. 3) surrounding the lobules of degenerating acini was generally noted. The small arteries and the precapillary arterioles uniformly showed a definite thickening of the intima and the media. In many of the lobules the epithelium appeared to be replaced by a rather dense fibrous tissue. Mitotic figures or other indications of hyperactive epithelial proliferation was not observed.

In each of the rats in which the above thyroid findings could be demonstrated, the testes were also found to be undergoing abnormal or pathological changes, (Fig. 4). The testes were all normal in size as compared to the normal littermate controls. The tunica was increased in thickness with a very dense fibrous tissue. It was noted that most of the tubules were filled with immature and degenerating germ cells. No evidence of normal mature sperm was found. In some areas some inter and intratubular lymphocytic infiltration could be seen. The interstitial cells appeared to be normal in most areas of the testis.

The adrenal glands were smaller in size than those of the normal controls but all of the cellular elements appeared to be normal in structure and relative proportions. The pituitary glands of all of the rats in the series are now being studied and will be reported.

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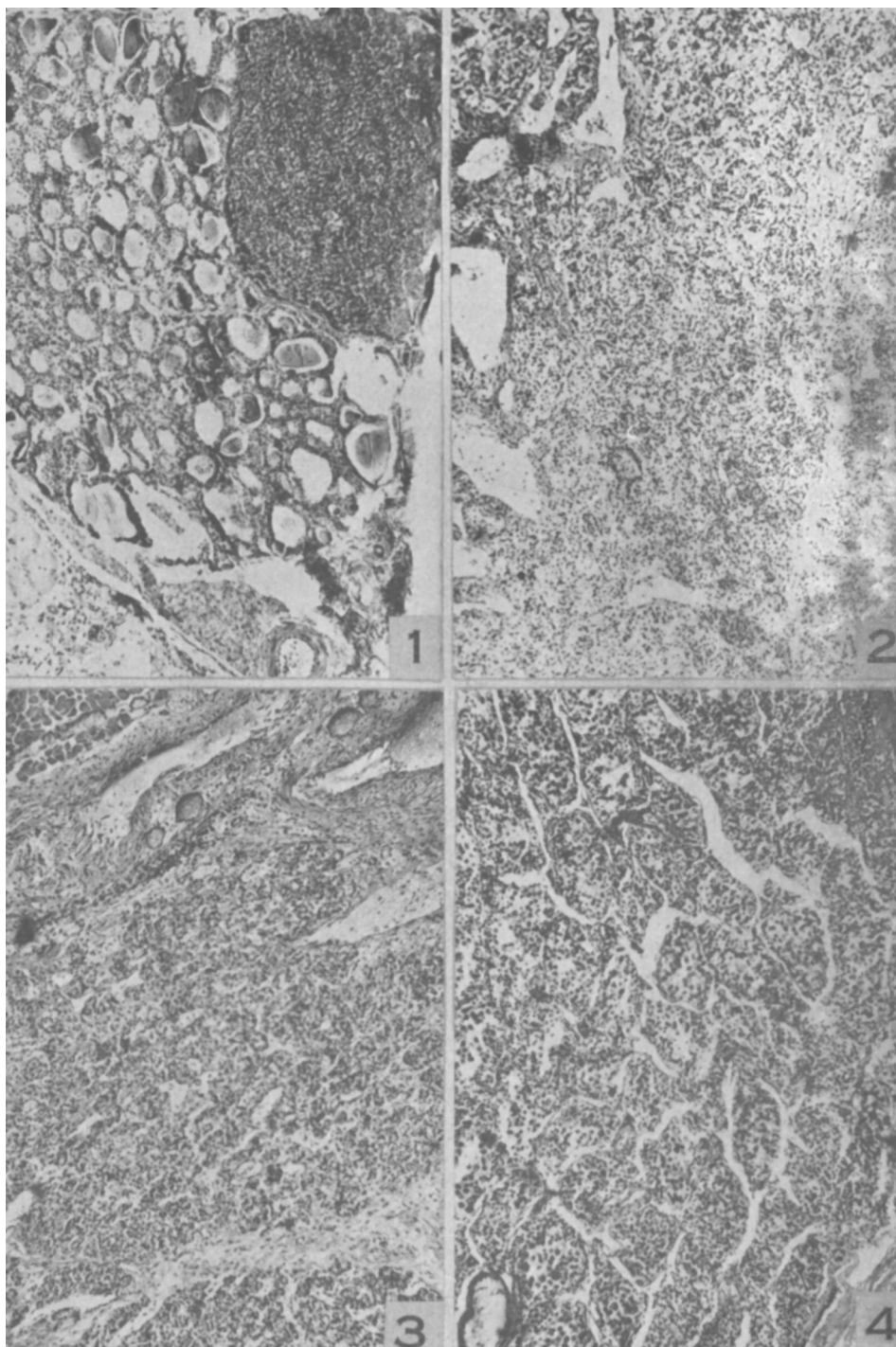


FIG. 1. Normal thyroid and parathyroid glands of a rat. A littermate control. (H & E) $\times 100$.

FIG. 2. Thyroid gland after thiouracil administration. Fibrolymphoid hyperplasia with lymphocytic infiltration involving the intervesicular connective tissue. A portion of the parathyroid is shown in the upper left corner. (H & E) $\times 100$.

FIG. 3. Thyroid of another experimental rat (K3). More advanced stage of fibrolymphoid hyperplasia. The widespread connective tissue deposition and almost complete absence of any follicular structures may be noted. (H & E) $\times 100$.

FIG. 4. Testis of experimental rat (K3). Lymphocytic infiltration may be noted in some of the intertubular areas. Tubules appear to be filled with immature and degenerating germ cells. (H & E) $\times 100$.

Discussion. Inflammation in which the thyroid tissue was to a large extent replaced by lymphoid tissue was described by Hashimoto (7). Microscopically, the lymphoid tissue in the 4 human cases he reported was so abundant that he chose the name "struma lymphomatosa" for the lesion.

The etiology of struma lymphomatosa is unknown. Infections of various types have been thought at times to be the causative factors. Cultures of glands, whenever carried out, have been sterile and no cases could be produced when bacteria were injected directly into the thyroid arteries of dogs and rabbits(5). Furthermore, if infection were the causative factor it is unlikely that our littermate control rats would have entirely escaped the infection. It is entirely possible that infection might have played an indirect role. The administration of thiouracil for such a prolonged period might have lowered the metabolic activity and thus decreased the resistance of the animals involved.

That iodine ingestion is a possible factor in the production of this characteristic thyroid picture has been suggested(8). However, in many of the human cases reported no history of iodine ingestion was present. The frequency of iodine administration to patients having thyroid disease of any sort and the relative rarity of struma lymphomatosa should tend to eliminate iodine as the etiological agent concerned.

Certain dietary deficiencies have been considered and McCarrison(6) has produced lesions in rats which showed a definite microscopic resemblance to struma lymphomatosa. He obtained this thyroid condition in the same percentage of cases in the series as the author is reporting. The above investigator has suggested that a vitamin-deficient diet was the possible etiological factor. It is possible that some goitrogenic substance may have been present in the diet that the above investigator used. No dietary insufficiency appeared to be in evidence in either our control or experimental rats. Furthermore, in many human

cases of this disease no history of any dietary inadequacies has been reported.

Testicular changes similar to those obtained in our experimental rats have not been reported in any of the human cases of Hashimoto's disease so far as the author was able to determine. However, since this disease occurs chiefly in females and also in the older age groups of either sex it is possible that these changes may not have been severe enough to have been reported for the human. While numerous reports on the thyroid-sex gland relationships are somewhat contradictory(9), our results would tend to suggest that the hypothyroid condition which must exist in these cases had no influence on the interstitial cells of the testis. The results obtained in relation to the germ cells might have been caused by the direct irritation of the chemical used or it might be mediated through thyroid-pituitary secretions. Further studies in this regard are now being made.

Summary. 1. The effects of prolonged administration of thiouracil to male rats was studied. Following the drug administration for a 600-day period, 25% of the rats showed thyroid glands which exhibited histological characteristics similar to that found in struma lymphomatosa. 2. The testes of these animals also showed a failure of germ cell development and maturation as well as some lymphoid infiltration.

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