have the human karyotype. Most cells contain 41-44 chromosomes, but some have 49-50 chromosomes. There are also cells with a 1.5-fold and double set of chromosomes. On transplantation of the cells from culture into nude mice, the animals developed tumors corresponding to an undifferentiated carcinoma, i.e., the transplanted strain of carcinoma of the body of the uterus from which this cell line was obtained. The cell line of Wilms' tumor has gone through more than 40 passages in tissue culture. The monolayer culture is polymorphic and consists mainly of epitheloid and single fibroblast-like cells. The nuclei are mainly round and oval and the cytoplasm of the cells is relatively wide and vacuolated. The culture has a tendency to grow in islets. The cells have the human karyotype. Most cells contain 39-42 chromosomes but some cells have 55-60 chromosomes. About 30% of the cells have a hypodiploid set of chromosomes, although polyploids also are found (Fig. 2a, b). During transplantation of the cells from culture into nude mice the animals developed tumors with a morphological picture identical to the strain of Wilms' tumor from which this cell line was obtained. The tumors consist of two tissue components: eipthelioid, consisting of polygonal cells, forming tubular-trabecular structures, and mesenchymal cells, which are elongated cells forming interweaving bands.

The cell lines thus obtained and also the strains from which they arise make it possible for experiments to be conducted with cells of the same human tumor under different conditions: both in tissue culture and in animals.

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POSSIBLE NEOPLASTIC TRANSFORMATION OF THYROID CELLS DURING THE GRAFT VERSUS HOST REACTION

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In the graft versus host reaction (GVHR) proliferation of lymphoid tissue is observed, and under certain conditions the tissue may undergo malignant transformation [6]. The possibility cannot be ruled out that in other organs, under GVHR conditions, when their function is disturbed and when immunologic reactivity is altered in the host, tumors may develop. It was shown previously that during GVHR there is marked inhibition of thyroid function [2].

This paper gives data on morphological changes in the thyroid tissue during GVHR (acute and chronic forms).

EXPERIMENTAL METHODS

Experiments were carried out on 60 F_1 hybrid rats. A systemic acute GVHR was induced by intravenous injection of $60 \cdot 10^6$ spleen cells (SC) from the C57Bl/6 parent into (CBA × C57Bl/6)F_1 hybrids. The thyroid gland was investigated at successive stages of development of GVHR on the 3rd, 10th, and 24th days after injection of the donor's cells. The chronic GVHR was studied on the traditional model. (C57Bl/6 × DBA/2)F_1 hybrids were given an injection of $50 \cdot 10^6$ SC of the DBA/2 parent [7]. The thyroid gland was investigated 6 months after induction of the donor's cells. The chronic GVHR was tested, allowing not only for the dura-

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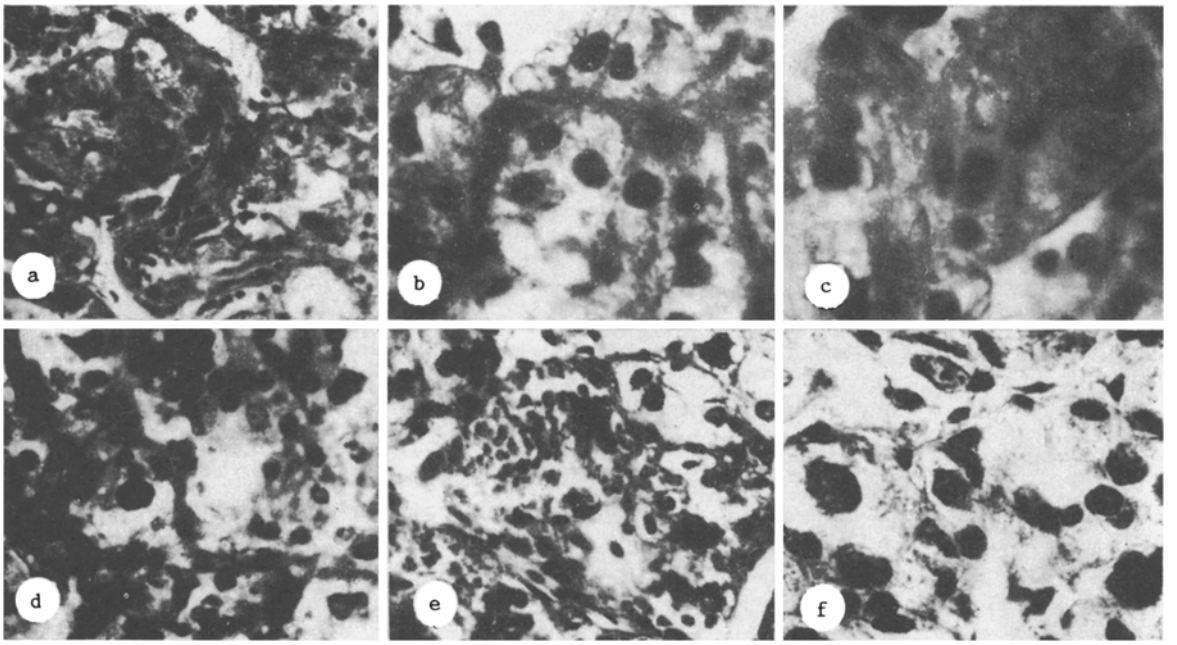

Fig. 1. Morphological changes in thyroid gland during GVHR. a) Changes in thyroid gland resembling follicular adenoma composed of B cells with some degree of atypia. 280×; b) Proliferating B-cell adenoma of the thyroid gland. 280×; c) Adenoma composed of B cells with marked atypia. 630×; d) Adenoma consisting of B cells with atypia and with many effector lymphocytes. 280×; e) Atypical B-cell adenoma, with wide blood vessels of sinusoid type in its stroma. 280×; f) atypical B-cell adenoma, similar to follicular carcinoma. 630×. Hematoxylin and eosin.

tion of the process, but also the morphological changes in the central (thymus) and peripheral organs of immunogenesis. The thyroid glands were fixed in toto in 12% neutral formalin solution and embedded in paraffin wax. Sections 7 μ thick were stained with hematoxylin and eosin and by Van Gieson's method. To differentiate the cell composition, succinate dehydrogenase activity was determined by Nachlas' method [4].

EXPERIMENTAL RESULTS

In the acute systemic GVHR the morphological structure of the thyroid gland was indistinguishable from that of the control until the 10th day. The follicles were lined with simple and two-layered epithelium, among which were A and B cells [1, 3]. The B cells contained many formazan granules. The relative numbers of A and B cells differed. In some cases A cells predominated, in others – B cells. Colloid was present in all the follicles, and it stained quite intensively with eosin.

On the 10th day of development of GVHR the structure of the thyroid gland was characterized by definite changes: a decrease in the number of follicular A cells, and in some cases B cells were seen with marked atypical features, namely hyperchromatosis and deformity of the nuclei. Cell complexes resembling a follicular adenoma composed of B cells, with some atypia, were found. The colloid was most frequently liquid and it stained unevenly with eosin (Fig. 1a). After 24 days the GVHR corresponded histologically to the picture of follicular B-cell adenoma, with signs of marked atypia. Microscopically the adenoma consisted mainly of follicles of different sizes, among which groups of proliferating cells with nuclei of different sizes and with signs of hyperchromatosis could be distinguished (Fig. 1b, c). A sharp decrease was observed in the number of A cells.

The investigations showed that in the chronic form of GVHR borderline states regularly arise in the thyroid gland between atypical follicular adenomas and proliferating atypical B-cell adenomas, or again, atypical B-cell adenomas with multi- and unicentric growth, going on in some cases to form structures similar to follicular carcinoma. The borderline state between typical follicular adenoma and adenoma composed of atypical B cells was characterized by the presence of thyroid gland follicles with and without colloid, and by proliferation of the epithelium. Some B cells contained atypical nuclei with round and angular shape,

with features of hyperchromatosis. Close to or actually in structures resembling proliferating B-cell adenomas, effector lymphocytes with proteolytic properties, and noneffector (Fig. 1d) lymphocytes, in contact with B cells, were regularly found. There were few A cells, and they were flattened or compressed by B cells. In addition, blood vessels of sinusoid type, containing erythrocytes, were found in these same zones, evidence of switching of the circulation from diffusion to perfusion. This was associated with secretion by the atypical cells of an angiogenesis factor, inducing growth of the endothelium [8]. In some cases proliferating adenomas with multicentric growth were seen. Histologically they were characterized by the presence of multiple foci consisting of epithelial B cells, less frequently mixed with C cells. B cells with signs of atypia, differing in size and marked by deformity of their nuclei, showed particularly marked hyperchromatosis. In addition, effector and noneffector lymphocytes (Fig. 1d) and blood vessels of sinusoid type were regularly seen. The vessels of sinusoid type in these cases were much larger than in the boundary states (Fig. 1e). In the B cells there were far more formazan granules, confirming the B-cell nature of the adenomas. The number of A cells was reduced, for hardly any were visible. During unicentric growth diffuse multiplication of B cells with marked atypia was observed. In addition, many wide vessels of sinusoid type and also effector and noneffector lymphocytes, with lytic properties, were discovered. The discovery of many effector lymphocytes with lytic properties in the thyroid gland tissue is evidence of disturbance of the tissue–blood barrier for immunocompetent cells. Hardly any A cells were found and the impression was created that hardly any were present, or that they were strongly compressed by the multiplying B cells. The histological picture described above is very similar to that of follicular carcinoma (Fig. 1f). Staining for succinate dehydrogenase revealed preservation of the formazan granules in the cells, despite malignant change, confirming the B-cell origin of the tumor.

The results are thus evidence, first, that the disturbances in the concentrations of thyroid hormones in the blood observed previously are combined with a full range of morphological changes in the gland. The number of A cells, producers of thyroid hormones, was sharply reduced. In some morphological preparations hardly any A cells were found. Meanwhile the development of the GVHR was combined with well-marked proliferation of B cells. Many preparations had evidence that a B-cell follicular adenoma with marked atypia develops in the thyroid gland under GVHR conditions, and that in the chronic form of GVHR, the histological structure is similar to that of follicular carcinoma. The A and B cells of the thyroid gland develop from a single precursor [5], and subsequently differentiate. It can be tentatively suggested that during the development of the GVHR transformation of precursor cells into A cells is inhibited, but conversely, their conversion into B cells is strongly intensified. Under these circumstances atypical forms of B cells characterized by unequal size, distorted shape of the nuclei, and hyperchromatosis, are formed. All these changes are evidence of changes in the genetic apparatus of the cells. The discovery of a large number of effector lymphocytes in the thyroid gland tissue is evidence, first, of disturbance of the tissue–blood barrier for immunocompetent cells and, second, of a direct connection between the function of these cells and structural changes in the thyroid gland tissue during GVHR.

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