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Autoimmune Granulomatous Thyroiditis in Inbred Mice: Resemblance to Subacute (de Quervain's) Thyroiditis in Man (41664)

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Abstract. Mice in various inbred strains were immunized with mouse thyroglobulin emulsified in Freund's complete adjuvant. Granulomatous thyroid lesions were observed only in RF and SJL mice. These lesions were studied ultrastructurally and showed similarities with subacute (de Quervain's) thyroiditis in man. Thyroid function tests, e.g., the concentration of serum thyroxine and thyroid radioiodine uptake showed similarities between these two diseases. Such findings have not been previously described in experimental thyroiditis.

Since the work of Roitt *et al.* (1) and Witebsky *et al.*, (2) it has been generally agreed that lymphocytic thyroiditis (Hashimoto's thyroiditis) in man resembles autoimmune thyroiditis in animals immunized with thyroglobulin and adjuvants. In animals and in man circulating thyroglobulin antibodies can be demonstrated and the thyroid is infiltrated with mononuclear cells. Subacute (de Quervain's) thyroiditis in man differs from lymphocytic thyroiditis in clinical, laboratory, and histopathological findings (3). Although thyroid histopathology of subacute thyroiditis can vary in some details, characteristic lesions in the glands comprise marked disruption of follicles and the presence of numerous histiocytes (macrophages), including multinucleated giant cells (3–6). The role of an immune process in the pathogenesis of subacute thyroiditis was discarded since thyroglobulin antibodies were found infrequently in this disease (7). We have observed distinct granulomatous thyroid lesions in experimental autoimmune thyroiditis induced in RF and SJL mice by immunization with mouse thyroglobulin emulsified in Freund's complete adjuvant. The thyroid lesions appeared initially as mononuclear/lymphoid cells infiltrations and the mice developed high titers of thyroglobulin antibodies. Changes in the serum thyroxine concentration and in the thyroid radioiodine uptake in these animals resembled those described for the severe form of subacute thyroiditis in man. Such findings have not been reported in experimental autoimmune thyroiditis (8–11).

Materials and Methods. Female mice, 7–9 weeks old, of strains RF, SJL, AKR, B10.BR, B10.D2, and 129 were obtained from The Jackson Laboratory, Bar Harbor, Maine. Mice were bled from the retroorbital sinus before the experiments, for determining the background level of thyroxine and for ascertaining the absence of detectable thyroglobulin antibodies. They were injected twice, subcutaneously, at 7-day intervals, with mouse thyroglobulin (prepared from thyroids of CF-1 mice) emulsified in Freund's complete adjuvant (12). The Freund's adjuvant contained four parts of *n*-hexadecane, one part of glycerol monooleate, and 6 mg/ml (wet weight) of *Mycobacterium tuberculosis* strain $H_{37}Ra$ (12). Thyroglobulin was prepared by salt fractionation and gel filtration, as previously described (12). Each animal received 100 μg thyroglobulin and 190 μg mycobacteria per injection.

Groups of six mice were killed at 1 to 7-day intervals during a period of 11 weeks, starting 1 week after the first antigenic challenge. The blood was collected and the serum was separated for measurement of thyroxine concentration and for determination of thyroglobulin antibodies titer. The concentration of serum thyroxine was measured with an automated radioimmunoassay (RIA) system (Concept IV, Micromedic System, Horsham, Pa.). Thyroglobulin antibodies did not interfere with the measurement of thyroxine in this RIA. The titer of thyroglobulin antibodies was measured by passive agglutination of chromium chloride-treated human red cells, group O, coated with mouse thyroglobulin (from strain CF-1).

For the light microscopy, thyroid glands were fixed in 10% buffered formaldehyde (pH

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7.4) and were embedded in paraffin. Serial transverse sections of each gland were stained with hematoxylin and eosin, periodic acid–Schiff (PAS), and methyl green pyronine. For the electron microscopy, representative sections of the glands were fixed in 2.5% glutaraldehyde (pH 7.4), postfixed in 2% osmic acid (pH 7.4), and embedded in epoxy. These specimens were cut and then treated with uranyl acetate and lead citrate before the examination (13). In another experiment, groups of 6 to 10 mice, similarly immunized, were injected intraperitoneally with 20 μCi of ^{131}I (Amersham, Chicago, Ill.), 2, 4, or 8 weeks after the first antigenic challenge. Twenty-four hours later, the thyroid uptake of radioiodine was measured with a scintillation spectrometer (model 1197, Searle, Skokie, Ill.). As controls, we used mice immunized with bovine serum albumin (BSA) emulsified in Freund's complete adjuvant, and normal (nonimmunized) mice.

In additional experiments, groups of 10 mice of high-responder strains DBA/1 and C3H as well as of low-responder strains BALB/c, C57BL/6, and DBA/2 (The Jackson Laboratories) were immunized as just described and were sacrificed 4 weeks after the first antigenic challenge, when the titer of thyroglobulin antibodies was at the peak and the thyroid lesions had the highest magnitude. Thyroids were processed as mentioned for light microscopy and transverse sections were stained with hematoxylin and eosin and examined histopathologically.

The Wilcoxon rank sum test for nonparametric statistics was used to analyze the results (14).

Results. The following morphological findings were seen in RF mice. The thyroid glands of mice immunized with thyroglobulin were slightly enlarged. Mild adhesions to the underlying soft tissue were seen about 4 weeks after the initial antigenic challenge. At first, the histopathology of the glands appeared to be different from one animal to another even within the same group of mice. However, it became apparent that the differences were due to various stages of the disease, which followed a rather uniform, progressive pattern. Two weeks after the immunization, the thyroid with typical lesions showed focal mononuclear/lymphoid cell infiltrations associated with mild depletion of the colloid. Polymorphonuclear leukocytes were present mainly in the interfollicular connective tissue as well as in the follicular lumen. The lesions were at times unilateral, involving one lobe of the gland. By the 16th day, polymorphonuclear leukocytes were increasing in number and there was further depletion of the colloid. In most thyroids, a mixed infiltrate of polymorphonuclear leukocytes and lymphoid cells was seen in the perithyroidal connective tissue (perithyroiditis). There were a few follicles filled solely with polymorphonuclear leukocytes (microabscesses and/or pseudotubercles). By the 18th day, while the colloid was further depleted, early granulomatous lesions emerged in some glands and by the 23rd day, granulomata became recognizable in the thyroids of all immunized mice (Fig. 1). At about the time of the appearance of these lesions, polymorphonuclear leukocytes began to decrease in number and were progressively replaced by macrophages, lymphoid cells, and plasma cells. By the 4th to 5th week, the granulomata became most extensive and often involved the entire gland symmetrically. A total loss of colloid was common in most of the thyroids. While earlier granulomata were composed largely of epithelioid cells, those in the later stages varied in appearance and included multinucleated giant cells of various types (Figs. 2A, B) which appeared to contain colloid-like material in cytoplasm, as demonstrated by the PAS stain. During the 6th through the 10th week, follicles with colloid began to reappear and progressively replaced the granulomatous areas. At the 11th week, recovered as well as newly formed follicles predominated in most of the glands, although focal lymphoid and plasma cell infiltration remained in the glands and granulomatous areas were still discernible. In the recovered glands and perithyroidal regions fibrosis was minimal.

Ultrastructurally, the granulomatous lesions had various patterns. Early granulomata consisted largely of proliferating follicular epithelial cells mixed with polymorphonuclear leukocytes and lymphoid cells. There were limiting basement membranes. Some of the granulomata were packed with disorderly arranged follicular epithelial cells in such a manner that they appeared as giant cells at

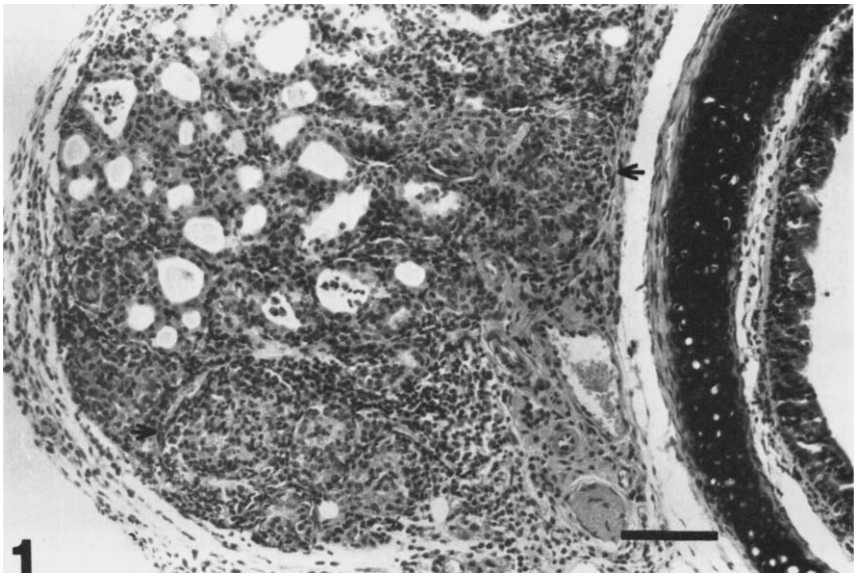

FIG. 1. Paraffin section of thyroid gland of RF mouse 23 days after immunization with thyroglobulin. Granulomata in early stage (arrows) as well as mononuclear/lymphoid cell infiltration. Scale bar, 100 μm.

lower magnification. In the later stages, granulomata consisted of numerous infiltrating, mature macrophages accompanied by authentic syncytial giant cells of the macrophage type (Figs. 3A, B). Follicular epithelial cells showed abundant, often dilated rough endoplasmic reticulum, junctional complexes and desmosomes, prominent Golgi apparatus, and apical cytoplasmic protrusions. Mitochondria were not abundant. The follicular basement membrane showed gaps through which invading lymphocytes, plasma cells, and macrophages could be seen (Fig. 3A). Foreign body particles or electron-dense deposits resembling immune complexes were not seen in the granulomata. Viral inclusions were not found in the follicular epithelial nuclei or cytoplasms. The thyroids of control animals were normal.

In all immunized SJL mice thyroid granulomata, similar to those in RF mice, were observed (Figs. 2C, D). The evolution of the thyroid pathology followed a similar sequence as observed in RF mice, although cellular infiltrates in SJL mice appeared more intense in the glands and perithyroidal regions and granulomata in SJL mice tended to develop earlier and persist longer than those in RF mice. Granulomatous lesions were found occasionally in AKR mice. However, these lesions differed from those of RF and SJL mice with respect to their magnitude and their frequency. Thyroids of B10.BR, B10.D2, and 129 mice examined at various times (from 1 to 11 weeks) as well as thyroids of C3H, DBA/1, BALB/c, C57BL/6, and DBA/2 mice, examined at 4 weeks after immunization, showed various magnitudes of lymphoid infiltration but granulomatous infiltration was not observed in any of the strains of mice just mentioned.

The thyroid radioiodine uptake 2 weeks after the immunization was low in RF mice immunized with thyroglobulin, in comparison with that of mice injected with BSA ($P < 0.01$). Although the uptake gradually recovered, it did not attain, at the 8th week, the level found in mice injected with BSA (Table I).

Thyroglobulin antibodies were detectable in serum 2 weeks after the immunization and their titers gradually rose. They reached a peak at the 8th week and remained high at the 10th week (Table II). The concentration of serum thyroxine was elevated at the 7th day ($P < 0.02$), decreased and reached the lowest level at the 14th day, and then gradually rose to the preimmunization level by the 10th week.

Similar findings with respect to thyroid ra-

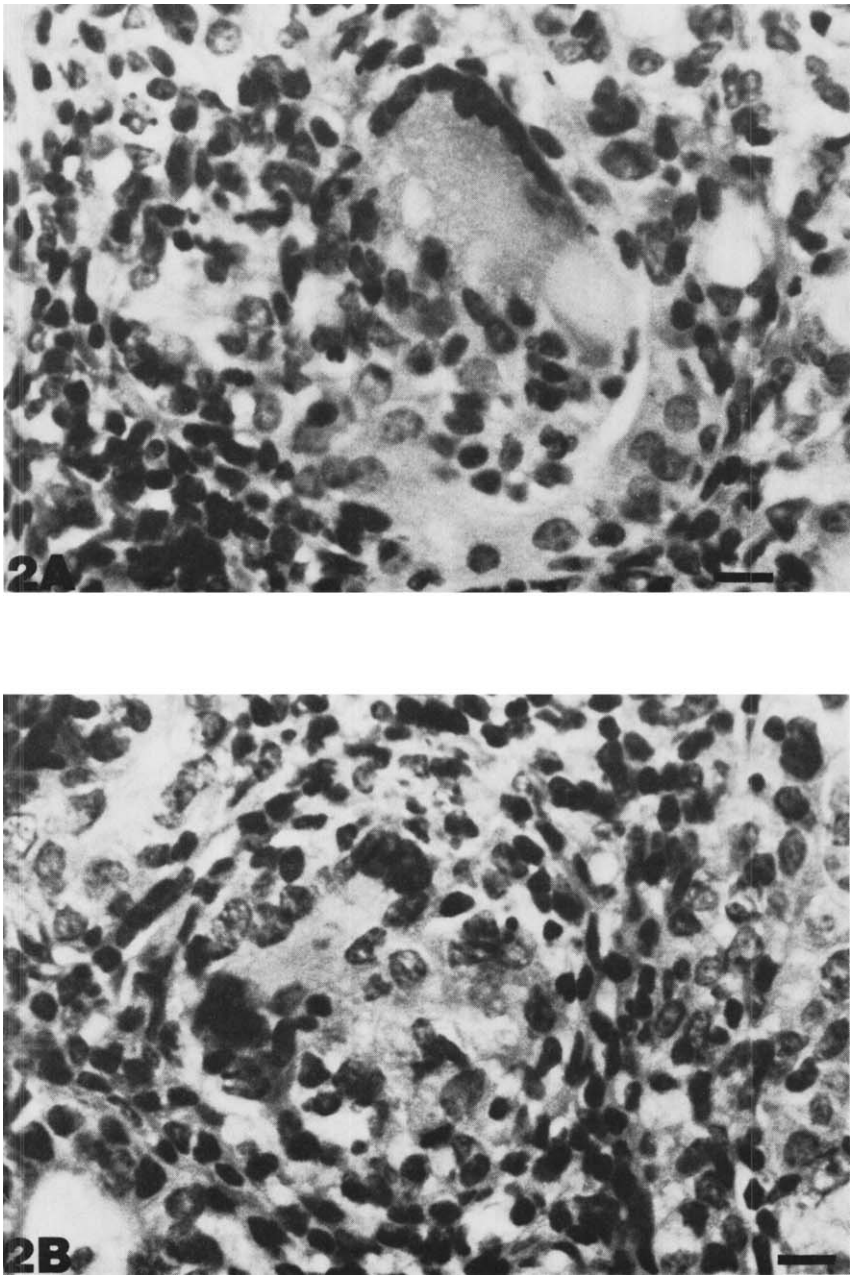

FIG. 2. Paraffin sections of thyroid glands showing granulomata with multinucleated giant cells of various pattern. (A and B) RF mice 6 weeks postimmunization. (C and D) SJL mice 23 days and 8 weeks postimmunization, respectively. Scale bar, 10 μm.

dioiodine uptake and thyroxin concentration were observed in SJL mice but not in other strains of mice tested (manuscript in preparation).

Discussion. During the course of autoimmune thyroiditis in RF and SJL mice, we observed a distinct thyroid lesion characterized by multiple foci of compact collection of mac-

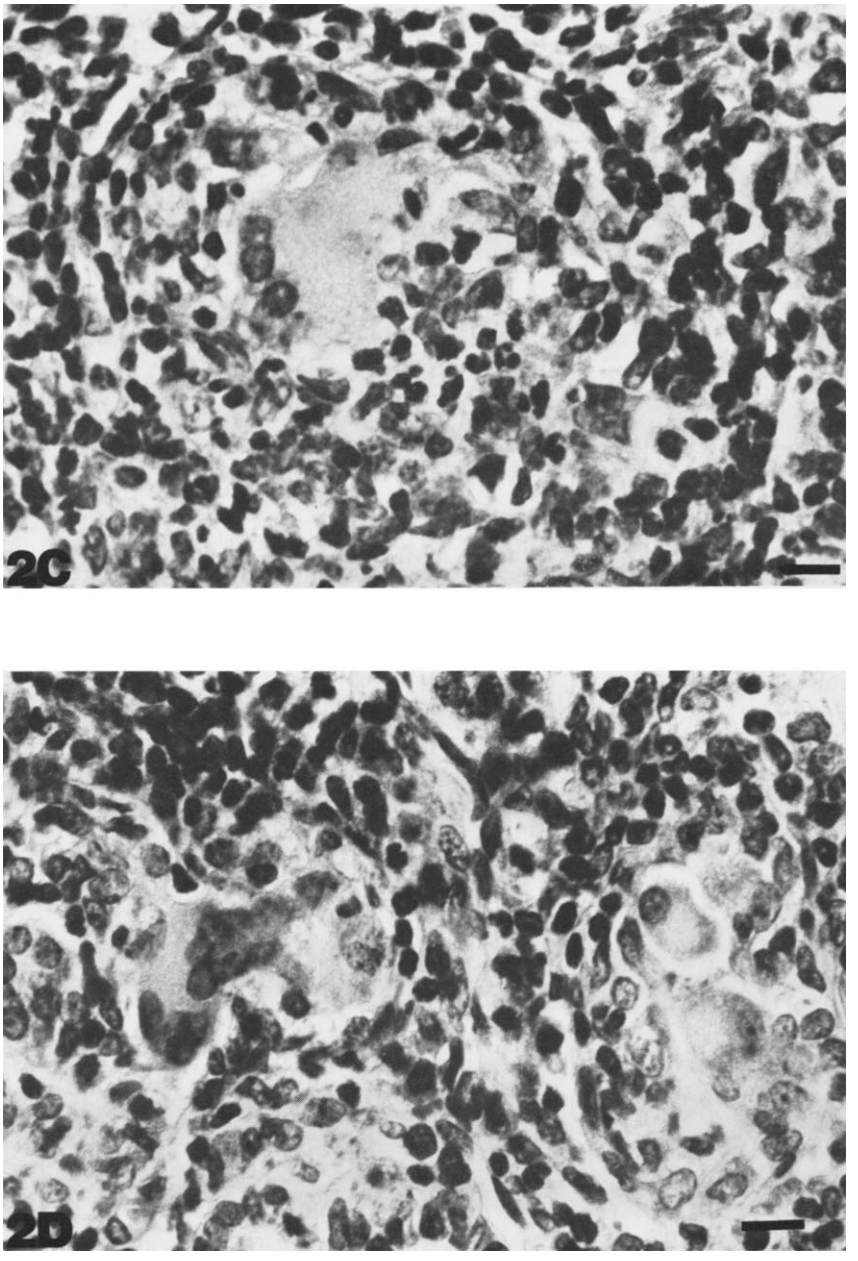

FIG. 2—*Continued.*

rophages with and without multinucleated giant cells. This lesion appears to fulfill the criteria for granuloma set by Adams (15) and has similarities with the lesion of subacute thyroiditis in humans. In both murine autoimmune thyroiditis just described and subacute thyroiditis, the basement membrane limiting a nodule of the "granulomatous" lesion could be seen (Fig. 3A). This is an unusual feature for a granuloma and therefore, the lesions in these two diseases may be called pseudogranulomata (Table III). Other ultrastructural features reported for subacute thyroiditis, e.g., dilated rough endoplasmic reticulum,

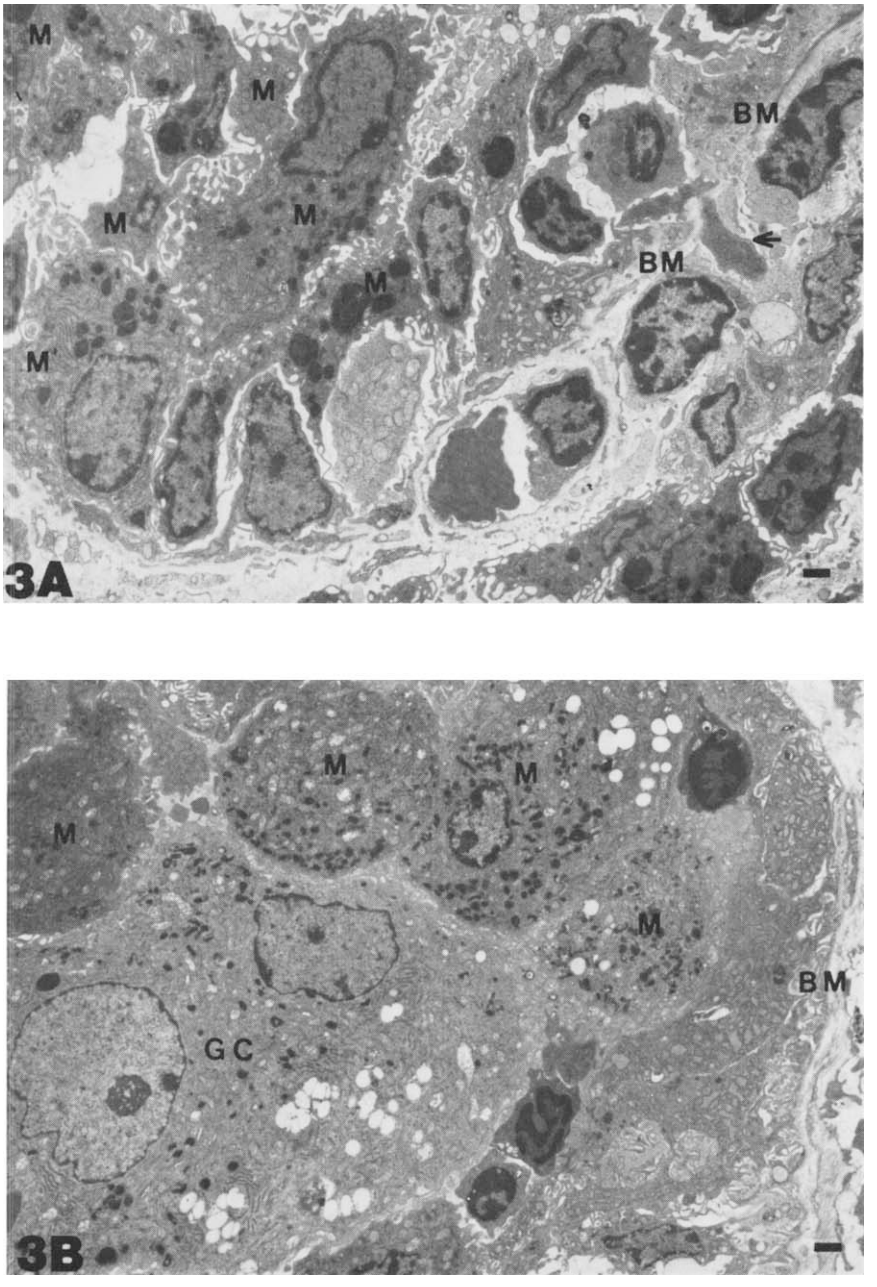

FIG. 3. Transmission electron micrographs. (A) Part of a granulomatous follicle showing numerous macrophages (M) with one mononuclear cell invading the follicle through a gap (arrow) in the basement membrane (BM). (B) A granulomatous follicle packed with macrophages (M). Note one double nucleated giant cell (GC) devoid of separating plasma membranes and with the internal structure similar to those of nearby macrophages. Scale bar, 1 μm.

gaps in the follicular basement membrane (17), as well as light microscopy features, e.g., giant cells with colloid ingestion, pseudogiant cells, microabscesses, and perithyroiditis (18–20) were found in the thyroids of mice. The results of thyroid function tests in subacute

TABLE I. THYROID RADIOIODINE (^{131}I) UPTAKE OF RF MICE IMMUNIZED WITH BOVINE SERUM ALBUMIN OR THYROGLOBULIN[a]

Time after immunization (weeks)	Antigen	
	BSA	Tg
	Radioiodine uptake (cpm × 10^3 ± SEM)	
2	1164 ± 102	227 ± 58
	$P < 0.01$	
4	1003 ± 72	473 ± 48
	$P < 0.01$	
8	873 ± 97	521 ± 108
	$P < 0.05$	

[a] Mice were immunized with bovine serum albumin (BSA) or mouse thyroglobulin (Tg), both emulsified in Freund's complete adjuvant (12). Groups of 10 mice were injected intraperitoneally, at 2, 4, and 8 weeks after the first antigenic challenge, with 20 μCi ^{131}I. Mice were killed 24 hr later and their thyroids were collected. The radioactivity in the thyroid was measured by counting the thyroid attached to the trachea for 1 min in a gamma scintillation spectrometer. Figures represent the average of counts per minute (cpm) × 10^3 ± SEM for each group. *P* values were obtained using the Wilcoxon rank sum test.

thyroiditis vary depending upon the stage of the disease at the time of testing, its severity, and pattern (i.e., classical vs "variant"). Our findings on the thyroid function tests in RF and SJL mice during the disease were also similar to those reported in severe forms of subacute thyroiditis in man (21), i.e., initial hyperthyroidism followed by hypothyroidism and finally recovery to euthyroidism, as well as profound depression of thyroid radioiodine uptake which gradually returns to normal. These findings are not specific for subacute thyroiditis, because hyperthyroidism followed by a period of transient hypothyroidism was described during the postpartum period (22).

Although in subacute thyroiditis antibodies to a colloid antigen were often found (23) and cell-mediated immunity to thyroid antigens was also reported (24, 25), circulating thyroglobulin antibodies were seldom found, their presence was brief and they correlated poorly with the occurrence of the disease (26, 27). However, this does not exclude the participation of an immune response to thyroglobulin in the pathogenesis of subacute thyroiditis. Thus, thyroglobulin antibodies could be fixed in the thyroid or bound to their antigen in circulating or *in situ* immune complexes. In the murine autoimmune thyroiditis described here, thyroglobulin antibodies remained at a high titer during the course of the disease in contrast to subacute thyroiditis. Besides histopathological similarities (Table III), there were some differences between murine granulomatous thyroiditis and subacute thyroiditis. The lesions in the former tended to be synchronous, the colloid was depleted more profoundly, and fibrosis was minimal.

Previous experiments showed that immunization of mice with Freund's complete adjuvant alone did not induce any thyroid lesions. Furthermore, immunization of mice with thyroglobulin in Freund's incomplete adjuvant virtually did not induce autoimmune thyroiditis (12). Yet the granulomatous inflammation developed only in RF and SJL mice after immunization with thyroglobulin. Mice of these strains showed the highest titers of thyroglobulin antibody, among many

TABLE II. CONCENTRATION OF SERUM THYROXINE AND TITER OF THYROGLOBULIN ANTIBODIES IN RF MICE IMMUNIZED WITH THYROGLOBULIN[a]

	Before immunization	Weeks after immunization				
		1	2	4	8	10
Thyroxine (μg ml^{-2})	3.5 ± 0.2	4.5 ± 0.4*	1.7 ± 0.1**	2.3 ± 0.5**	2.1 ± 0.6***	3.0 ± 0.6
Tg antibodies (log_2)	0	0	7.5 ± 0.3	15.5 ± 1.1	17.0 ± 1.9	16.4 ± 1.4

[a] RF mice were immunized with mouse thyroglobulin (Tg) emulsified in Freund's complete adjuvant (12). Groups of six mice were killed at various time intervals, and the thyroxine (μg/100 ml) and titers of Tg antibodies (log_2) were measured in serum. Figures represent mean ± SEM. Statistical analysis, using the Wilcoxon test: *$P < 0.02$, **$P < 0.01$, ***$P < 0.05$ (all values are compared to the preimmunization value).

TABLE III. ULTRASTRUCTURAL SIMILARITIES BETWEEN MURINE GRANULOMATOUS THYROIDITIS (MGT) AND SUBACUTE THYROIDITIS (ST)

Feature	MGT	ST[a]
Giant cells' origin		
Macrophage	+	+[b]
Epithelial (pseudogiant cells)	+	+
Granuloma:		
Limiting basement membrane (pseudogranuloma?)	+	+
Basement membrane gaps	+	+

[a] Data for subacute thyroiditis were taken from Nève (6) and Reidboad and Fisher (17).

[b] Satoh considers that they are epithelial in origin and are "true" giant cells (16).

inbred strains of mice previously tested (11). One mechanism of granuloma formation is delayed-type hypersensitivity reaction elicited by insoluble antigens (28). It is possible that immune complexes of thyroglobulin-antithyroglobulin, in large excess of antibodies, become insoluble. This insoluble thyroglobulin would trigger a granulomatous response in mice that have a cell-mediated immunity to it. Indeed, immune complexes containing thyroglobulin were shown in the thyroids of RF mice immunized with thyroglobulin (29) and delayed-type hypersensitivity to thyroglobulin was also described in murine autoimmune thyroiditis (30).

Among various forms of thyroiditis in man, subacute thyroiditis has been shown to have the strongest association with HLA antigens of the A, B, and C loci (31). The association of Hashimoto's thyroiditis with HLA antigens of these loci is not clearly established (32–35). Furthermore, the association of the goitrous form of Hashimoto's thyroiditis with HLA-DR5 is much weaker (relative risk 3.5) than the association of HLA-B35 with subacute thyroiditis (relative risk 11.5) (36). Interestingly, a strong genetic influence on the development of autoimmune thyroiditis was shown in mice (11). A gene in the *I-A* sublocus of the *H-2* region controls the extent of the thyroid lesions in these animals (37). It is possible that the morphologic expression of autoimmune thyroiditis, not only the susceptibility to this disease, is genetically controlled. As mentioned by Farid, it is possible that a subacute thyroiditis-like inflammatory response represents a stereotype response to a variety of insults (36). The pathogenesis of subacute thyroiditis and that of lymphocytic thyroiditis in man may have common factors, i.e., the participation of an immune response in both diseases, despite the difference in the frequency and titer of circulating thyroglobulin antibodies in these two diseases. As pointed out by Volpé (38), the relationship between subacute thyroiditis and other thyroid diseases remains to be defined clearly.

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