THYROIDITIS IN THE MARMOSET* (CALLITHRIX SPP. AND SAGUINUS SPP.)

By

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INTRODUCTION

Human chronic thyroiditis is characterized histologically by varying degrees of lymphocytic infiltration of the thyroid glands. Thyroiditis also occurs spontaneously in the dog (Schlotthauer, McKenney, and Caylor, 1930; Tucker, 1962; Musser and Graham, 1968) and in the Obese strain of White Leghorn chicken (Witebsky, Kite, Wick and Cole, 1969; Kite, Wick, Twarog and Witebsky, 1969). In 1956 the disease was first induced experimentally in rabbits given injections of autologous or homologous thyroid extract (Witebsky and Rose, 1956; Rose and Witebsky, 1956). Since then, autoimmune chronic thyroiditis has been produced in guinea pigs (Terplan, Witebsky, Rose, Paine and Egan, 1960; Flax, 1963; Lerner, McMaster and Exum, 1964), dogs (Terplan et al., 1960), rats (Jones and Roitt, 1961; Metzgar and Grace, 1961), mice (Metzgar et al., 1961), goats (Rose, Kite, Doebbler and Witebsky, 1964) and rhesus monkeys (Rose, Skelton, Kite and Witebsky 1966). A chronic thyroiditis histologically similar to the naturally occurring and experimental forms has been found in many of the marmosets examined in our laboratory. In these small South American primates the disease appears to be species-related and may be associated with oestrus. The frequency of occurrence and the histopathological changes in the thyroid glands of the afflicted animals are detailed in the present report.

MATERIALS AND METHODS

Complete necropsies were performed on 494 marmosets. The series included 231 Saguinus oedipus (cotton top marmoset), 40 Saguinus fuscicollis (white-lipped tamarin), 14 Saguinus leucopus (white-footed tamarin), 201 Callithrix jacchus (common marmoset, cotton ear marmoset) and 8 Callithrix argentata (silver marmoset). Most have been used as controls for various biomedical studies, and some were breeders. Fifty-five (18 Saguinus oedipus, 3 Saguinus fuscicollis, 32 Callithrix jacchus and 2 Callithrix argentata) were colony-born and ranged in age from one month to six years. The two laboratory-born Callithrix argentata had been killed as part of a study of “spontaneous runt disease” (Fig. 1).

All tissues removed at necropsy were fixed in 10 per cent. neutral formalin, processed in paraffin, and sectioned at 6 microns. The sections were stained with haematoxylin and erythrosin B, PAS and haematoxylin, Weigert’s iron haematoxylin and Masson’s trichrome stain. The degree of thyroiditis demonstrable microscopically was

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arbitrarily rated +, + +, or + + + on the basis of the number of follicles involved. Scores of + for less than 100 affected follicles per midsagittal section, + + for more than 100 affected follicles, and + + + for almost total glandular involvement were assigned.

RESULTS

The thyroid gland in the adult marmoset is located on either side of the trachea. It appears as translucent pale amber or yellowish coloured bodies measuring approximately $3 \times 8 \times 1$ mm. The upper pole of the thyroid is located at the lower border of the larynx (Fig. 2). Only occasionally is a transtracheal isthmus noted. The average weight of the thyroid gland in an adult marmoset is 150 mg.

Histologically the thyroid gland of the normal marmoset is similar to that of man and other mammals. It is composed of colloid-filled follicles surrounded by a delicate fibro-elastic connective tissue capsule. The follicular walls usually consist of a single layer of low cuboidal epithelium (Fig. 3) with only a rare light or C-cell. The histological pattern is most obvious in S. fuscicollis. The follicles are separated by a fine fibrous connective tissue stroma. Mature animals show considerable variation in the size of the follicles. In many, especially in S. oedipus and C. jacchus, the thyroid gland contains large distended follicles with flattened epithelium (Fig. 4). Occasional small foci of parenchymatous hyperplasia may be present. The pattern in these thyroids resembles colloid goiter and/or parenchymatous goiter, but the glands are rarely enlarged and never nodular.

Chronic thyroiditis in marmosets occurs primarily in the genus Callithrix. Approximately 60 per cent. of the colony-born females, 12 per cent. of the wild-caught females, 28 per cent. of the colony-born males and 9 per cent. of the wild-caught males in this genus have evidence of the disease. Both runted male C. argentata had chronic thyroiditis. In contrast, only one female of the 26 colony-born animals and 6 (4 females and 2 males) of the 259 wild-caught marmosets of the genus Saguinus had the microscopic manifestations of chronic thyroiditis. There were no abnormalities in the thyroids of the 40 tamarins (S. fuscicollis) examined (Table 1).

The chronic inflammatory infiltration in the affected thyroid glands ranged from scattered focal collections of round cells to almost total replacement of the follicular architecture by the inflammatory cells. The infiltration consisted of a perivenous accumulation of mononuclear cells populated mainly by large and small lymphocytes and occasional plasma cells. Vascular necrosis, haemorrhage and polymorphonuclear leucocytes were not seen. In some animals large masses of mononuclear cells were found in the interstitial tissue confined to a single area of the gland; in others, there were several well-demarcated large and small focal collections of chronic inflammatory cells. Bands of fibrous connective tissue were frequently infiltrated with mononuclear cells. Disorganization of the adjoining epithelial cells was frequently seen. Acini adjacent to the interstitial lesions were atrophic and lined by large cells with abundant acidophilic cytoplasm. The small follicles contained little or no colloid. Many of the acini in close proximity to the interstitial lesions contained mononuclear cells. The dissociated epithelial cells were frequently displaced from the basement membrane. Examples of chronic inflammatory cell infiltration rated + and + + are shown in Figs. 5 to 8.
TABLE 1

FREQUENCY AND DEGREE OF THYROIDITIS IN GENUS Callithrix

<table>
<thead>
<tr>
<th>Species</th>
<th>Age range (Months)</th>
<th>Number of animals</th>
<th>Number thyroiditis</th>
<th>Percent. thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
<td>M+</td>
</tr>
<tr>
<td>Callithrix jacchus:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colony born</td>
<td>1-6</td>
<td>11</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>6-12</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>12-24</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>&quot;Wild caught&quot;</td>
<td>Adult</td>
<td>90</td>
<td>79</td>
<td>169</td>
</tr>
</tbody>
</table>

| Callithrix argentata: |      |        |       |     |    |      |       |       |      |        |
| Colony born           | 1-6  | 1 (runt) | 1    | 1   | 100|
|                       | 6-12 | 1 (runt) | 1    | 1   | 100|
| "Wild caught"        | Adult| 2      | 4     | 6   |    |      |       |       |      |        |

Total 209

+ = Less than 100 follicles affected per midsagittal section.
++ = More than 100 follicles affected.
+++ = Total glandular involvement.

of the runted marmosets the gland was invaded by lymphocytes to give the appearance typical of Hashimoto's disease in man (Fig. 9). There was a diffuse interacinar infiltration of large and small lymphocytes with the formation of lymphoid follicles containing germinal centres. Scattered plasma cells were present throughout the infiltration. The acini were small, lacking in colloid and lined by large, eosinophilic-staining cells in the fibrous connective tissue stroma. A scattering of normal-appearing thyroid follicles occupied the small portion of the gland not involved in the inflammatory reaction.

DISCUSSION

There was a striking variation in the vulnerability to thyroiditis in the various species of marmosets examined. Species specificity in susceptibility to spontaneous thyroiditis has been noted in chickens (Witebsky et al., 1969; Kite et al., 1969) and in dogs (Musser and Graham, 1968). Strain specificity to the induction of autoallergic thyroiditis has been demonstrated in guinea pigs (Lerner et al., 1964). All of these findings are strongly suggestive of a possible genetic determinant for the thyroiditis response.

The chronic lymphocytic thyroiditis in the marmosets mimicked that of autoimmune thyroiditis in other animals. The preponderance of diseased thyroids in the colony-born animals indicates that those which are carefully maintained are able to survive a viral and/or bacterial infection which might trigger an autoimmune thyroiditis. In contrast, marmosets in the wild are either less prone to the disease or succumb to the precipitating factors at an earlier age.

The sex distribution of spontaneous thyroiditis in the colony-born marmosets paralleled that reported for man. In a series of 724 post-mortem examinations, Williams and Doniach (1962) found focal thyroiditis in 22 per cent. of the women...
and 6 per cent. of the men, and diffuse thyroiditis in 5 per cent. of the women and 1 per cent. of the men. The female to male ratio was approximately 5:1.
The corresponding ratio of the colony-born marmosets was approximately 2:1.
There was, however, no apparent sex difference in the incidence of thyroiditis in either the older or wild-caught animals.
It is important to note that the two runted C. argentata both showed chronic thyroiditis, in one animal involving the entire gland. Since the thyroid plays such an important role in the growth of young animals, the small size of the animals might reflect a reduction in thyroid hormone production. The question of a genetic aetiology for the runting syndrome must await further births from the breeding pair.
Interest in the immunology of thyroiditis was aroused when Rose and Witebsky (1956) created an autoimmune thyroiditis in rabbits, and Roitt, Doniach, Campbell and Hudson (1956) demonstrated antithyroid antibodies in the serum of patients with Hashimoto's disease. The sera of many subjects with chronic thyroiditis, thyrotoxicosis, spontaneous adult myxoedema and thyroid carcinoma have been found to contain antibodies which couple with antigens located in the colloid and in the cytoplasm of the thyroid acinar cells (Torrigiani and Roitt, 1963). The present demonstration that the marmosets of the genus Callithrix are highly predisposed to chronic thyroiditis provides a primate model for the study of the natural history of this disease.
The immunochemistry of the disease in marmosets is currently under study and will be reported later.

SUMMARY
Naturally occurring, histologically evidenced chronic thyroiditis has been found in 40 of 494 (8.1 per cent.) marmosets examined. Susceptibility to chronic thyroiditis in this primate appears to be generically related. Chronic thyroiditis was noted in 33 of 209 (11.0 per cent.) members of the genus Callithrix and in 7 of 285 (2.5 per cent.) animals of the genus Saguinus. Approximately 60 per cent. of the colony-born females, 28 per cent. of the colony-born males, 12 per cent. of the wild-caught females and 9 per cent. of the wild-caught males of the genus Callithrix had chronic thyroiditis. In one runted Callithrix argentata the histological changes in the thyroid mimicked those of Hashimoto's disease. The pronounced vulnerability of marmosets of the genus Callithrix to chronic thyroiditis provides a new primate model for the study of the natural history of this disease.

REFERENCES
Fig. 1. Gross appearance of a "runted" *C. argentata*, 90 days of age. Note the very sparse hair coat and hunched appearance of the runted animal. The larger normal animal is 78 days old.

Fig. 2. Photograph of thyroid gland of *C. jacchus*. The transtracheal isthmus is not evident.
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Fig. 3. Histological appearance of a normal thyroid of *C. jacchus*. The follicles are composed of low cuboidal epithelium. \times 21.

Fig. 4. Thyroid of *C. jacchus* showing the large distended colloid-filled follicles with flattened epithelium. These follicles are seen more frequently in *S. oedipus*. \times 21.

Fig. 5. A small well-demarcated focal collection of lymphocytes in the interstitial tissue of a + thyroiditis. \times 84.

Fig. 6. A band of fibrous connective tissue infiltrated by lymphocytes in the thyroid showing + thyroiditis. \times 21.
Fig. 7. + + reaction in C. jacchus. Note the larger involvement of the thyroid gland by focal collections of lymphocytes and the increase in interstitial fibrous tissue. × 21.

Fig. 8. + + thyroiditis. There is a lymphocytic and monocytic infiltration with an increase in interstitial fibrous connective tissue. Note the dissociated epithelial cells and inflammatory cells within the acini. × 150.

Fig. 9. Low power photomicrograph illustrating diffuse (Hashimoto's) lymphocytic infiltration. + + + thyroiditis. × 21.


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