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Solid cell nests (SCN) in Hashimoto's thyroiditis

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Summary. In Hashimoto's thyroiditis squamous metaplasia has been described by several authors. Such foci resemble the so-called solid cell nests (SCN) of the thyroid, epidermoid structures thought to be remnants of the fourth endodermal pouch. These cell nests can be identified by their particular histological appearances and by their positive reaction with polyclonal anti-CEA. In order to study this phenomenon more closely we examined the H&E-stained histological sections of 79 cases of Hashimoto's thyroiditis systematically. In 39 cases cell nests of three different types could be demonstrated: Small groups of elongated cells organized into solid epidermoid clusters, larger epithelial cells forming solid nests or similar epithelial but cystic structures. 29 of these 39 cases were further investigated immunohistochemically for the presence of thyroglobulin, CEA (polyclonal antiserum) and calcitonin. The first type of cell nest did not show any CEA-positivity, whereas the second and third type contained CEA-positive cells in 73% of the cases. In no cases were thyroglobulin- or calcitonin-positive cells identified in these epidermoid foci. Slide series of 25 of the 39 cases have further been investigated immunohistochemically for the presence of CEA (monoclonal antiserum), chromogranin, keratin and the epitope for Lu-5. In these additional series foci of epidermoid cells could be demonstrated in up to 15 of the 25 cases. They showed a positive reaction for the monoclonal CEA antiserum in only 3 of 15 cases, for anti-keratin in 5 of 14 cases and for Lu-5 in 13 of 15 cases. Immunoreactions for chromogranin were negative in all cases. Our findings suggest that epidermoid cell nests in Hashimoto's thyroiditis more closely resemble SCN than foci of follicular cell squamous metaplasia.

Key words: Thyroiditis lymphomatous – Solid cell nests (SCN) – Immunohistochemistry

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Introduction

In Hashimoto's thyroiditis several authors have reported squamous metaplasia in addition to the classical findings of numerous large oxyphilic thyroid cells, extensive lymphoplasmocytic infiltrates and considerable loss of colloid. Woolner et al. (1959) described squamous metaplasia of the residual epithelium in half of their cases with diffuse Hashimoto's thyroiditis and extensive epithelial destruction. Lindsay et al. (1952) and Katz and Vickery (1974) found such foci occurring particularly in the fibrous variant of Hashimoto's thyroiditis. Dubé and Joyce (1971) observed, in a case of Hashimoto's disease, extensive involvement of an entire lobe by large and irregular clusters of squamous epithelial cells surrounded by a dense avascular fibrous stroma. Shamsuddin and Lane (1981) examined squamous metaplasia of follicular epithelial cells by electron microscopy. Squamous cells were also found in normal glands and thyroids with pathological changes other than Hashimoto's disease (Jaffé 1937; Klinck and Menk 1951; Goldberg and Harvey 1955; Harcourt-Webster 1966). In general, however, all these glands showed chronic inflammation and fibrosis. The squamous cells, grouped in solid clusters or lining cystlike spaces, were surrounded by fibrous tissue and lymphocytes. The prolonged irritation by chronic inflammation was thought to constitute a triggering mechanism for the squamous metaplasia of the regenerating epithelial cells. Occasionally, such foci have also been explained as remnants of the thyroglossal duct or the postbranchial body (Klink and Menk 1951; Goldberg and Harvey 1955; Dubé and Joyce 1971).

In our own cases of Hashimoto's thyroiditis we have observed similar clusters of epidermoid cells. These are more reminiscent of the so-called solid cell nests (SCN) described by Yamaoka (1973) than squamous metaplasia of follicular epithelium. SCN are groups of polygonal or elon-

gated-oval cells organized into solid epidermoid clusters and surrounded by clearly visible basal membranes. Larger epithelial cell groups may include cysts and mucous material. Isolated C cells are often found in and around such SCN (Nadig et al. 1978; Janzer et al. 1978). SCN are believed to derive from the ultimobranchial body and C cells, being of neural crest origin (Le Douarin and Le Lièvre 1970), seem to migrate into the thyroid gland with the help of the ultimobranchial body (Pearse and Carvalheira 1967). Harach (1985b) found that epidermal keratin, CEA and calcitonin are usefull tracers for SCN. In own studies on normal thyroid we have also established that CEA is a reliable marker for SCN, often, however, not for the whole SCN but for larger cell groups in such nests (unpublished data). Autelitano et al. (1987) also investigated SCN with immunohistochemical methods employing polyclonal antibodies to keratin, CEA and calcitonin. However, looking at the pictures and descriptions of the SCN published by these authors, it seems probable that at least in some cases foci of hyperplastic C cells have been misinterpreted as SCN.

In order to find out whether epidermoid foci of Hashimoto's thyroiditis more closely resemble SCN than foci of squamous metaplasia we reexamined systematically the routine H&E-stained slides from our cases of Hashimoto's thyroiditis for the presence of solid or cystic structures composed of epidermoid cells. Cases containing such conspicious cell groups were further investigated immunohistochemically for the presence of thyroglobulin, CEA, calcitonin, keratin, chromogranin and the epitope for Lu-5.

Material and methods

The material available for examination consisted of thyroid glands from 76 patients with Hashimoto's disease. 4 were autopsy cases and 72 thyroidectomies. 71 patients were women (=93%) and 5 were men (=7%) whose ages ranged from 12–88 years, mean 53 years. Hashimoto's thyroiditis was diagnosed if 50% or more of the sections was occupied by diffuse or focal lymphoplasmocytic infiltrates. Further essential features were epithelial destruction and oxyphilic change of the follicular cells. Apart from Hashimoto's thyroiditis five patients also showed evidence of a malignant lymphoma of the thyroid gland (plasmocytic lymphoma, lympho-plasmocytic lymphoma, follicular and diffuse centrocytic-centroblastic lymphoma, follicular centrocytic-centroblastic lymphoma, diffuse centroblastic lymphoma). An additional carcinoma of the thyroid gland was diagnosed in three patients (undifferentiated carcinoma, papillary carcinoma, follicular carcinoma). The routine H&E stained microscopic slides were examined for the presence of groups of cells with the appearances of squamous metaplasia or SCN. Such foci could be demonstrated in 39 cases, but in only 29 of these were blocks of paraffin embedded material available. In the remaining 10 cases we had at our disposal only stained slides sent to our institute for consultation. Additional sections were cut from the available blocks of the 29 cases and stained with alcian blue (AB) and PAS. For the immunohistochemical investigations a slightly modified immunoperoxidase method (Sternberger et al. 1970) was used. Sections of all 29 cases were examined with polyclonal antisera for thyroglobulin (Dako, Denmark), carcinoembryonic antigen (CEA) (Dako, Denmark) or calcitonin (Dako, Denmark). 25 of the 29 cases were additionally stained with monoclonal antisera for carcinoembryonic antigen (CEA) (Bio-Science), keratin (Dako-CK1), chromogranin (ENZO) or the epitope for Lu-5[1]. The antisera were applied at a dilution of 1/800 (thyroglobulin), 1/200 (CEA, polyclonal), 1/30 (CEA, monoclonal), 1/200 (calcitonin), 1/40 (keratin), 1/1000 (chromogranin) and 1/3 (Lu-5).

Results

Solid and cystic clusters of epidermoid cells were demonstrated in 39 out of 76 cases (=51%). 35 patients were women (90%) and 4 were men (10%) with an average age of 55 years (17–88 years). In 33 of the 39 cases we found small round or oval groups of elongated cells with scanty cytoplasm and poorly defined cellular borders. The cells were arranged close to each other on a conspicious basement membrane. The elongated ovoid nuclei showed a pronounced nuclear membrane and a fine chromatin structure (Fig. 1). In 22 of the 39 cases a second and larger type of cell nest could be demonstrated. The periphery of these larger foci was occupied by the same elongated cells mentioned above or by flattened cells. The centre of these foci contained larger polygonal cells with abundant cytoplasm and distinct cell boundaries. In some cases the cytoplasm of these large cells appeared optically clear or vacuolated (Fig. 2). Mucoid degeneration of these cells was occasionally present. In 17 cases this second type of cell nest occurred together with the small groups of elongated cells. Cystic structures lined by flattened cells or large cells similar to those seen in the centre of the second type were found in 12 cases (Fig. 3). Their colloid-like or granular content contained AB and PAS positive material. In 9 cases these cystic structures were found in addition to the second type of cell nest and in 10, together with the smaller nests of elongated cells. All three types of cell nest were seen in 7 cases (Table 1). In none of the cases were definite prickle cells or horn pearls identified. In most instances the cell groups were surrounded by collections of lymphocytes or fibrous tissue. In atrophic Hashimoto's thyroiditis with abundant fibrosis these distinctive epithelial structures seemed to be more numerous and more prominent.

[1] The monoclonal antibody Lu-5 was kindly provided by C. Stähli, F. Hoffmann-La Roche AG, Basel, Switzerland

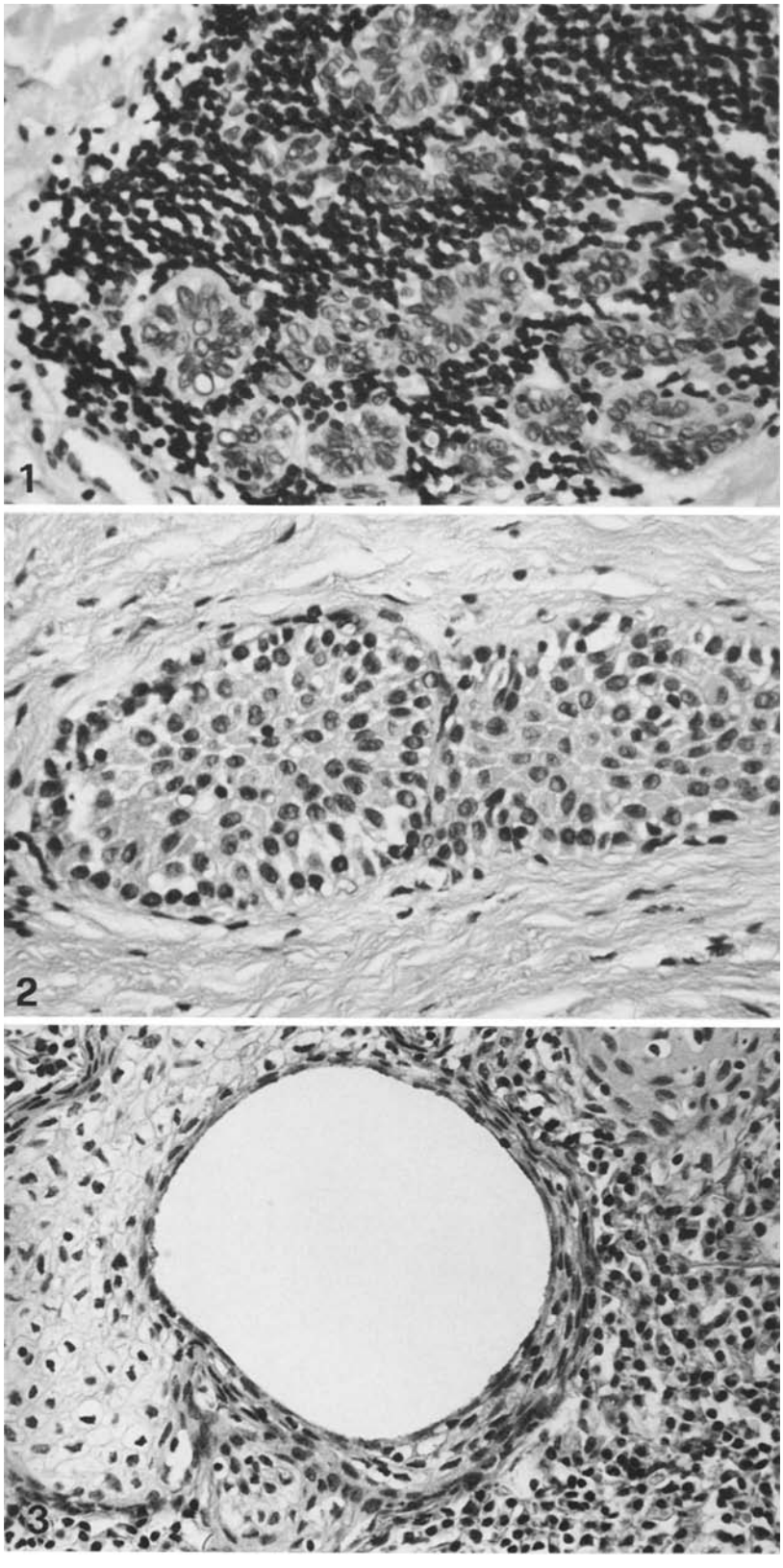

Fig. 1. Atrophic Hashimoto's thyroiditis; Solid cell nests (*first type*): small round or oval groups of elongated cells with scanty cytoplasm surrounded by a collection of lymphocytes. H&E ×323

Fig. 2. Atrophic Hashimoto's thyroiditis; Solid cell nests (*second type*): large polygonal cells with abundant cytoplasm and distinct cell boundaries. (Same case as Fig. 1). H&E ×323

Fig. 3. Hashimoto's thyroiditis; Solid cell nests (*third type*): Cystic structure lined by flattened or large polygonal cells. H&E ×323

Table 1. Occurrence of SCN in thyroid glands with Hashimoto's thyroiditis

	HE-staining			PAP	CEA pos.
Numbers of thyroid glands with Hashimoto's thyroiditis	79			29	
Numbers of cases with SCN	39			23	11
First type	33	17	7	20	0
Second type	22	9		15	11
Third type	12			10	7

PAP: immunoperoxidase method; CEA: polyclonal CEA antiserum

In the extra sections cut from those 29 cases in which such foci of epidermoid cells could be demonstrated in the routine slides, similar cell clusters could be seen in only 23 cases. In these additional slides of the remaining 23 cases small round or oval clusters of elongated cells were found in 20 cases, larger cell groups with polygonal cells in 15 and cystic structures in 10. In all these cases no thyroglobulin- or calcitonin-positive cells could be identified in the epidermoid foci (Fig. 4). Thyroglobulin, however, was always present in the surrounding follicular cells and in the colloid. In 10 cases calcitonin-containing cells were found between follicular cells and in the interfollicular spaces, but they showed no special relationship to the cell nests. The immunohistochemical reaction with polyclonal CEA antiserum was positive in cell nests of the second type in 11 out of 15 cases and in cystic structures of 7 out of 10 cases (Figs. 5, 6). The small cell groups of the first type did not show any CEA positivity. CEA positivity was found in the polygonal cells in the middle of the larger solid cell nests and the cells lining the lumen of the cystic structures. The cysts also contained CEA positive material. However, even in CEA positive cell nests not all of the cells showed a positive reaction and in cases with several cell groups not all these clusters stained positively for CEA, although they displayed the same morphological appearance. The intensity of the immunohistochemical staining varied from a weak reaction of the whole cytoplasm to a very intense staining, particularly of the cellular boundaries.

In further immunohistochemical studies foci of epidermoid cells were demonstrated in a maximum of 15 of the 25 cases. These cell nests showed a positive reaction for the monoclonal CEA antiserum in 3 of 15 cases, for anti-keratin in 5 of 14 cases and for Lu-5 in 13 of 15 cases. In these 13 cases follicular cells also stained with Lu-5. Immunoreactions for chromogranin were negative in all cases.

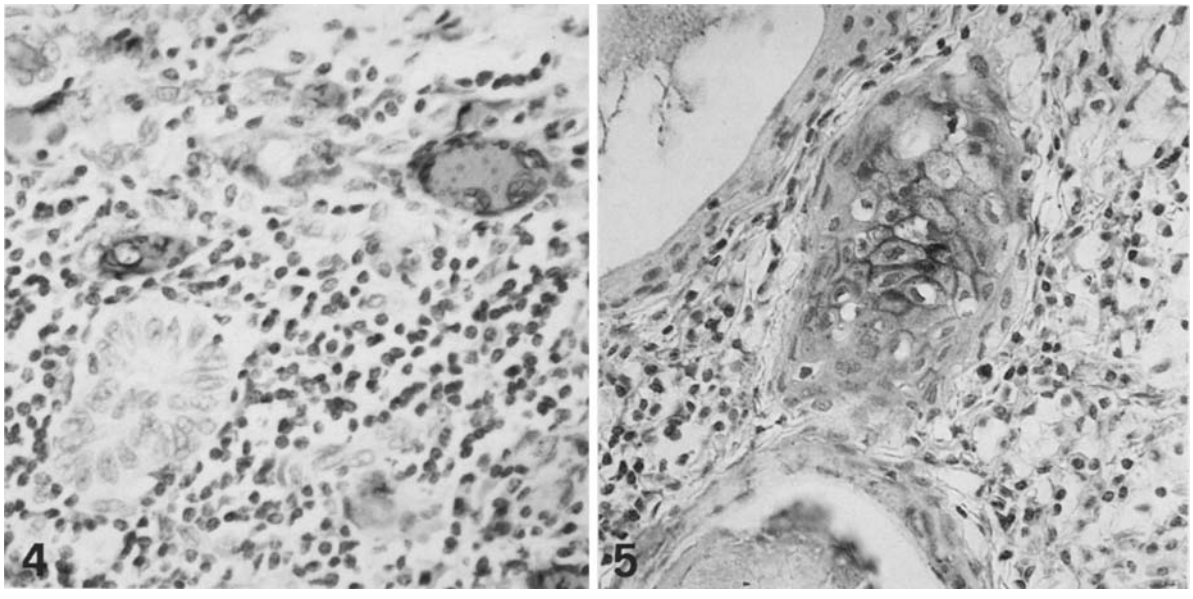

Fig. 4. Hashimoto's thyroiditis; Small thyroglobulin negative solid cell nest (*first type*) surrounded by lymphocytes and two small thyroglobulin positive follicles. PAP-method (anti-thyroglobulin) × 360

Fig. 5. Hashimoto's thyroiditis; Solid cell nests (*second and third type*). CEA positive large cells with intense staining of the cellular boundaries in the second type of solid cell nests. PAP-method (anti-CEA, polyclonal) × 360

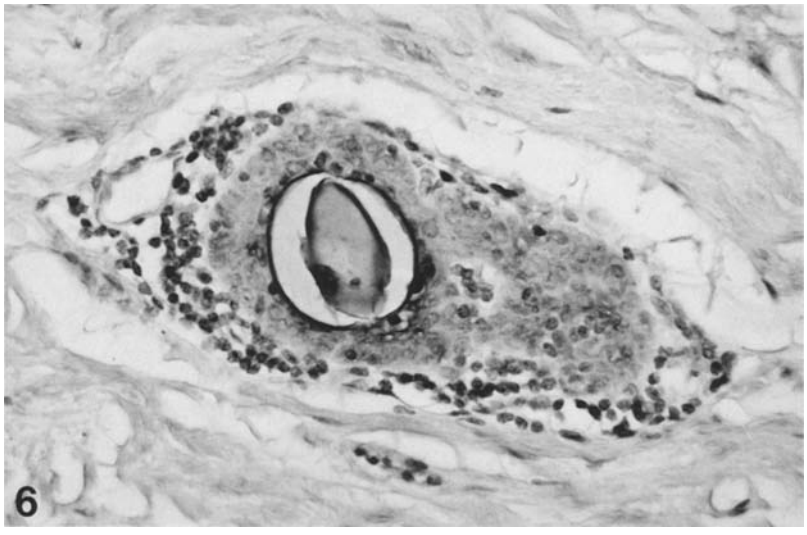

Fig. 6. Hashimoto's thyroiditis; CEA positive material in a cystic cell nest (*third type*). PAP-method (anti-CEA, polyclonal) × 323

Discussion

Studying routine H&E-stained slides of thyroid glands with Hashimoto's thyroiditis we found groups of epidermoid cells in 51% of the cases. The cell nests could be classified into three different types. The first type consisted of small elongated cells arranged on a conspicious basement membrane. The second type was characterized by large polygonal cells with abundant cytoplasm and distinct cellular boundaries surrounded by a circle of elongated or flattened cells. The third type was similar but with cystic structures lined by polygonal or flattened cells.

The elongated cells typical of the first type look like the basaloid cells of LiVolsi and Merino (1978) or like the elongated cells at the periphery of the solid cell nests (SCN) described by Yamaoka (1973). LiVolsi and Merino (1978) felt such foci represented embryological rests, probably derived from ultimobranchial or thymic remnants. The second type of cell nest corresponds closely to several descriptions of SCN, especially of Yamaoka (1973). In their reports on SCN Janzer et al. (1979) and Harach (1985c) mentioned cystic structures lined by epidermoid cells similar to our third type of cell nest. Getzowa (1907) first described such cystic and solid clusters of large polygonal cells with abundant cytoplasm in the atrophic thyroid glands of cretins. She interpreted these cell nests as remnants of the ultimobranchial body.

Studying SCN by immunohistochemical methods Harach (1985a) found thyroglobulin in small numbers of cells in SCN in 6 of 36 cases. In our study none of the foci of epidermoid cells contain thyroglobulin positive cells. Therefore it seems rather improbable that these cell clusters represent foci of regenerating follicular cells. CEA, however, was demonstrated by Harach (1985b) in SCN of 33 out of his 35 cases and all cells of the SCN reacted positively for this antigen. In our study only 48% of the 23 cases investigated with the polyclonal CEA antiserum showed positive cells in these groups of epidermoid cells. The first type of cell nests did not show any CEA positivity. The elongated cells surrounding the second type of cell nest were also CEA negative. In 11 of the 15 cases (73%) with the second or third type of cell nests CEA positivity was demonstrated in the large polygonal cells in the centre of the cell nest or in the cells lining the cystic structures. The monoclonal CEA antiserum revealed positively stained cell clusters in only 20% of 15 cases. The fact that not all the cell nests in our cases and not all cell nests in the positive cases stained for CEA may be due to alterations of SCN by the inflammatory process. The CEA negative cells, especially the small elongated cells, may produce too small a concentration of CEA. Prolonged storage of some of our paraffin blocks may also have had a deleterious effect on their immunohistochemical properties, especially on the epitope recognized by the monoclonal CEA antibody.

C cells could be demonstrated in 10 of 29 of our cases, only outside the groups of epidermoid cells. None of the cell nests showed positive staining for chromogranin. Nadig et al. (1978), however, demonstrated C cells within SCN and Janzer et al. (1979) showed a significant clustering of C cells around such SCN. Harach (1985b; c) found calcitonin containing cells in 51.5% and 54% respectively of the SCN in two different studies. The

negative result in our series may be due to the fact that our thyroid glands consisted mostly of specimens from elderly females. Harach (1985b) found calcitonin immunoreactive cells more frequently in males than in females and the prevalence of SCN including C cells tended to decrease with increasing age in females so that there was a striking difference between the sexes in the group over 60 years of age.

The pan-epithelial marker Lu-5, which recognizes an epitope on a molecule associated with a cytokeratin or an epitope shared by almost all cytokeratins described by Moll et al. (1982) (von Overbeck et al. 1985), showed a positive reaction in cell nests of 13 out of 15 cases. In both negative cases the follicular cells of the thyroid also failed to stain with Lu-5. This was probably indicative of poor tissue fixation. Epidermal keratin and antirenal tubular cell cytokeratin were found to be positive in all SCN of normal thyroid glands (Harach 1985b; Harach and Wasenius 1987). In our study groups of epidermoid cells in only 5 of 14 cases showed a positive reaction to monoclonal keratin antiserum. In 4 of these 5 cases the cell nests were also positively stained with polyclonal CEA antiserum and in 2 cases with monoclonal CEA antiserum as well. From these findings it seems rather improbable that the clusters of epidermoid cells found in Hashimoto's thyroiditis represent foci of simple squamous metaplasia.

Yamaoka (1973) reported the presence of SCN in about 3% of thyroids examined with one section from each lobe. Janzer et al. (1979) studying systematically the middle sagittal part of the upper two thirds of the lateral lobe of the thyroids found SCN in 7%. The frequency increased to 26% when the glands were cut at intervals of 3 to 5 mm (Fukunaga and Lockett 1971), to 41% (Yamaoka 1973) or to 60 or 61% (Harach 1985a; 1986) with sections at intervals of 2 mm to 3 mm and in a few cases to 100% with serial sections (Yamaoka 1973). We examined our thyroid glands with an average of only 2.7 blocks per thyroid, nevertheless, 51% of the glands contained foci of epidermoid cells with appearances to those of the so-called SCN. This finding provides evidence for a relationship between these cell clusters and Hashimoto's thyroiditis. Prod'hom and Hedinger (1985) discussed the hypothesis of Meeker (1925) that thyroid glands with SCN indicate an incompletely developed thyroid which may be predisposed to the development of auto-immune disease.

In accordance with Lindsay et al. (1952) and Katz and Vickery (1974) we found that the epidermoid cells demonstrate a slight tendency to occur more often in the fibrous variant of Hashimoto's thyroiditis. They may be particularly resistant to or perhaps stimulated by the inflammation.

In most of our cases the cell groups examined, especially the smaller foci, lay in a collection of lymphocytes. A close association of squamous cells with lymphocytic infiltration in Hashimoto's thyroiditis was described by Klink and Menk (1951). Prod'hom and Hedinger (1985) often found SCN surrounded by lymphocytic infiltrations in their study of focal lymphocytic thyroiditis. The relationship between SCN and lymphocytes may be explained by the similar origins of the thymus and the SCN. The epithelial cells in the medulla of the thymus derive from the third endodermal pouch (Cordier and Haumont 1980). The ultimobranchial body from which the SCN are believed to be derived corresponds to the fourth pharyngeal pouch (Pearse and Carvalheira 1967; Sugiyama 1971; Nadig et al. 1978; Janzer et al. 1979; Fraser and Duckworth 1979; Harach 1985a). It may be that the cells from the fourth pouch like the epithelia from the third endodermal pouch have the ability to attract lymphocytes. It is also possible that cells from the third pouch arrest in the thyroid during the development and mimick SCN. Clusters of small elongated cells may in particular represent remnants of the third endodermal pouch. This would explain why they do not contain calcitonin- and CEA-positive cells.

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