

## **An Autosomal Dominant Form of Adolescent Multinodular Goiter**

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### SUMMARY

Eighteen members of an extended pedigree have been found to have a form of euthyroid adolescent multinodular goiter. Histological examination showed multiple adenomata with areas of epithelial hyperplasia, hemorrhage, and calcification. In two subjects there were focal areas of epithelial hyperplasia reminiscent of low-grade papillary carcinoma, but capsular and vascular invasion was not found. The pattern of inheritance appeared to be autosomal dominant, with diminished penetrance in males. Although the patients were euthyroid, the likely basis for this disorder is an abnormality in thyroglobulin structure and function.

### INTRODUCTION

Multinodular goiter other than that due to chronic lymphocytic thyroiditis is unusual during childhood [1]. Its recurrence within a family suggests the possible existence of a defect in thyroxine or thyroglobulin synthesis, but frequently the exact enzymatic defect cannot be defined *in vivo* [2]. Here, we describe a pedigree in which 18 members have developed a form of euthyroid multinodular goiter. In contradistinction to the presently recognized inborn errors of thyroxine synthesis, which are autosomal recessive, the inheritance of this disorder appears to be autosomal dominant.

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## CASE DESCRIPTION

The pedigree is shown in figure 1. The proband (III-1) presented at age 15 with a nontender nodular goiter of several months' duration. She was clinically and biochemically euthyroid (table 1), and circulating antithyroid microsomal and thyroglobulin antibodies were not present. Thyroid scan showed a cold nodule in the right upper pole and a second nodule with normal uptake in the left upper pole. Following subtotal thyroidectomy, she received full thyroxine replacement and has shown no recurrence of goiter. Her 14-year-old sister (III-2) showed similar findings and also underwent subtotal thyroidectomy.

Subsequent investigation of the extended pedigree disclosed another 16 individuals with multinodular goiter, invariably with onset during the second decade of life. There was no consanguinity. All affected individuals were considered to be clinically euthyroid at the time of diagnosis. Nine of these were either not available for further study or had already been treated with thyroidectomy and/or thyroxine replacement. Thyroid function tests available in the remaining nine patients prior to thyroxine therapy showed no consistent abnormality (table 1), although one (III-52) had a low serum thyroxine, and another (II-27), a low serum triiodothyronine value, in both cases with normal TSH levels. Thyroxine-binding globulin ( $T_3$ -resin uptake) studies were normal. No patient showed a positive titer of antithyroid microsomal or thyroglobulin antibodies. Radioiodine uptake was normal in eight individuals studied, but thyroid scans showed at least one cold nodule in each. Physical examination and thyroid function tests in the other family members were within normal limits.

Initial thyroxine replacement therapy caused regression of the thyroid nodules in three patients (I-1, III-52, III-57), but had little effect in two others (III-53, III-54). In two patients (II-6, III-53), in whom subtotal thyroidectomy was carried out, subsequent failure to take replacement thyroxine led after several years to recurrence of goiter with

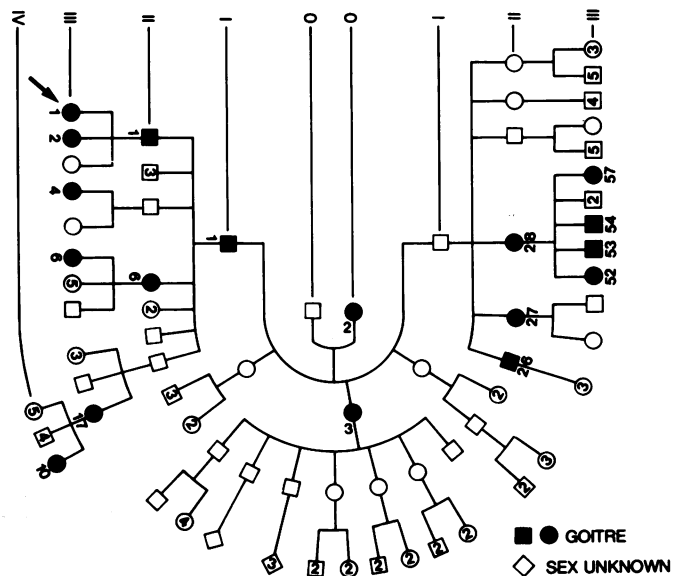


FIG. 1.—Pedigree of family with multinodular goiter. Affected individuals are shown by solid symbols and identified by numerical subscripts. Nos. within some open symbols show nos. of unaffected siblings.

TABLE 1  
LABORATORY FINDINGS IN PATIENTS WITH FAMILIAL MULTINODULAR GOITER

No.	Age (yr)	TSH (mU/l)	Serum thyroxine ( $\mu\text{g}/\text{dl}$ )	Triiodothyronine (ng/dl)	24-hr $^{131}\text{I}$ % uptake
II-26	54	1.5	6.6	97	...
II-27	46	3.6	5.3	63	...
II-28	43	1.5	4.2	85	11
III-1	15	1.0	6.0	...	21
III-2	14	1.8	6.5	...	22
III-52	17	1.5	3.3	83	19
III-53	16	1.5	4.2	150	24
III-54	16	1.5	4.4	130	33
III-57	13	1.5	5.1	138	24
Normal range		< 6	4-11	80-170	10-30

cold nodules, necessitating repeat thyroidectomy. One patient (III-57) showed an entirely normal thyroid gland when examined at 8 and 9 years of age, but subsequently developed multinodular goiter at age 14.

Twelve of the 18 patients underwent subtotal thyroidectomy, and pathology reports or tissue were available for review in 10 of these. All showed similar features of multiple adenomata with abundant colloid (fig. 2), which compressed surrounding normal thyroid tissue. Many showed areas of epithelial hyperplasia, fibrosis, hemorrhage, and small foci of calcification. Multiple micronodular clusters of acini lined by tall columnar epithelium with relatively clear cytoplasm were seen. In two patients (III-1 and III-53), the tissue showed marked epithelial hyperplasia with nuclear atypia and irregular papillary folds (fig. 3). These findings were reminiscent of those seen in some low grade papillary carcinomata of the thyroid, but no evidence of invasion of capsule, nerves, or vessels was seen.

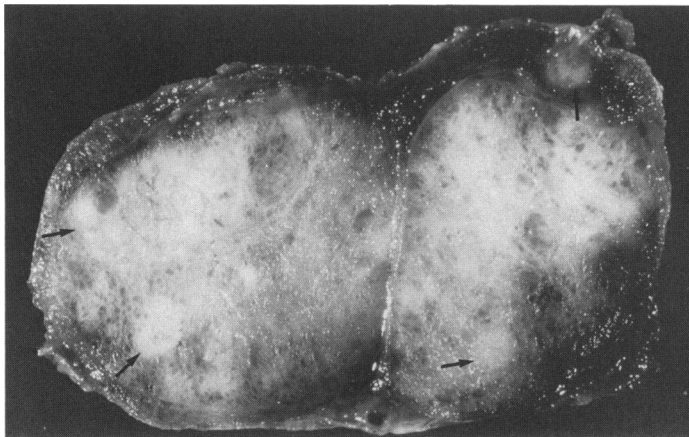


FIG. 2.—The cut surface of the thyroid gland from individual III-53 shows multiple colloid containing lobules with at least four denser rounded nodules (arrows) (scale in mm).

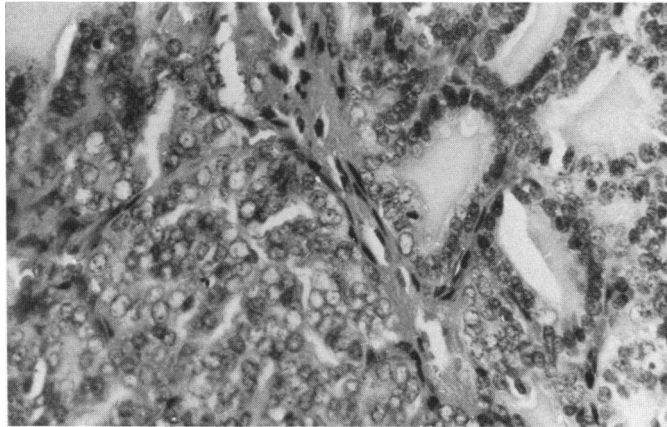


FIG. 3.—Histological examination of the thyroid gland showing areas with blunt papillary folds lined by hyperplastic epithelium (*in upper right of illustration*) near areas of densely packed cells with clear nuclei (*in lower left of illustration*), reminiscent of those seen in papillary carcinomata of the thyroid. Hematoxylin and eosin,  $\times 400$ .

#### DISCUSSION

The occurrence of multinodular or adenomatous goiter in 5 generations of this family, with at least one example of male-to-male transmission, strongly favors autosomal dominant inheritance. In three instances, unaffected males have had female children with multinodular goiter, a finding that suggests there may be reduced penetrance in males.

The occurrence of goiter in the second decade and its recurrence in two patients not receiving adequate thyroxine replacement suggests that even though these individuals were all clinically euthyroid they have an underlying defect in thyroid hormonogenesis. The histological appearance of the thyroid, with hyperplasia, calcification, and bizarre acini, is also suggestive of dys-hormonogenesis [3]. Both Murray et al. [4] and Cooper et al. [5] described families with similar clinical and histological findings; in those pedigrees, autosomal dominant inheritance was suspected, but not established. It seems reasonable to assume that the initial development of goiter was TSH-dependent, even though, as is frequently found in patients with large goiters [6], basal TSH concentrations were not elevated at the time of evaluation. The role of TSH in the pathogenesis of thyroid malignancy is more controversial, although several cases of carcinoma in association with familial goiter have been described, including two with metastatic disease [5]. Although the glands in two of our subjects showed focal areas suggestive of low-grade papillary carcinoma, no capsular or vascular invasion was seen, and therefore definitive proof of malignancy is lacking.

The nature of the genetic thyroid defect in this family remains undefined at present. An iodide trapping defect can be excluded on the basis of normal thyroidal uptakes and the known autosomal recessive inheritance of this disorder [7]. Investigations to rule out other known inborn errors of thyroxine syn-

thesis or metabolism were not possible; however, these also show autosomal recessive inheritance and usually present with at least compensated hypothyroidism [8].

Following active transport of iodide into the thyroid cell, each subsequent event in thyroxine synthesis occurs within the thyroglobulin molecule. This 660,000 dalton glycoprotein provides the matrix within which iodotyrosyl residues can be aligned to form iodothyronines [9]; lysosomal proteases then digest the thyroglobulin to release thyroid hormones into the circulation. It seems reasonable to postulate that a genetic defect in the structure of thyroglobulin may be the basis for goiter in the present pedigree. Qualitative abnormalities of thyroglobulin structure [10, 11] or its cellular transport [12] have been described in man, while aberrant processing of the thyroglobulin mRNA may be associated with goitrous hypothyroidism in goats [13]. Medeiros-Neto et al. [14] suggested that defects in the synthesis or release of thyroglobulin might be distinguished from other forms of congenital goiter by their failure to show a rise in serum thyroglobulin concentrations following administration of TSH, although this test would be of little value after thyroxine therapy had been initiated. Recently, several laboratories have cloned DNA from mammalian thyroglobulin genes, and the human gene has been mapped to the distal long arm of chromosome 8 [15]. As appropriate probes become available, it should be possible to define specific defects in the structure of thyroglobulin and to develop a more precise classification of these various forms of familial goiter.

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