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The influence of preoperative drug treatment on the extent of hyperplasia of the thymus in primary thyrotoxicosis

J. G. SIMPSON, ELIZABETH S. GRAY, W. MICHIE & J. SWANSON BECK*
Department of Pathology, University of Aberdeen

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SUMMARY

Thymic biopsies taken from women at the beginning of the operation of subtotal thyroidectomy were studied by the point-counting histometric technique. In all patients with primary thyrotoxicosis, the thymus is hyperplastic. After pretreatment with antithyroid drugs, the pattern of thymic involution with age is similar to, but at higher levels, than that in control groups of patients with non-toxic goitre in whom there is no evidence of immunological abnormality. By contrast, after propranolol pretreatment very little age involution is seen. The differences in the appearance of the thymus in female primary thyrotoxicosis patients prepared for operation with different drug treatment regimes are probably related to the pharmacological actions of the drugs and may indicate an interaction between primary immunological and secondary endocrinological factors in the disease process.

INTRODUCTION

It has long been known that the thymus is enlarged in patients dying with untreated thyrotoxicosis (Matti, 1912; MacKenzie, 1916); the early literature on the subject has been extensively reviewed by Fisher (1964). This feature was apparently so prominent that attempts were made earlier this century to treat the disease by thymectomy, with conflicting reports as to their success (Von Haberer, 1918; Melchior, 1927); the latest attempt showed that thymectomy did not alter the course of the disease (Van Herle & Chopra, 1971). The thymus has also been shown to be enlarged (Irvine & Sumerling, 1965) and hypertrophied (Michie *et al.*, 1967) with excessive numbers of medullary lymphoid follicles (Gunn, Michie & Irvine, 1964) during life in primary thyrotoxicosis patients in whom the disease activity has been controlled with antithyroid drug treatment.

In preparing thyrotoxic patients for operation, two different drug regimes may be used. The traditional therapy involves the use of antithyroid compounds, such as methylthiouracil and carbimazole, which block the iodine metabolism of the gland, so reducing circulating

* Present address: Department of Pathology, University of Dundee.

Correspondence: Dr J. G. Simpson, Department of Pathology, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD.

thyroid hormone levels (Astwood, 1970). More recently the beta-adrenergic blocking agent propranolol has been introduced as an alternative preparation (Michie *et al.*, 1974); in therapeutic doses, this drug does not appear to influence thyroid function directly (Hadden *et al.*, 1969), but it appears to neutralize the peripheral actions of the raised circulating thyroid hormones on cardiovascular receptors. Neither type of drug regime alters the natural history of the disease (Alexander *et al.*, 1973; McLarty *et al.*, 1973).

Having established the pattern of normal age involution in the adult thymus (Simpson, Gray & Beck, 1975), we decided to compare quantitatively the age involution in thymuses biopsied from primary thyrotoxicosis patients immediately prior to subtotal thyroidectomy. Since some of the patients in this study had been prepared for operation with antithyroid drugs and others with propranolol, it was also possible to compare the influence of the two drug treatment regimes on the thymus in an attempt to evaluate to what extent thymic hyperplasia was related directly to an inherent disease abnormality or secondarily to endocrinological factors.

MATERIALS AND METHODS

Thymic biopsies were obtained from 158 female patients with primary thyrotoxicosis for whom subtotal thyroidectomy was regarded as the treatment of choice. 131 of these patients were prepared for operation with antithyroid drugs and twenty-seven with propranolol.

(a) *Antithyroid group.* Of the 131 patients, ninety were prepared for operation with carbimazole only and thirty-eight with methylthiouracil only, while three patients had received both drugs. All the patients were euthyroid at the time of operation, but there was considerable variation in the duration of preoperative antithyroid therapy. Most patients had received a relatively short period of drug treatment (3–4 months), although a few referred to the Thyroid Clinic at Aberdeen Royal Infirmary by other physicians had had a more extended course of drug therapy (up to 5 years). Most of these patients were studied before the clinical decision was made to introduce propranolol premedication.

(b) *Propranolol group.* Twenty-seven patients were prepared for operation only with propranolol for at least 6 weeks. These were consecutive new patients, not previously treated with antithyroid drugs, who attended the Thyroid Clinic after the decision to introduce propranolol premedication; we have no reason to believe that there was any conscious bias in allocation of patients to this group.

Both groups of patients in addition received potassium iodide for 10 days before operation. During this final pre-operative period, treatment with antithyroid drugs was stopped whereas propranolol continued until the day of operation. Details of both types of antithyrotoxic drug therapy have been given by Michie *et al.* (1974).

(c) *Control group.* Thymic biopsies were also obtained from fifty-one female patients undergoing partial thyroidectomy for non-toxic nodular goitre. Our findings in these patients have been reported previously (Simpson *et al.*, 1975). None of these patients had received antithyroid drugs, propranolol or potassium iodide.

The thymic biopsy (weight 1–3 g) was taken from the left superior cornu of the gland. Samples removed in this manner have been shown previously to be representative of the organ as a whole (Michie *et al.*, 1967). The specimens were fixed in 4% neutral buffered formaldehyde and 6-μm sections prepared from paraffin blocks stained with haematoxylin and eosin by standardized histological techniques used previously (Simpson *et al.*, 1975).

The volume percentage of the thymus occupied by cortex, medulla and non-parenchymal tissue (fat, connective tissue and blood vessels) was measured by a point-counting system using a $\times 4$ objective and $\times 8$ focusing eye-piece containing a graticule with twenty-five line intersections. The principle of the histometric technique is that the relative numbers of line intersections that overlay any particular component in the section will be directly proportional to the volume of that component in the tissue sample (Hennig & Meyer-Arendt, 1963). The entire section (area approximately 1 cm^2) was scanned.

RESULTS

All results were expressed as a volume percentage of the total anatomical thymus in the biopsy and compared to age since in the normal individual the thymus undergoes pronounced age involution.

Antithyroid drug-prepared thyrotoxic group

For convenience the patients were grouped by age into half-decades. The percentage of the total anatomical thymus occupied by lymphoid parenchyma in thyrotoxic patients prepared for operation with antithyroid drugs is compared with that in patients with non-toxic goitre in Fig. 1. At all ages, the lymphoid component of the primary thyrotoxicosis patients'

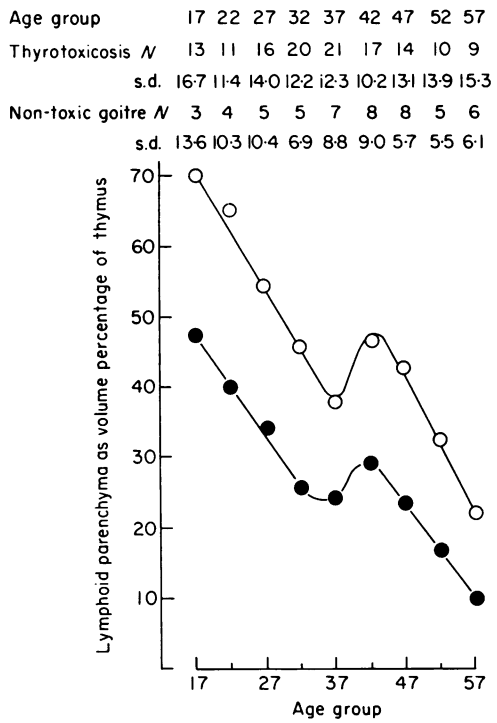

FIG. 1. Age involution of total thymic lymphoid parenchyma in 131 primary thyrotoxic patients pre-treated with antithyroid drugs (○) and in fifty-one control patients with non-toxic nodular goitre (●).

thymus is greater than that in patients with non-toxic goitre. This difference is statistically significant ($P<0{\cdot}001$) when mean percentages for each age interval are compared: this simple analysis is justified because the numbers of patients at different age intervals are approximately the same. In female thyrotoxicosis patients, the thymus shows a biphasic age involutionary curve interrupted by a premenopausal rise at mean age 42; the general pattern is similar to that seen in women without immunological disease.

The pattern of involution in the cortex and medulla in the patients and the controls is

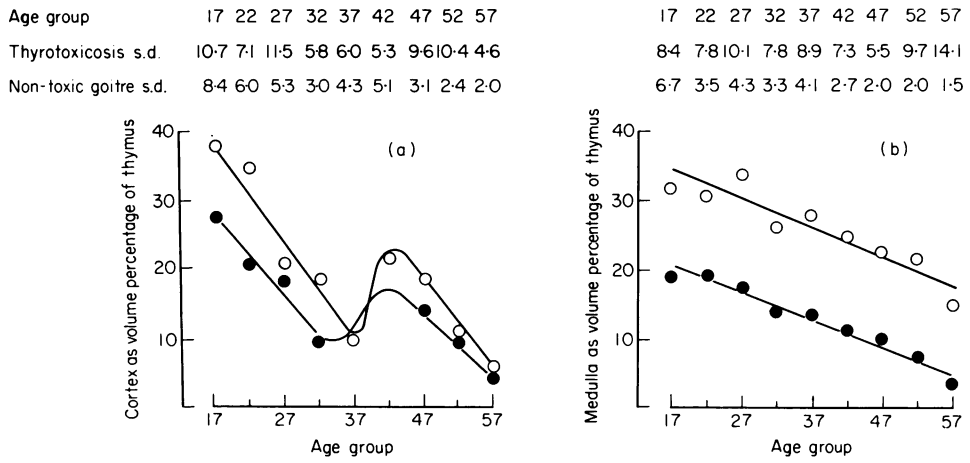

FIG. 2. Age involution of (a) thymic cortex and (b) medulla in 131 primary thyrotoxic patients pre-treated with antithyroid drugs (○) and in fifty-one control patients with non-toxic goitre (●).

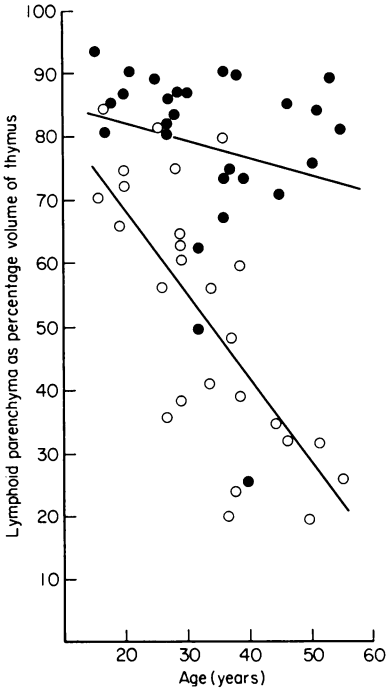

FIG. 3. Age involution of total thymic lymphoid parenchyma in twenty-seven pairs of age-matched primary thyrotoxic patients pre-treated with propranolol (●) or with antithyroid drugs (○).

shown in Fig. 2. The medulla is significantly greater ($P<0{\cdot}001$) in antithyroid drug-treated thyrotoxicosis patients, when means at each age interval are compared with means for non-toxic goitre patients. The cortex, however, shows no definite difference between the two groups. It follows, therefore, that the greater volume of lymphoid parenchyma, shown in Fig. 1, results from hyperplasia of the medulla rather than the cortex.

Propranolol-prepared thyrotoxic group

The twenty-seven patients prepared for operation with propranolol were matched (±year) for age with twenty-seven patients from the antithyroid drug-prepared group. With these small numbers, no grouping by age was attempted.

The percentage of the total thymus occupied by lymphoid parenchyma in each of these patients is seen in Fig. 3. The slopes derived from the two sets of data, representing age

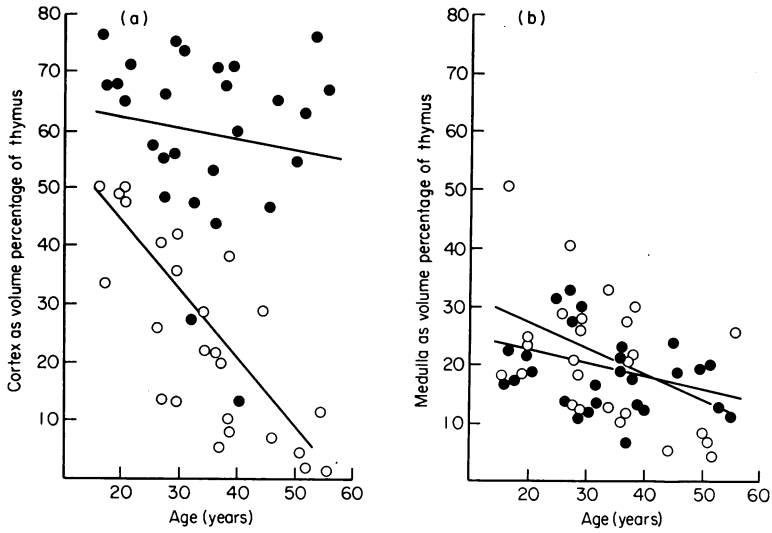

FIG. 4. Age involution of (a) thymic cortex and (b) medulla in twenty-seven pairs of age-matched primary thyrotoxic patients pre-treated with propranolol (●) or with antithyroid drugs (○).

involution, are significantly different ($P<0{\cdot}001$): the rate of involution in the propranolol-prepared group appears much slower than in the comparable group of antithyroid drug-prepared patients due to the relative lack of involution in the thymuses of the older patients treated with propranolol.

The pattern of involution in the cortex and medulla in both groups is shown in Fig. 4, which shows that the medulla in both groups involutes at the same rate. The overall difference is seen to be a reflection of the difference in the rate of involution of the cortex ($P<0{\cdot}001$) between the two drug treatment groups.

DISCUSSION

The enlargement of the thymus in untreated primary thyrotoxicosis is a prominent feature of the disease. It is probable that this is partly due to the stimulatory effect of raised circulat-

ing thyroid hormone levels since lymphoid hyperplasia has been induced in experimental animals by feeding thyroxine (Warner, 1964). However, this is unlikely to be the only factor since thymic enlargement is also present in certain 'autoimmune diseases', such as myasthenia gravis (Castleman, 1960), where affected patients are euthyroid.

This study has demonstrated by an accurate histometric technique the marked thymic hyperplasia which occurs in drug-controlled primary thyrotoxicosis patients. In patients prepared for operation with antithyroid drugs, the overall curve of thymic age involution is parallel to that for normal subjects and shows the same biphasic cortical curve in females; in these patients the thymic parenchyma is more abundant than normal mainly because of an increase in the size of the medulla. After propranolol, not only the medulla but also the cortex is more abundant and little involution is seen in older patients.

The striking differences between the two groups of primary thyrotoxicosis patients may be related to the pharmacological actions of these drugs. Since antithyroid drugs reduce the levels of circulating thyroid hormone(s) while propranolol merely neutralizes the peripheral endocrine effects on cardiovascular receptors, antithyroid-prepared patients become euthyroid or even hypothyroid for some time prior to operation, whereas propranolol-prepared patients are endocrinologically still hyperthyroid at the time of operation.

The most plausible explanation of our findings would therefore be that the thymus (in particular, the cortex) in antithyroid drug-prepared patients has been released from excessive thyroid hormone stimulation and has partly reverted to normal by the time of operation, whereas the propranolol-prepared thymus continues to be subjected to excessive thyroid hormone stimulation. This suggestion is supported by the experimental observations that adrenocortical-induced thymic involution in the chicken can be reversed by the administration of thyroxine (Warner, 1964) and that thyroxine given to adult chickens causes thymic enlargement secondary to an increase in cortical volume (Höhn, 1959).

Other explanations for these differences have also to be considered. First, it is possible that they are related to the differences in the duration and regime of premedication. Antithyroid drug therapy was administered for a longer period than propranolol; antithyroid drug treatment was stopped 10 days before operation, whereas propranolol was given up to the day of operation. Michie *et al.* (1967) have shown previously that the extent of thymic hyperplasia in antithyroid drug-controlled thyrotoxicosis is much less prominent after 3 months drug treatment. Secondly, it is possible that the drugs used to control thyrotoxicosis may have direct actions on the thymus. Antithyroid drugs might possibly have immunosuppressive properties in view of their chemical similarity to uracil, although this pharmacological action has not been investigated; if this were so, these drugs could induce lymphoid tissue atrophy in treated patients. It is also remotely possible that propranolol directly causes hyperplasia of the thymus: this explanation is, however, unlikely in view of the similarity of the thymus in propranolol-prepared patients to the historical pathological descriptions of untreated primary thyrotoxicosis (Doniach, 1966).

This study has demonstrated the presence of thymic medullary hyperplasia in both groups of primary thyrotoxicosis patients, suggesting that this lesion may be a basic abnormality perhaps associated with the immunopathology of the disease. In propranolol-prepared patients there is, in addition, cortical hyperplasia probably arising secondary to the endocrinological effect of hyperthyroidism, which results in appearances resembling those seen in the thymus of untreated primary thyrotoxicosis patients.

The thymus does not appear to be the only component of the lympho-reticular system

affected by the secondary endocrinological effects of hyperthyroidism. Peripheral blood lymphocytosis may occur in untreated primary thyrotoxicosis, occasionally with generalized lymph node enlargement and splenomegaly (Wallerstein & Castle, 1971). We have also examined the extent of lymphoid infiltration of the thyroid gland itself in primary thyrotoxicosis patients premedicated with these two different drug regimes and found that the infiltrate is more extensive in patients prepared for operation with propranolol (Young *et al.*, 1975).

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