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AGE INVOLUTION IN THE NORMAL HUMAN ADULT THYMUS

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SUMMARY

Thymic biopsies taken under general anaesthetic prior to partial thyroidectomy for non-toxic nodular goitre were studied with histometric techniques: evidence is presented that the tissue studied is representative of the normal adult human thymus. The pattern of age involution of the normal adult thymus is described: there is a striking sex difference in the curves of involution, due to differences in behaviour of the cortex.

INTRODUCTION

The main bulk of the human thymus is situated in the anterior mediastinum. In view of its apparent inaccessibility, most studies on its morphology have been based on tissue removed at necropsy examination.

On the basis of such necropsy studies it has been shown that the thymus grows rapidly during embryonic life and childhood, reaching its maximum absolute size about the time of puberty: thereafter growth ceases and it involutes gradually until old age, when the gland is often smaller than at birth (Hammar, 1926). This age involution is shown by a decrease in the overall weight of the organ associated with lymphoid tissue atrophy and replacement by mature adipose tissue (Young & Turnbull, 1931). The growth curve suggests that the organ is of primary importance in early life, and most studies of its structure have concentrated on this period of its development. There is, however, no certainty that these findings are truly representative of the normal structure of the thymus in living individuals since 'stress involution' may occur rapidly in any terminal illness (Boyd, 1932), although it is generally assumed that involution is minimal when the terminal illness lasts less than 24 hours (Goldstein & Mackay, 1969).

Gunn & Michie (1965) introduced a simple, safe method for biopsy of the thymus from patients in whom the only disturbance is a short general anaesthetic. In this paper we

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report histometric studies on thymic biopsies removed with this technique from patients undergoing operation for non-toxic nodular goitre. We consider that our observations on the structure of these thymuses will be representative of the normal population since these patients do not show any evidence of immunological disease, which in certain circumstances can be associated with thymic pathology.

MATERIALS AND METHODS

Thymic biopsies were obtained from eighty-nine patients immediately prior to partial thyroidectomy for non-toxic nodular goitre: fifty-one patients were female and thirty-eight male. The 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, embedded in paraffin wax and 6-μm sections were stained with Haematoxylin and Eosin by standardized histological techniques.

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 a $\times 8$ focusing eye-piece containing a graticule with 25 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.

The cortex consists of densely packed lymphocytes with occasional macrophages: the medulla is much less homogeneous, its lymphocytic component dispersed amongst easily recognized macrophages, epithelial reticular cells and fibroblasts. In occasional microscope fields within certain biopsies from older patients there was difficulty in distinguishing between cortex and medulla, but, in practice, such unallocable lymphoid parenchyma was never more than 5% of the total parenchyma.

RESULTS

For convenience, the patients were divided by sex and grouped by age into half decades. All results were expressed as a volume percentage of the total anatomical thymus in the biopsy.

The lymphoid parenchyma of the organ declines from about 50% of the gland in late adolescence to 10% in late middle age. The results show a striking sex difference (Fig. 1). In men, age involution is linear: in women, it is biphasic, interrupted by a premenopausal rise at mean age 42. In the second and third decades, the proportion of the gland occupied by parenchyma is less in women than in men, but, by the sixth decade, there is little sex difference.

The pattern of involution in the cortex and medulla in each sex is shown in Fig. 2. The medulla shows a continuous linear involution with age that is similar in men and women. In men, the cortex shows a similar pattern of continuous atrophy. By contrast, in women the cortex involutes in a biphasic manner with a pattern similar to that observed for total lymphoid parenchyma: from this we attribute the sex difference in age involution of the total thymus parenchyma to the different patterns of atrophy of the cortex.

Age group		17	22	27	32	37	42	47	52	57
Males	N	—	4	4	5	5	6	5	5	4
	SD	—	12·7	9·8	7·0	5·9	6·4	8·1	7·0	7·7
Females	N	3	4	5	5	7	8	8	5	6
	SD	13·6	10·3	10·4	6·9	8·8	9·0	5·7	5·5	6·1

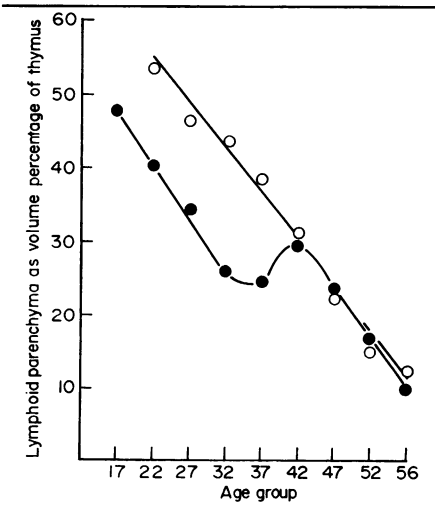

FIG. 1. Age involution of total lymphoid parenchyma in the normal human thymus. (●) Female. (○) Male. N = number of patients. SD = standard deviation.

Age group		17	22	27	32	37	42	47	52	57
Males	SD	—	7·1	5·4	4·3	2·9	4·0	4·3	3·8	4·8
Females	SD	8·4	6·0	5·3	3·0	4·3	5·1	3·1	3·4	2·0

Age group		17	22	27	32	37	42	47	52	57
Males	SD	—	4·8	3·9	3·1	2·6	2·1	3·6	3·0	1·4
Females	SD	6·7	3·5	4·3	3·3	4·1	2·7	2·0	2·0	1·5

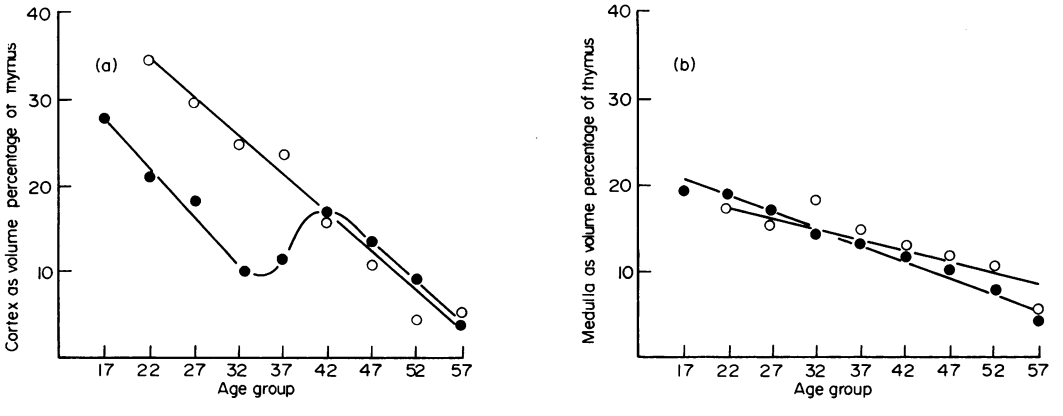

FIG. 2. Age involution of (a) cortex and (b) medulla in the normal human thymus. (●) Female. (○) Male. SD = standard deviation.

DISCUSSION

Earlier reports on normal thymic age involution have been reviewed by Goldstein & MacKay (1969). Most of these observations have been based solely on weight changes and all have the disadvantage of employing tissue removed at necropsy with the consequent risk that the structure of the thymus had been modified by 'stress involution'. The earliest report on the quantitation of the structural changes occurring within the thymus with age is that of Hammar (1926): however, the numbers of adults in his study are small and, in graphs prepared from his data by Good, Martinez & Gabrielsen (1964) and Mackay (1966), there is no evidence for a sex difference in age involution. Young & Turnbull (1931) reported the findings on a larger number of adults, but the quantitative technique they employed is highly suspect: Bratton (1925) used valid quantitative methods, but his study was restricted to childhood and adolescence. Clearly, the pattern of age involution in the normal adult human thymus has not been established previously.

The present report is an attempt to rectify this omission. We consider that the thymuses reported in this paper are normal, since the biopsies were taken from patients with non-toxic nodular goitre, a disease where there is no evidence of immunological abnormality and in which thymic pathology has never been reported. The appearances cannot have been modified by 'stress involution', since the thymic biopsy was removed at the beginning of the operation when the patients had been subjected to a general anaesthetic for only a short time. The shrinkage artefact in the sections has been minimized by use of standardized histological techniques and the measurements of defined components were made with an accurate histometric technique. The major disadvantage of this study is that the numbers of patients in the half-decade age groups are small, but the patterns of age involution of the thymus reported here are probably meaningful in view of the relatively small standard deviations in the mean values.

Both components of the lymphoid parenchyma of the thymus atrophy with age, the cortex at a slightly faster rate than the medulla. In both sexes, medullary atrophy was regular and linear. The sex difference in age involution of the cortex, linear in males and biphasic in females, has not been noted previously. This difference is probably referrable to the susceptibility of the cortex to hormonal influences (Goldstein & Mackay, 1969).

This paper describes the age involution of the normal adult human thymus and so establishes standards against which studies on the pathology of the thymus, particularly in immunological disease, can be compared.

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