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THE HUMAN THYMUS GLAND: THE PROBLEM OF THE THYMUS-MAST-CELLS

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In previous reports it was shown that in conditions associated with tissue proliferation the thymus of the rat and the mouse exhibited a uniform tissue reaction. For example, pregnancy, tumours, the proliferative form of tuberculosis provoked an increase in the number the corpuscles of Hassall, the appearance in them of a considerable amount of PAS-positive substance; at the same time, many PAS-positive thymocytes and a strong mast cell reaction were observed. This process was taking place in each of the above-mentioned conditions, though there were differences in rate, depending on the rapidity of the pathological sequence of events [1, 2]. Similar reactions were noted in response to other effects as well [8, 9, 10].

Our experiments have proved that mast cells were formed in the thymus during certain phases of ontogenetical development and that explanted thymus cells were capable of producing metachromasic heparin from broken-down heparin (*i. e.* heparin showing PAS-positivity only). Both the cells of the epithelial reticulum and the thymocytes were found to convert heparin; the cells of the spleen and lymph nodes were not capable of performing this [2]. This reaction of the thymus in response to stress, but first of all to effects associated with tissue proliferation was observed to occur in several animal species (rat, mouse, guinea pig), and it has been decided to study human thymus glands in order to determine whether the above observations were applicable to man. This has been the principal aim of the present studies.

Methods

78 human thymus glands removed shortly after death were examined. Care was taken to get thymus glands from subjects of various age groups and from both tumorous and non-tumorous cases. The age groups are shown in *Table I*, the classification according to cause of death in *Table II*.

The thymus gland or the adipose thymus was studied histologically, excising a random specimen, about 1 cu. cm in size and fixing it in Carnoy's fluid. After embedding in paraffine sections were cut at 2 or 4 planes and prepared by the periodic acid-Schiff, or tri-PAS, Giemsa and toluidine blue techniques.

Table I

Age	Number of cases
foetus	6
0— 1 year	7
1—16 years	10
16—30 years	5
30—50 years	10
50—70 years	15
70—81 years	12
age unknown	13

Table II

Cause of death	Number of cases
malignant tumour	22
bacterial, viral disease	34
circulatory failure	7
other conditions (death, following surgery; agranulocytosis; uraemia, contusio cerebri, marasmus senilis etc.)	6
undiagnosed disease	4
foetal asphyxia	5

Results

The *foetal thymus glands* were compact; lymphatic tissue abound in them. There were numerous big and slightly swollen corpuscles of Hassall, many of them containing PAS-positive substance. There were few mast cells.

At the age of from *0 to 1 year* the pattern was closely similar except that there were more corpuscles of Hassall and more mast cells in the capsule and at sites also in the cortex.

In the age group of from *1 to 16 years* the thymus showed great individual variations. In the thymus from a child 7 years of age an excessive increase of fat and connective tissue was seen, whereas in some children around 15 years of age the thymus was still intact. The number of the corpuscles of Hassall and of the thymocytes was mostly on the decrease, but the epithelial-lymphatic tissue was still preponderating over the fatty and connective tissues.

In this group there were two children with myeloid leucaemia; one child was 5, the other 7 years old. In both glands masses of mast cells, in some visual fields as many as 30 or 50 were visible both in the cortex and the medulla *(Fig. 1)*. Their nuclei were similar to those of thymocytes. A similar massed

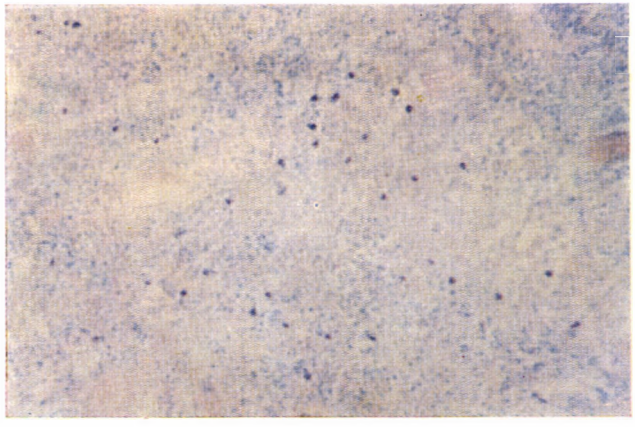

Fig. 1. Thymus from a child 5 years of age died of myeloid leucaemia. Mast cell reaction. Giemsa, ×200

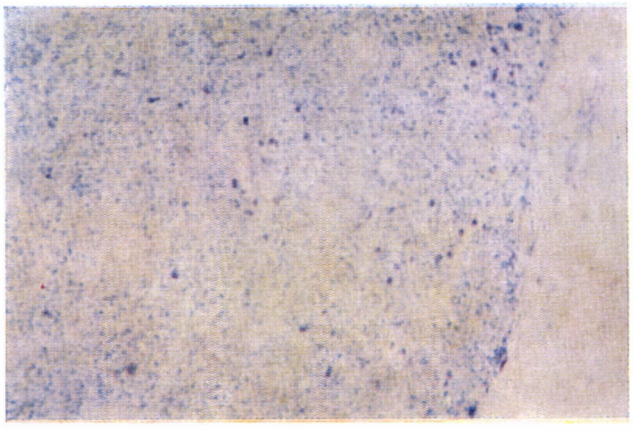

Fig. 2. Thymus from a child 12 years of age, died of agranulocytosis. Metachromasia of thymocytes and regular mast cells. Giemsa, ×200

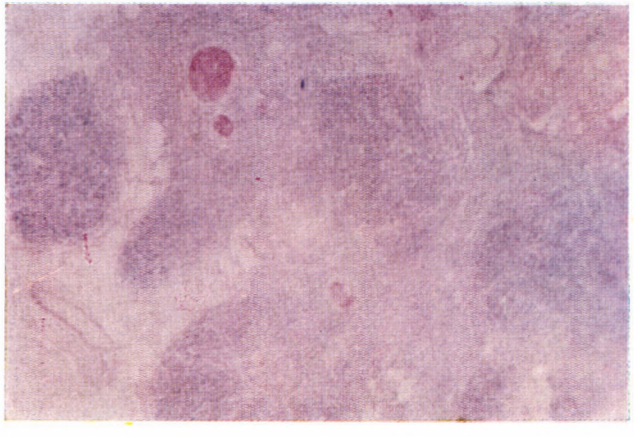

Fig. 3. Thymus from a subject 40 years of age, died of tetanus. Many PAS-positive cysts, minimal fatty tissue, complete thymus. PAS, ×100

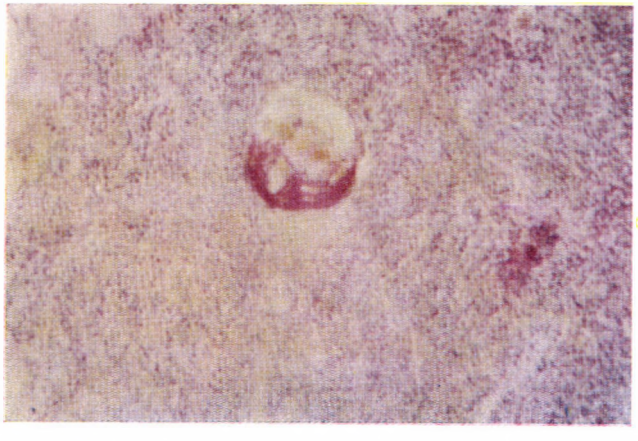

Fig. 4. Thymus from a subject who had died of meningitis at the age of 57 years. Corpuscle of Hassall containing PAS and orange-positive substance. Tri-PAS, ×200

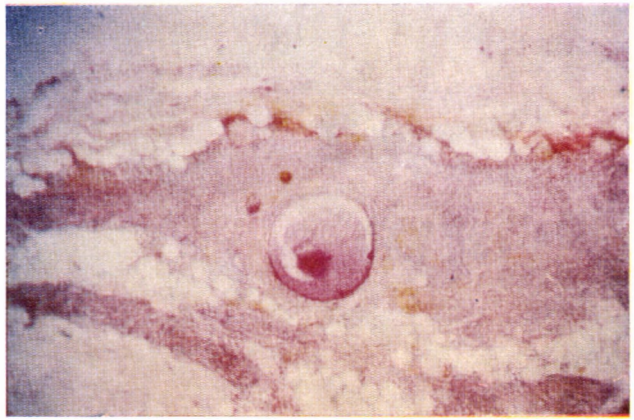

Fig. 5. Thymus from a subject who had died of leucaemia at the age of 60 years. Big PAS-positive cyst and small corpuscles of Hassall. Tri-PAS, ×100

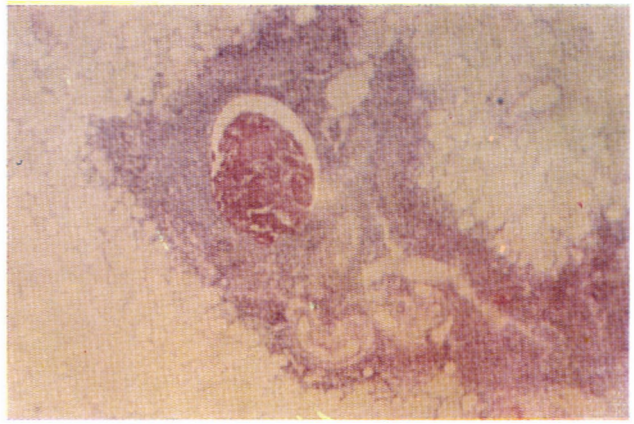

Fig. 6. Thymus from a subject who had died of tetanus at the age of 58 years. Cyst filled with PAS-positive substance. PAS, ×100

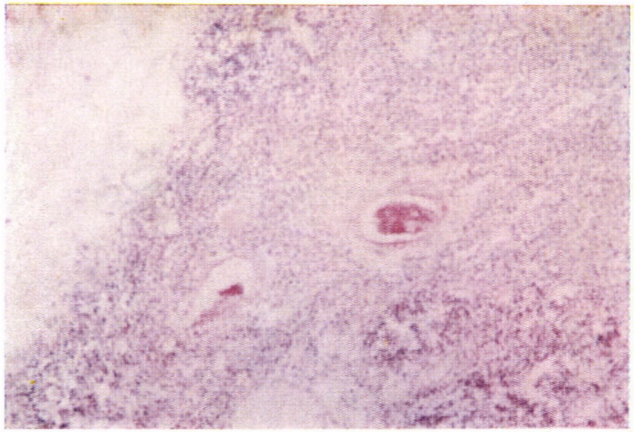

Fig. 7. Thymus from a subject who had died of pneumonia at the age of 58 years. Many corpuscles of Hassall containing PAS-positive substance. Big thymus, minimal fatty tissue. PAS, ×100

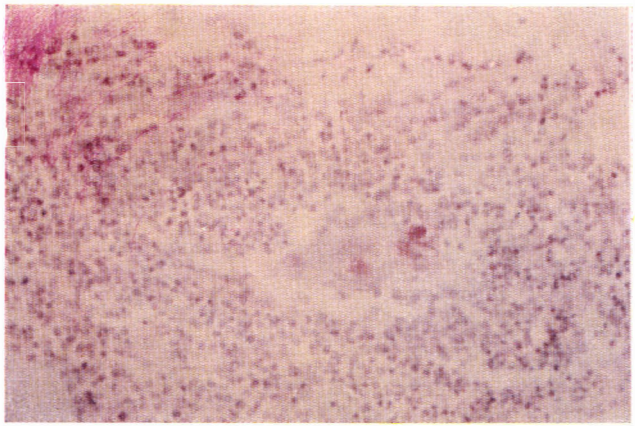

Fig. 8. Same as *Fig. 7.* Epithelial islet with PAS-positive substance. PAS, ×450

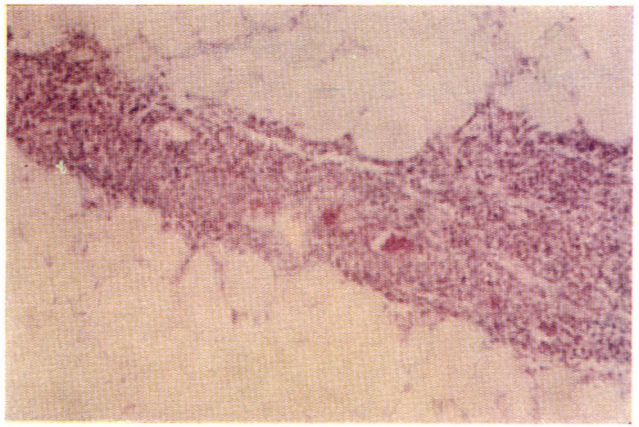

Fig. 9. Thymus from a subject who had died of influenza at the age 79 years. Cysts filled with PAS-positive substance, corpuscles of Hassall, epithelial elements. PAS, ×200

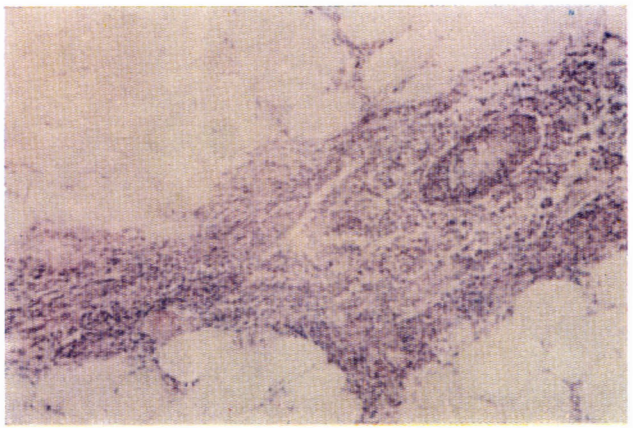

Fig. 10. Thymus from a subject aged 81 years. Small PAS-positive cyst, epithelial elements. PAS, ×200

appearance of mast cells was observable in the thymus of a child (aged 12 years) with agranulocytosis *(Fig. 2)*. In the thymus from other children of similar age the number of mast cells was normal, though more than in the age group of 0—1 year.

The pattern in the *16 to 30 years* age group was just as variable as in the previous one. A patient who had died of encephalitis at the age of 27 exhibited a regular thymus adiposus. At the same time most of the glands contained significant quantities of thymus tissue, about as much as fat. At many sites there was a marked mast cell reaction to be seen.

In the age group *30 to 50* the pattern also varied. The thymus from an individual 40 years of age contained as much epithelio-lymphatic tissue as is regular at 20 years of all *(Fig. 3)* but in most cases fat was preponderating over thymus tissue. However, the PAS-positive cysts and the conversion of cells into mast cells were detectable in every thymus without exception. The majority of the thymus glands exhibited well-developed, young corpuscles of Hassall containing PAS-positive substance. In the *50 to 70* years age group the thymus was fatty but just as in the previous group thymic matter was present in almost every gland, with corpuscles of Hassall containing much PAS-positive substance, and with an increased number of mast cells *(Figs. 5, 6, 7, 8)*. Epithelial elements other than those forming the corpuscles of Hassall also abounded.

In the *70 to 81 years* age group fatty tissue was preponderating but the epithelial-lymphatic matter was still detectable, with epithelial cysts filled with PAS-positive substance and young corpuscles of Hassall *(Figs. 9, 10)*. At many sites the thymocytes were metachromasic and some mast cells exhibited hypergranulation and signs of destruction.

The thymus from *tumorous* patients did not differ from those of other individuals. Although some of these glands (especially those from young subjects) contained many corpuscles of Hassall, almost no PAS-positive substance was found in them.

Discussion

As it has been mentioned in the introduction, the purpose of the present study was to determine whether the results of our animal experiments would be valid for man.

The first and most important question is whether the thymus is at all functioning in the adult man and whether it plays any role in the organism of adults. The view has been universally accepted that the thymus ceases to be an active factor in the organism by the end of puberty [4, 5, 6, 7). Our experiments however indicate that the function of the thymus must be taken into account in more advanced age as well. If it is realized that con-

siderable quantities of epithelial elements capable of producing PAS-positive substance occur in the thymus of subjects over 70 years of age and if we accept the view that the production of the PAS-positive substance is inherent in the gland's function, it will be clear that the thymus is still active at that age, even though in a reduced measure [3]. We feel rather reluctant to accept the view that a quantitative decrease in thymic matter would by itself indicate that the thymus is not any longer necessary or that it cannot function at a time when the morphological signs of active function are present. We think that the size of some endocrine gland alone will not decide whether or not the gland is functioning, either in the qualitative or in the quantitative sense.

The basis of our reasoning is that the production of PAS-positive substance is an important feature of the function of the thymus. Our earlier experiments proved that any time the thymus is activated this PAS-positive substance increases in quantity, then it leaves the gland mainly by cellular transport, forming the metachromasic substance of mast cells. When the thymus empties itself, the amount of this PAS-positive substance also decreases. We believe that the evidence we obtained *in vitro* and *in vivo* convincingly prove this view. Thus, a similar phenomenon in the human thymus should be interpreted in the same way as in the animal experiments. In view of the fact that this representation of thymus function was demonstrable in every age group (including senile age) we feel bound to state that the adipose thymus is a functioning thymus, though its activity is reduced.

A further problem is that of the mast cells. Most of the human thymus glands examined exhibited a marked mast cell reaction, not only in the marginal areas and the capsule of the tymus, but in the cortex and medulla as well. Metachromatic substance was frequently present in thymocytes. These characteristics were not restricted to certain age groups, they occurred at every age.

The thymus glands from subjects who had died of malignant tumour showed no substantial differences from the others. The divergence from our animal experiments might have been due to the fact that while the experimental tumours and thymus glands were removed for study at predetermined times, the human thymus glands were examined in the end stage, after death.

The thymus glands from the cases of leucaemia merit separate consideration. An extreme degree of mast cell formation was observable in those glands, but exclusively in cases of myeloid leucaemia. In a case of lymphoid leucaemia compact lymph tissue or lymph nodes free of mast cell reaction were found throughout the thymus. All these indicate that in the thymus the intense leucaemic cellular proliferation manifests itself with a mast cell reaction.

Summary

Seventy eight human thymus glands from autopsy material have been studied to determine whether the tissue reaction previously observed in animal experiments was detectable in them. The mast cell reaction, the increase of PAS-positive substance was detectable in the human thymus glands. Actively functioning corpuscles of Hassal were found in the thymus glands of aged subjects. On the basis of the evidence obtained it has been concluded that in adult age the thymus gland is still functioning.

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ИССЛЕДОВАНИЕ ЧЕЛОВЕЧЕСКОЙ ЗОБНОЙ ЖЕЛЕЗЫ С ТОЧКИ ЗРЕНИЯ ТУЧНЫХ КЛЕТОК ЗОБНОЙ ЖЕЛЕЗЫ

ДЬ. ЧАБА

Полученные при 78 вскрытиях человеческие зобные железы исследовались с точки зрения описанной в экспериментах на животных однородной тканевой реакции. Было установлено, что в человеческих зобных железах также всюду можно обнаружить тучноклеточную реакцию и размножение ПАСК-положительного вещества. У пожилых лиц также наблюдались активно функционирующие гассалевские тельца. Автор того мнения, что выявляемые морфологические признаки указывают на функцию зобной железы у взрослых.

UNTERSUCHUNG VON MENSCHLICHEN THYMUSDRÜSEN IN BEZUG AUF DAS THYMUS-MASTZELLEN-PROBLEM

GY. CSABA

Aus Sektionen stammende 78 menschliche Thymusdrüsen wurden auf die in Tierversuchen beobachtete einheitliche Gewebsreaktion untersucht. Es wurde festgestellt, dass die mastzellige Reaktion, die Vermehrung des PAS-positiven Stoffes auch im menschlichen Thymus überall nachgewiesen werden kann. Bei alten Individuen wurden gleichfalls aktiv funktionierende Hassalsche Körperchen beobachtet. Verfasser ist der Meinung, dass die nachgewiesenen morphologischen Zeichen das Funktionieren der Thymusdrüse bei Erwachsenen bestätigen.

Dr. György Csaba, Budapest, IX., Tűzoltó u. 58. Hungary