Fine structural evidence for hormone secretion by the human thymus

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SYNOPSIS The epithelial cells of the Hassall's corpuscles in 11 human thymus glands (nine cases of myasthenia gravis and two glands from patients undergoing surgical correction of congenital heart disease) have been examined by electron microscopy. In every instance the epithelial cells have the cytoplasmic organelle complex necessary for 'export'-type secretory activity and in addition contain large numbers of membrane-limited small spheroidal secretion granules.

Hassall's corpuscles are avascular anatomical units and a pericorpuscular zone, at least 50 μm broad, is also without blood vessels.

It is therefore suggested that the secretory product(s) of the corpuscular epithelial cells has a purely intrathymic function.

Clark (1963) described electron-dense granules within the cytoplasm of epithelial cells of mouse thymus. This report has been confirmed by Kohnen and Weiss (1964) and similar observations have been made in other species such as the rat (Pfoch, 1971) and the monkey (Chapman and Allan, 1971). These findings have been generally accepted as evidence for secretory activity by the thymus and such behaviour is supported by experimental studies (Metcalf, 1956; Osoba and Miller, 1964). To date there is no evidence that an analogous state of affairs exists in the normal human thymus, although Macadam and Veters (1969) reported electron-dense secretory granules in an epithelial thymoma as did Kay and Willson (1970) in an ACTH-secreting thymic tumour. Tomasi and Yurchak (1972), in a fluorescence study, described the synthesis of S component of IgA molecules in human thymic Hassall's corpuscles. We have carried out an electron-microscope examination of 18 human thymuses from 15 cases of myasthenia gravis and three patients with congenital heart disease. Our primary object was the detection of morphological evidence of secretory activity.

Materials and Methods

All tissues were processed in an identical fashion, namely, glutaraldehyde fixation followed by osmication and araldite embedding. Ultra-thin sections were double-stained with uranyl acetate and lead citrate.

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Results

Surprisingly, despite the common impression that Hassall's corpuscles are effete anatomical units, these were the only structures in the thymus which showed evidence of secretory activity. Eleven of the 18 samples of thymus processed for electron microscopy (nine cases of myasthenia gravis and two controls from patients with congenital heart disease) contained Hassall's corpuscles. In all corpuscles the epithelial cells contained the cytoplasmic apparatus (figs 1, 2, and 3) associated with secretory activity of the 'export' type, ie, a product of secretion destined for expulsion from the cell. Rough endoplasmic reticulum, Golgi apparatus, and related small vacuoles were present in all of the epithelial cells. Large numbers of small spheroidal secretion granules were found in every instance (figs 1, 2, and 4). These were limited by a single unit membrane and had an average diameter of 139 nm. The secretion material consisted of a dense core situated eccentrically within the limiting membrane, the remainder of the secretory vacuole being filled with a less electron-dense material (fig 4). Blood vessels were never detected within Hassall's corpuscles, and a pericorpuscular ring, at least 50 μm broad, was similarly avascular.

Discussion

In the human thymus, organelles other than secretion units which might resemble the structures identified

Fig 1

Fig. 1 *Low-power view of Hassall's corpuscles. Note the prominent (dilated) units of rough endoplasmic reticulum in the central cells and the large number of small spherical granules (arrows) in the surrounding cells. $\times 1500$*

Fig 3

Fig. 3 *Part of a 'rosette' of epithelial cells showing microvillous (arrows) cell borders. L = lumen. $\times 6500$.*

Fig 2

Fig. 2 *Higher-power view of Hassall's corpuscular epithelial cells. Note the membrane-bound granules (arrows). $\times 2500$.*

Fig. 4 High magnification of small portion of cytoplasm showing the internal fine structure of an optimally preserved secretion granule (arrowed.) Note the eccentric dense cone and the less dense crescent. $\times 36\,000$. (Reproduced by permission of the Editor of Lancet.)

are lysosomes, lipid spherules, elements of Golgi complex, and units of smooth endoplasmic reticulum.

Lysosomes are usually larger structures (averaging 500 nm as opposed to 139 nm) and commonly vary in size, shape, intravesicular contents, and 'staining' density. The cells containing them frequently show the activity and general morphology of phagocytes. With the exception of complex lysosomes, ie, autophagic vacuole type, and 'aged' lysosomes, the intravesicular content of lysosomes is homogeneous. The cells of Hassall's corpuscles do not exhibit features suggestive of phagocytic activity and the secretion granules are spheroidal with an eccentric dense core. We have twice attempted unsuccessfully to demonstrate acid phosphatase activity in the granules using the Gomori technique; because the technique may not have been adequate we are reluctant to consider these negative findings as yet

being conclusive proof that the structures are not lysosomes.

Lipid spherules, such as those seen in the absorptive cells of the small gut, would resemble the units described above in size and shape. However, their intravesicular material is homogeneous and no evidence exists for unusual lipid metabolic activity in the cells of Hassall's corpuscles.

It is not possible that the appearances we have described are Golgi vesicles. All Hassall's corpuscle cells (except the central effete ones) contain a clearly identifiable Golgi complex. The small secretion units are spatially related to the Golgi complex and perfectly distinct from it.

Spheroidal elements of smooth endoplasmic reticulum comparable in dimensions to the units under discussion are commonly seen in hepatocytes and conceivably could be confused in other cell types for partially depleted (vacuolated) secretion units. The problem does not arise in this case since the cells of Hassall's corpuscles do not contain this organelle. A further fine-structural feature of Hassall's corpuscle organization is the presence of small intracellular and intercellular 'acini' bounded by microvillous cell surfaces. Such appearances are commonly observed in endocrine tissue neoplasms such as intestinal carcinoid tumours (Macadam, Hamilton, and Brown, 1970). In this study, Hassall's corpuscles have been consistently avascular units and a pericorpuscular tissue zone (at least 50 μm broad) was similarly devoid of vessels. In view of these features we suggest that the secretion(s) may exert a purely intrathymic regulatory function or be concerned in the transfer of material to lymphocytes.

We therefore consider that our results constitute evidence for possible hormone secretory activity by the epithelial cells of Hassall's corpuscles in the human thymus. The similarity of the structures which we have identified to those described in mouse thymus by Clark (1963) and generally accepted as endocrine secretion granules is further support for our hypothesis.

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Addendum

Since the paper was prepared, we have had the opportunity to examine additional material. These were four thymus glands from patients with myasthenia gravis and eight thymic biopsies obtained during operations to correct congenital heart lesions. All the specimens contained Hassall's corpuscles in which endocrine secretion granules were detectable. We believe that the hormone concerned is probably thymosin.

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