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Inclusions in the human thyroid

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During the course of an inquiry into perinatal thyroid discharge Sagreiya & Emery (1970) noted the presence of non-thyroid tissue within the thyroid capsule in about 1 in 15 of randomly selected sections. As only small samples of the gland were studied, it is likely that such inclusions are common, and perhaps exist in every thyroid.

There is a certain amount of information about thyroid inclusions in the literature. Thymic tissue is perhaps the best recognized: Gilmour (1937) found thymus, apparently derived from pharyngeal pouch IV (that is thymus IV), entirely within the thyroid capsule, and separate from parathyroid IV. He also noticed thymus IV in the thyroid taken from a 2 day old infant. He later described a further seven cases where thymus IV was enclosed within the thyroid; six of his cases were in children under three days and the seventh was in a 73 year old man (Gilmour, 1941). In no case did he find parathyroid IV within the thyroid.

The presence of striated muscle within the thyroid (and thyroid tissue in striated muscle) is also well recognized. Klink (1964) showed several examples of striated muscle mixed with thyroid follicles in infants. He suggested that there is a great deal of thyroid–muscle mixing in the infant but later the muscle disappears. Wöffler (1883) found muscle in the thyroid in one case and Zielinska (1864) reported eight further cases, in none of which was she able, in serial sections, to trace the muscle beyond the thyroid capsule. Gardner (1956), in four out of fourteen infants in which the thyroid was examined in sections taken at intervals of 0·2 cm, found infiltration of thyroid gland into cervical skeletal muscle.

The presence of squamous epithelium in the thyroid has also been described (Goldberg & Harvey, 1956; Harcourt-Webster, 1966). In most instances, the squamous epithelium lined an intra-thyroid cyst and the squamous epithelium itself was not in direct contact with recognizable thyroid epithelium. The suggestion has been made that such cysts are remnants of the ultimobranchial bodies. In two of Harcourt-Webster's cases the squamous epithelium was not associated with a cyst, but in all four of his cases there was chronic inflammation and fibrosis. He concluded that the squamous epithelium arose by metaplasia of thyroid epithelium.

Cartilage within the thyroid has been recorded by Finkle & Goldman (1973), who described two instances in old people with goitres, and by Weitzner & Appenzeller (1973) who found the tissue in an otherwise normal thyroid in an 81 year old man. Respiratory epithelium and cartilage are well recognized components of teratomas which sometimes occur in the thyroid in the infant.

The present study was undertaken in an attempt to determine the incidence and kinds of inclusions within the thyroid gland of infants and children.

Table 1. *Number and types of inclusions seen in single random sections from the thyroids of* 350 *infants*

'Thyroid cell' rests	12
Parathyroid	11
Fat	11
Muscle	10
Thymus	9
Cartilage	3
Ciliated epithelium	1
Epithelial cyst	1
Granular metaplasia	1

Table 2. *The age distribution of children whose single random thyroid sections showed the presence of inclusions, compared with those who did not show such inclusions*

Age	Control	Inclusion
Stillborn	29 (10 %)	2 (4 %)
< 1 week	72 (24 %)	10 (20 %)
1 week–1 month	36 (12 %)	8 (16 %)
1–6 months	91 (30 %)	15 (30 %)
6 months–1 year	21 (7 %)	3 (6 %)
1–3 years	20 (7 %)	5 (10 %)
3–6 years	17 (6 %)	5 (10 %)
6–10 years	11 (4 %)	3 (6 %)
10 years+	2 (1 %)	—
Total	299	51

MATERIAL AND METHODS

Sections of the thyroid gland were drawn from the files of the Pathology Department at the Sheffield Children's Hospital. A total of 350 thyroid glands was studied in the initial series, consisting of routine sections taken from three separate series of sequential necropsies. The routine sections were taken across the whole gland, incorporating both lobes and the isthmus, and they were stained with Masson's trichrome.

A final series of thyroids was taken from ten consecutive necropsies and serial sections were cut through these. Each twentieth section was examined and any inclusion within the capsule of the thyroid gland noted. The age at death and the cause of death in each case were documented. In certain selected glands, further staining techniques, which will be mentioned later, were employed.

RESULTS

Of the single sections taken from each of the 350 glands of the initial series, 51 were found to contain an inclusion of some sort and 8 contained more than one inclusion, a total of 59 inclusions being seen (Table 1).

The age distributions of children dying with, and without, inclusions were similar; the other 299 glands act as controls (Table 2). 10 % of the controls were stillborn as

Table 3. *Showing the main disease associations of children whose thyroids showed inclusions, and of children whose thyroids were without inclusions*

Cause of death	Control	Inclusion
Perinatal	46 (15 %)	5 (10 %)
Congenital anomaly	109 (36 %)	16 (32 %)
'Cot death'	69 (23 %)	10 (20 %)
Tumour	18 (6 %)	3 (6 %)
Others	57 (19 %)	17 (34 %)
Total	299	51

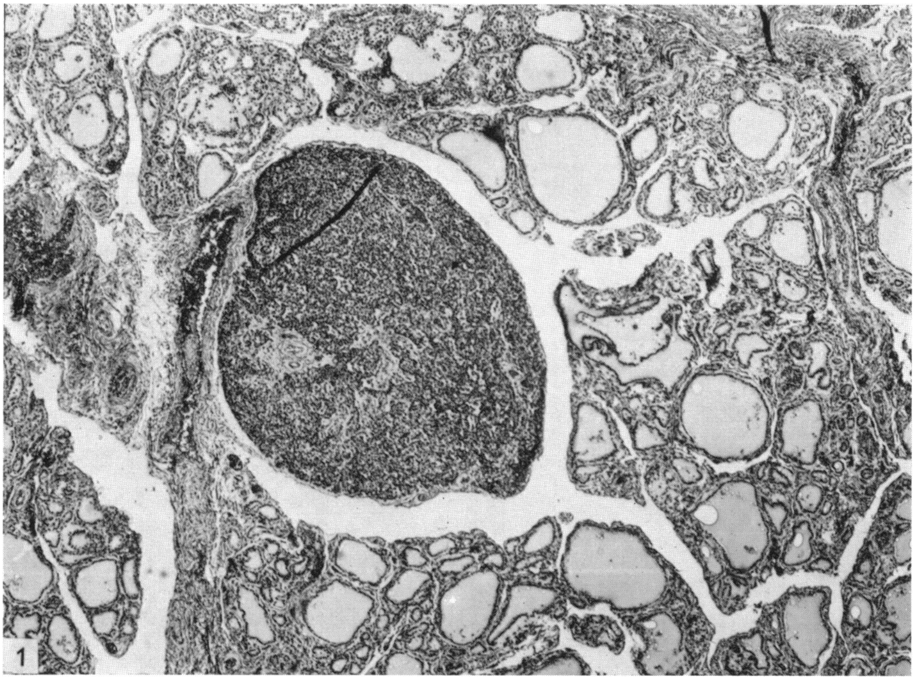

Fig. 1. Photograph of a mass of parathyroid tissue situated within the thyroid in a child dying at 10 weeks. This child had 17–18 trisomy. Masson's. × 50.

compared with 4 % of the 'inclusion' group; 66 % of both the control and inclusion groups were under 6 months at the time of death.

As the presence of a congenital anomaly in one organ tends to be associated with anomalies in others, the incidence of congenital abnormalities was investigated. It was found to be similar in the two groups (Table 3). The incidence of neoplasms was also similar in the control and inclusion groups.

A description of the inclusions now follows:

Brown fat and fat. Fat inclusions were found in eleven cases. In one or two cases actual pannicles of fat were seen, but mostly there were scattered fat cells along fibrous septa, similar to that seen in other organs, the thymus in particular.

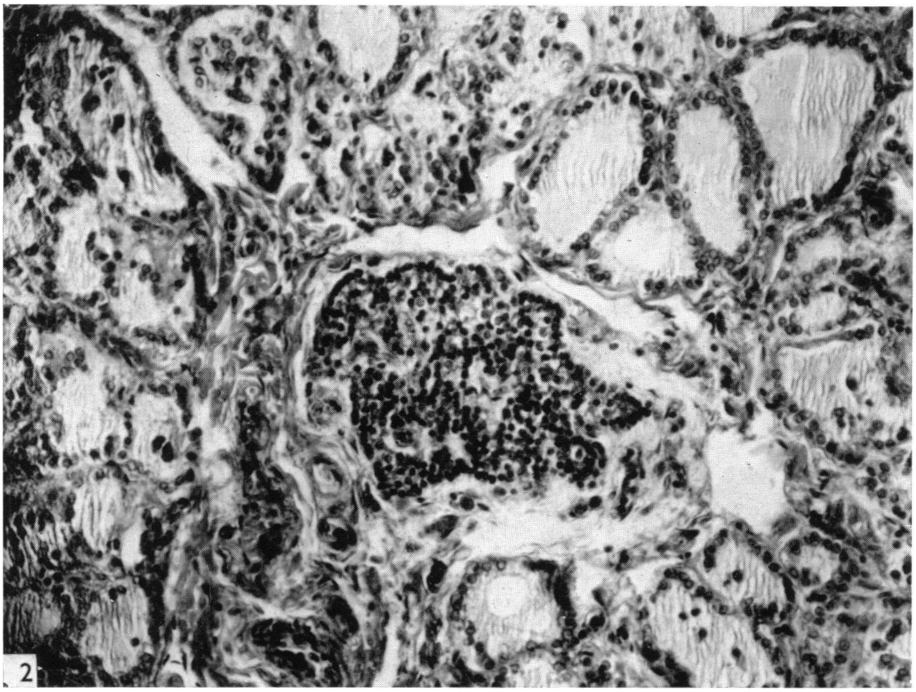

Fig. 2. A small mass of parathyroid tissue in a child, a 'cot death' of 4 weeks. Note the prominent local blood vessels like those in Fig. 1. Masson's. ×220.

Parathyroid. Parathyroid tissue was found in eleven thyroid glands. Usually this was just under the capsule, but in some cases the parathyroid tissue was deep within the thyroid. Serial sections showed that such parathyroid tissue was discrete and not part of a 'collar-stud' gland, i.e. it was not continuous with parathyroid tissue outside the thyroid capsule. The deeper parathyroid tissue was usually connected to the capsule by dense connective tissue (Figs. 1, 2).

Muscle. Muscle fibres were found in 10 of the thyroids, usually at the periphery of the gland. The fibres seemed to terminate within the gland. The fibres showed no signs of degeneration or other abnormality (Fig. 3).

Thymus. Thymus was found in 9 glands, its extent varying from a small area of thymic tissue containing one or two Hassall's bodies, to complete well differentiated glands deep within the thyroid tissue. The reactivity of the thymus was similar to that of the main thymus in the same child (Figs. 4, 5).

Cartilage. Ectopic cartilage was found in the subcapsular part of the thyroid of three children, two of whom had died from 'cot death' and one from burns at the age of 10 years. The cartilage was not in the midline, nor was it related to the trachea (Fig. 6).

Epithelial metaplasia. In one case (a child dying at 36 hours with exomphalos) an epithelial cyst was found; and in another (a 6 weeks old cot death), a small area of ciliated epithelium presumably, bronchogenic, was recognized. In the latter case the ciliated epithelium seemed to be continuous with that of a thyroid follicle (Fig. 7).

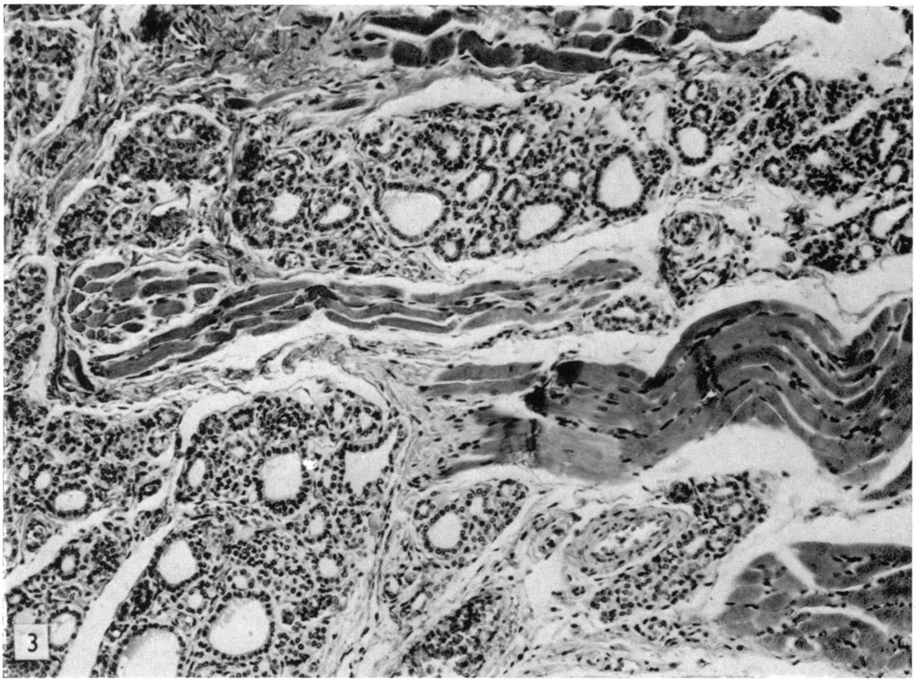

Fig. 3. Muscle fibres admixed with thyroid tissue in a 'term' child dying at 2 days with a gross heart deformity. H. and E. × 125.

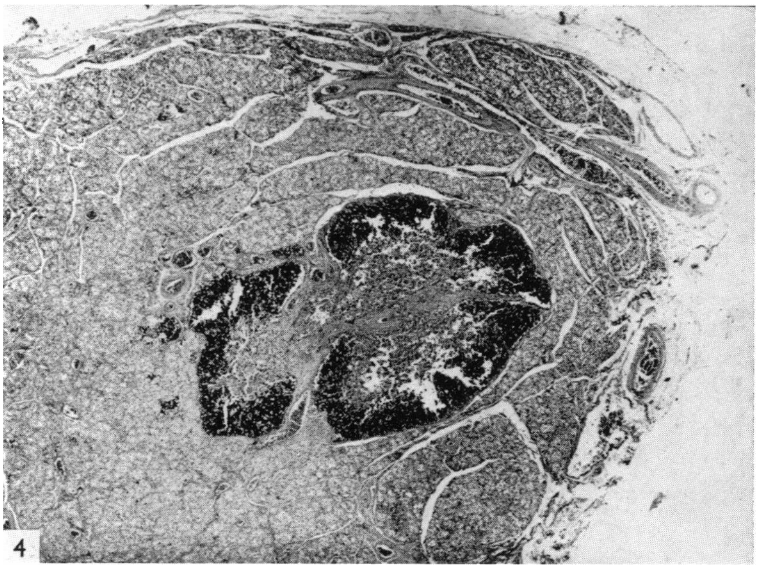

Fig. 4. A large, discrete mass of thymus tissue situated with the thyroid of an infant. H. and E. × 11.

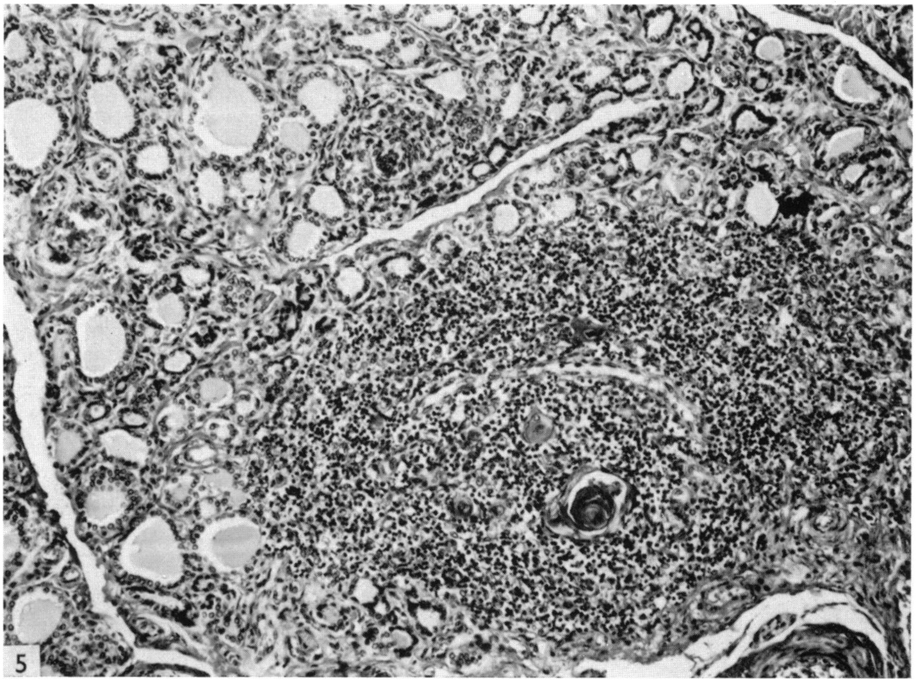

Fig. 5. A small fragment of thymic tissue, diffusely admixed with thyroid follicles, in a 3 week old child. Masson's. ×125.

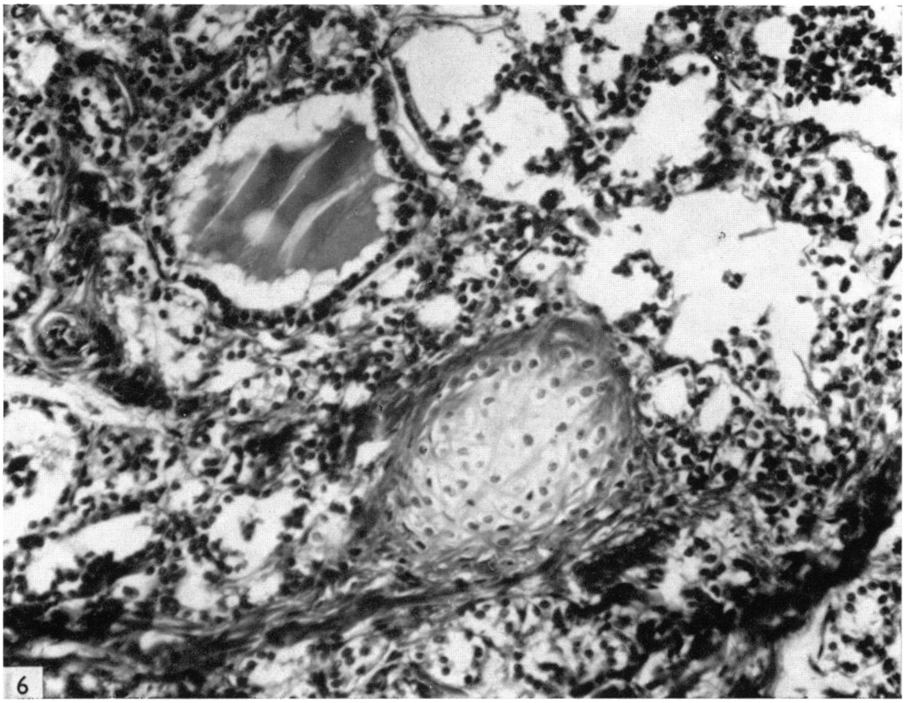

Fig. 6. A small isolated fragment of well differentiated cartilage lying peripherally in the thyroid. Masson's. ×250.

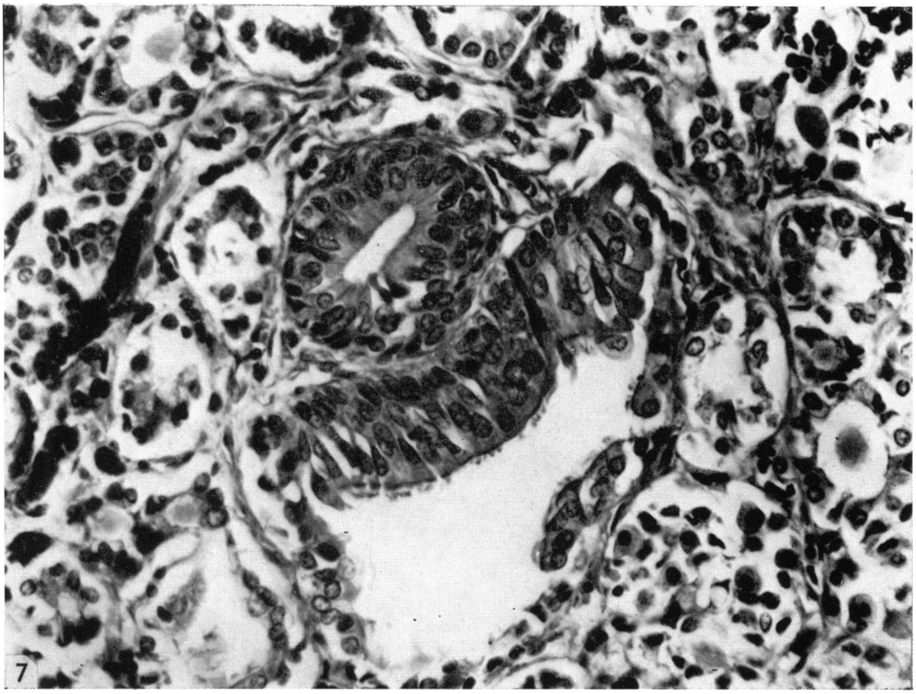

Fig. 7. A small mass of 'trachea-like' ciliated epithelium apparently continuous with normal thyroid epithelium within a follicle. Masson's. ×400.

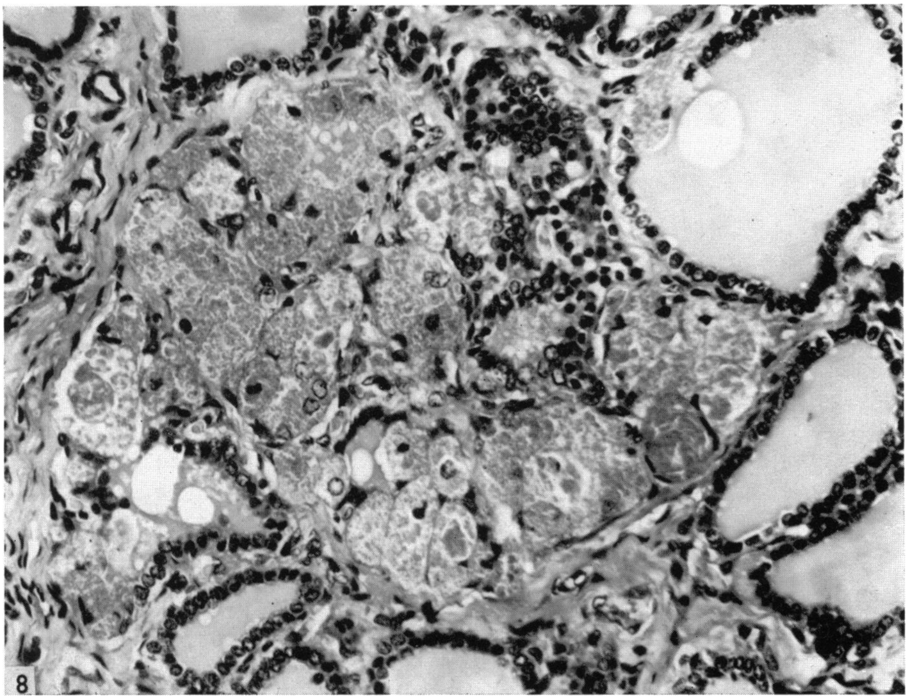

Fig. 8. An area where the normal follicular cells have been replaced by cells of coarse, granular appearance, with no associated colloid. Note how the change is present in isolated cells in some of the follicles. Masson's. ×350.

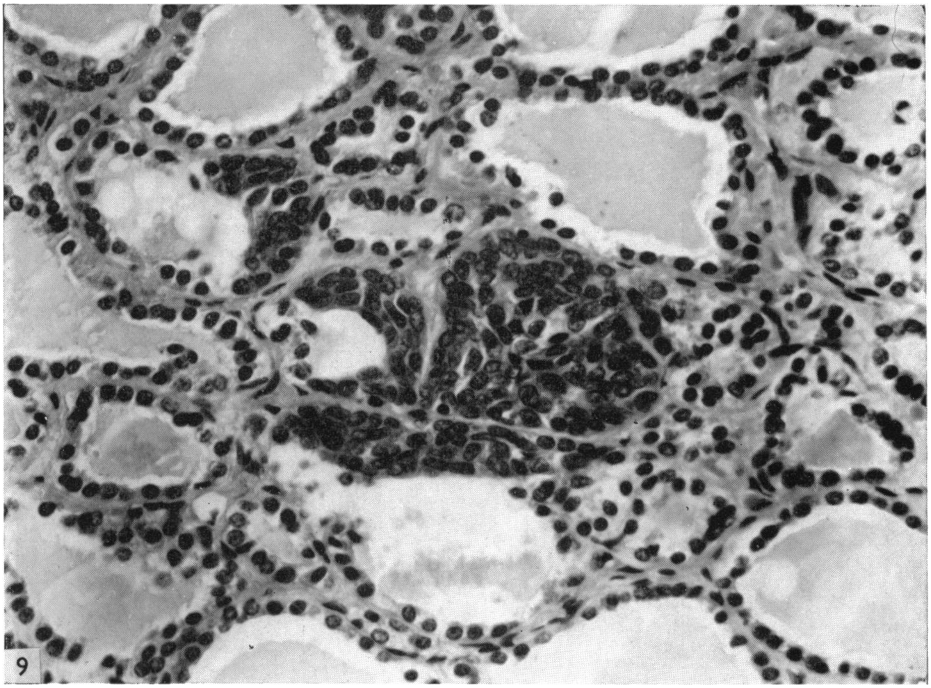

Fig. 9. Showing dense masses of cells, some of which seem to be continuous with the epithelial cells of the follicles. Masson's. × 300.

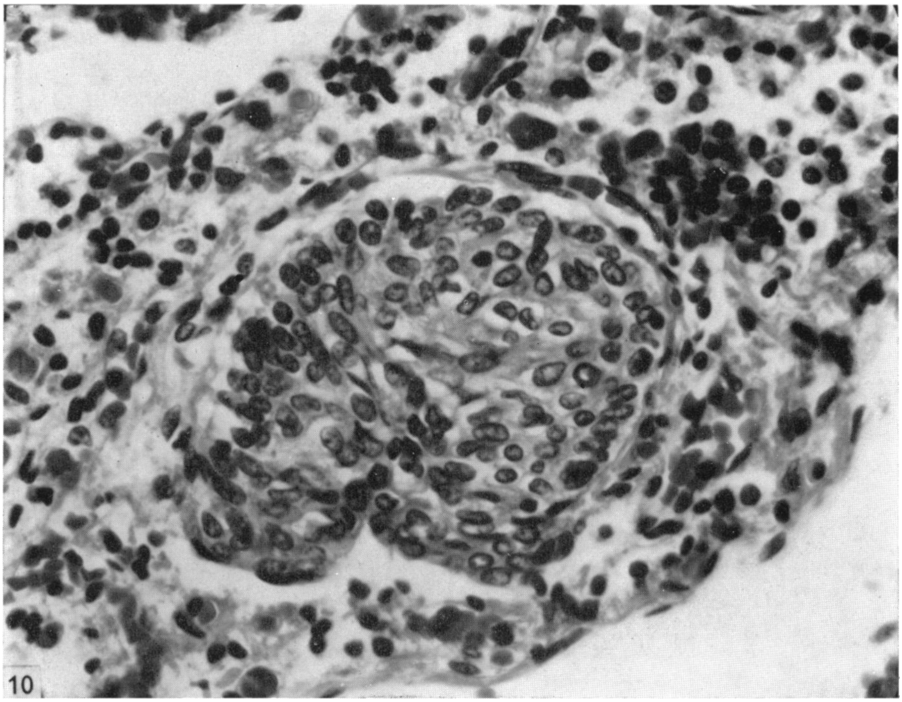

Fig. 10. An isolated, dense mass of cells forming a nodule surrounded by capillaries lying deep within a newborn thyroid. Masson's. × 300.

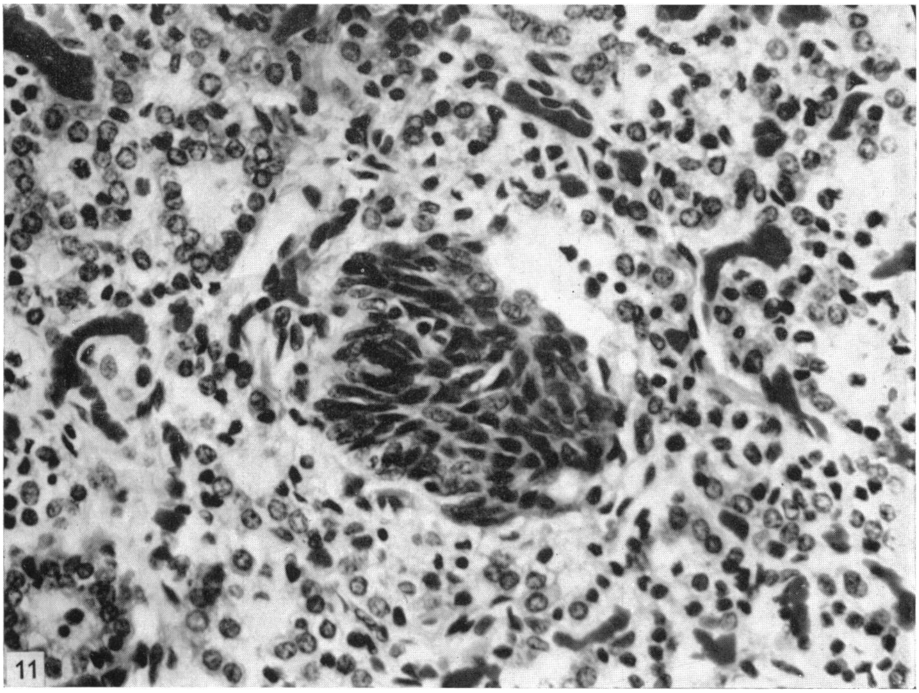

Fig. 11. A dense mass of cells having a variety of forms, lying among the thyroid follicles. Masson's. ×250.

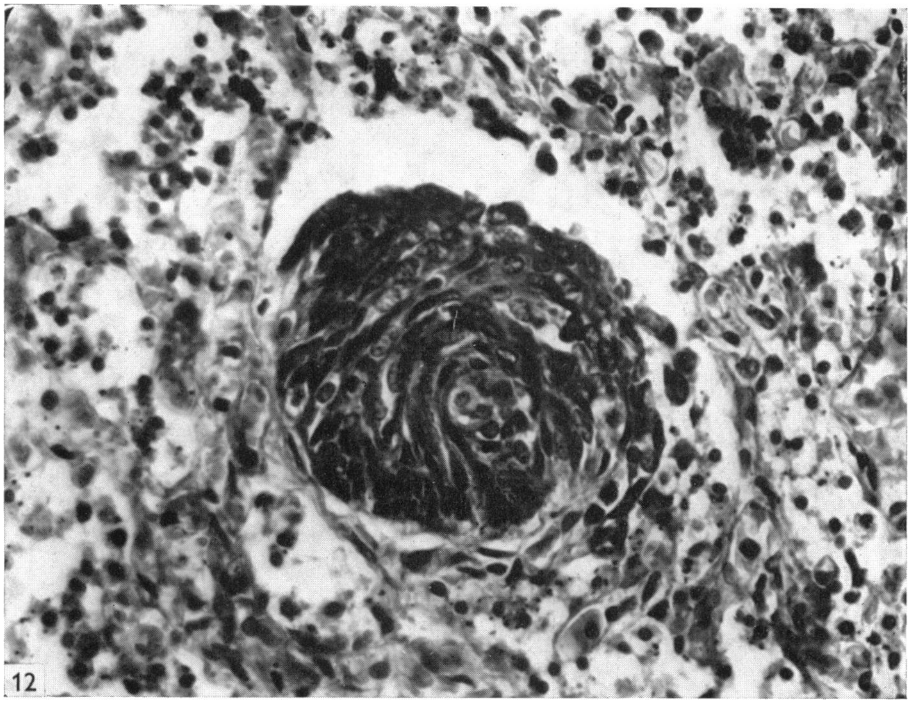

Fig. 12. A dense mass of cells of varying shapes but forming a dense epithelial-like whirl in a newborn child. Masson's. ×250.

Table 4. *Inclusions present in a series of step sections from a series of* 10 *infant thyroids*

Age	Cause of death	Inclusions						
7 weeks	Fibro-elastosis	Parathyroid	Thymus	—	—	—	—	—
2 days	Meningomyelocele	Parathyroid	—	Cartilage	—	—	—	—
6 years	Asthma	Parathyroid	—	—	Fat	—	—	—
2 years 9 months	Congenital heart disease	Parathyroid	Thymus	—	Fat	Thyroid cell rest	—	—
11 days	Mongol	Parathyroid	Thymus	—	—	—	—	—
6 months	Tracheobronchitis	—	Thymus	—	—	Thyroid cell rest	Muscle	—
6 months	Gastro-enteritis	—	—	—	—	Thyroid cell rest	—	—
2 months	'Cot death'	Parathyroid	Thymus	—	—	—	Muscle	Granular metaplasia
6 years	Bronchitis	—	—	—	Fat	—	Muscle	—
7 months	Encephalitis	Parathyroid	Thymus	—	—	Thyroid cell rest	—	—
	Total	7	6	1	3	4	3	1

Granular metaplasia. In a 12 day old child, who died with a meningomyelocele, we found an area in the thyroid in which these granular foamy cells replaced the normal follicular cells. These cells were continuous with the follicular cells and, at one point, they themselves formed a complete follicle or tubule. These strange cells did not stain positively with PAS or Sudan black (Fig. 8).

'*Cell rests.*' In 12 glands we found inclusions which at first were thought to be 'epithelial rests'. They were discrete masses of cells 100–150 μm in diameter, lying deeply within the thyroid. The cells were either elliptical (Figs. 9, 10), or spindle-shaped (Fig. 11) and some were arranged in 'whorls' (Fig. 12). These structures do not appear to have been described before: they were present in 3 % of the sections examined.

Like the others, these inclusions were not commoner in any particular age group and were not associated with any particular cause of death except that, of the 3 children in the series of 350 who died from progressive cerebral degeneration (Tay–Sach's disease), 2 had these inclusions in their thyroid glands.

It has been suggested to us that the cells in these tests could be calcitonin-secreting 'C' cells. Using Bodian's Protargol and hydrolysed Azure A dyes, we failed to confirm this, but as these histological techniques require fresh material and the sections studied in this series, unfortunately, were rather old, the negative result is obviously inconclusive. This line of investigation is therefore still being pursued.

Results of serial sections

The findings in the series of 10 thyroid glands submitted to 'step' sectioning are summarized in Table 4. Each gland contained at least one inclusion. Seven contained parathyroid, 6 thymus, 4 'thyroid cell rests', 3 fat, 3 muscle, 1 cartilage and 1 a focus of granular metaplasia.

DISCUSSION

It would seem likely that these inclusions found within the thyroid fall into different categories. The presence of brown fat pannicles in thyroid connective tissue is not particularly significant: identical inclusions are seen in the thymus.

The presence of striated muscle fibres in the thyroid may simply indicate a slight derangement in the gross organization of the tissues of the neck. Isolated striated muscle fibres are also found in the medulla of the thymus, where they are probably a normal constituent, and also may be involved in the aetiology of myasthenia gravis. This raises the question of the possibility of inclusions of muscle fibres in the thyroid being associated in some way with the myopathies which often accompany hyper- and hypo-functioning of the gland.

The presence in the thyroid of thymic and parathyroid tissue, originating in the third and fourth branchial pouches can be interpreted in two ways: it could be related to the idea that the thyroid itself partly originates from these branchial pouches, or it could mean that these parts of the thymus become permanently attached to the thyroid during the descent of the thymus into the thorax.

Inclusions of cartilage and ciliated epithelium can also be explained on an embryological basis: both these tissues are constituents of the upper respiratory tract which, like the thyroid, develops from the primitive pharynx. However, the ciliated epithelium could result from metaplasia of the cells of the thyroid follicles. The granular follicular cells are not characteristic of any stage through which the thyroid passes in its development. These cells are rather like those often seen in cases of thyroid adenoma, called 'Hürthle cells'.

The dark cells aggregated in such distinctive masses differ from all the other inclusions described here. The cells differ from ordinary follicle cells and can easily be distinguished from the cells that form the follicular plates that precede the formation of colloid. Such plates of cells can be found in almost all thyroids in neonates, and in many instances are prominent just beneath the capsule. These cell masses give the impression of being definite structures in their own right: they could well have some endocrine function. The suggestion that they represent the calcitonin-producing cells in the infant is an intriguing one which, at the moment, we are unable to confirm or refute. We were unable to stain these cells histochemically for C-cells because only previously fixed tissues were available. We were, however, unable to identify any other calcitonin-producing cells in the infant thyroid. These cell masses of 100–150 μm diameter were found in four of the serially sectioned glands that were examined. If they are calcitonin producing 'organs' they should have been present in every gland. However, because we only looked at 1 in 20 of the sections taken, it is possible that they were missed in the others. To confirm the presence or absence of these structures it looks as if it would be necessary to examine every serial section.

In our survey of thyroid glands in infancy, we have not included the large, branching, colloid follicle cysts as abnormalities. These are so common in infant thyroids that they must be regarded as a normal constituent of the gland at this age.

SUMMARY

A survey of the thyroids of 350 infants and children suggests that the presence of thymus and parathyroid tissue within the thyroid is so common as to be classified as normal. One in a hundred thyroids contains masses of cartilage, and one in a hundred shows small foci of ciliated epithelium. Compact masses of dark-staining cells that bear a resemblance to primitive follicular plate cells are also so common as to raise the possibility of their being a normal component with, possibly, an endocrine function. It has been suggested that they produce calcitonin, but this could not be confirmed. Peculiar granular cells replacing follicle cells were also noticed.

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