Perinatal Thyroid Discharge

A Histological Study of 1225 Infant Thyroids

K. SAGREIYA and J. L. EMERY

From the Department of Pathology, Children's Hospital, Sheffield

Sagreiya, K., and Emery, J. L. (1970). *Archives of Disease in Childhood*, **45**, 746. **Perinatal thyroid discharge: a histological study of 1225 infant thyroids.** A random sample of 500 infant thyroids in which post-mortem changes were, as far as possible, eliminated was studied histologically. In the great majority of neonatal thyroids there are distinct changes which suggest the occurrence of an acute 'perinatal thyroid discharge' probably due to over stimulation, and which are confined to the immediate perinatal period. These changes are characterized by (i) reduction and loss of colloid (often complete), (ii) vacuolation and detachment of cells, (iii) irregular and pyknotic nuclei, and (iv) the presence of nuclear knots. The thyroid changes are probably physiological and labour-related. The only clinical symptom found to be related to neonatal thyroid discharge was sclerema neonatorum, when there appeared to be an absence of thyroid reaction.

The histology of the thyroid of the young child is difficult to interpret as the gland so frequently shows changes of apparent cell death and degeneration simulating post-mortem autolysis. The 'degenerative' state of the thyroid even confuses the literature of its normal growth. In 1892, Biondi studied postnatal thyroids and described the thyroid follicle as discharging its contents after birth, collapsing, and then rearranging itself in the form of a number of small acini which, in turn, repeat the process.

Hesselberg (1910) described the normal structure of the thyroid as established from the 4th fetal month. He found desquamation of epithelial cells in about half of the children from the 7th to the 9th fetal month and the follicles almost entirely obliterated in the newborn. He noted degeneration of cells and loss of colloid around birth and thought that the epithelial desquamation was due to pressure on the thyroid during birth but that there was later regeneration. He also saw glands with collapsed follicles and very prominent blood vessels which he described as 'telangiectatioform'.

Norris (1916) described the thyroid as consisting mostly of small spherical follicles containing colloid by the 163 mm. stage. From this stage and up to the neonatal period the gland shows epithelial desquamation. Whether the process be physio-

logical or pathological was uncertain. He did not give details of postnatal thyroids.

Murray (1927) concluded that thyroids of the full-term fetus and newborn infants were composed of small follicles lined with cuboidal epithelium filled with colloid which stains well, and all variations from this are probably due to post-mortem degeneration.

Krinskaja (1932) examined 50 thyroids from newborn children and stressed that colloid was present quite regularly in infant thyroids, but he was unable to give an explanation for the different structural behaviour of the thyroid in early age. Sclare (1956) examined thyroids from 100 stillborn and liveborn infants. He concluded that the thyroid in the newborn bears little resemblance to the gland at other ages: the changes, resembling those of post-mortem autolysis, were considered to be a manifestation of hyperactivity; they bore no relation to the maturity of the child, sex, nature of labour, or cause of death, but were of decreasing frequency after the third day from birth. He suggested that the thyroid in late fetal life is in a state of heightened physiological activity and that a further powerful stimulus to activity often occurs at birth.

In 1961 Nicod described 180 thyroids from perinatal and stillborn children in Lausanne. He grouped his thyroids into four groups according to

the absence or presence of colloid and epithelial desquamation, and compared his findings with those of Murray (1927) and Sclare (1956). In the newborn, he found a decrease in the frequency of follicles containing colloid. Müller and Rämisch (1966) studied 63 thyroids from stillborn and newborn children noting colloid content, type of epithelium, desquamation, and hyperaemia. They took particular care to divide immature from mature births, but found no difference in the two groups. They confirmed the apparent overactivity of the thyroid around birth and thought that the stimulus after birth was 'cold stress'. The similar reaction in stillborns was more difficult to explain but they thought that it might be due to mistimed hormone stimulation from the mother.

We have become increasingly aware of the presence of large masses of conglomerate nuclei in thyroids of children dying after birth (Fig. 1), and of the presence in the thyroid epithelium of cells with

FIG. 1.—Thyroid from a 40-week child dying at 24 hours after caesarean section. The child's lung showed hyaline membrane. The mother was diabetic. The picture shows desquamation of cells, absence of colloid, and presence of nuclear aggregates. Note also the variation in size of the nuclei due principally to shrinkage and pyknosis ($\times 470$).

large irregular nuclei not unlike the cells that occur in adrenals after birth. The present study was carried out with four objectives. To attempt to eliminate the confusion of the post-mortem change; to trace the origin of the conglomerate nuclear masses; to determine the presence or absence of evidence of over-stimulation of the thyroid around birth; and while doing so, to survey enough thyroids to enable us to relate the findings to birth and to maturity.

Material and Methods

The materials used were the sections and record files of the Department of Pathology of the Sheffield Children's Hospital. Sections of thyroid were taken in a non-planned manner from the files and were examined deliberately for any signs of post-mortem change. Particular note was taken of the non-thyroid tissues, the red cells in the vessels, and the vascular endothelium. If obvious post-mortem changes were present involving the non-thyroid tissues of the section, the latter was immediately discarded. If the non-thyroid tissue showed no changes and possible changes were present in the thyroid cells, the sections of the pancreas and trachea of the same case were viewed and if these showed post-mortem changes, the thyroid was discarded. This involved discarding approximately 60% of cases. By this means, sections of 500 children's thyroids were selected with no reference to the ages of the children or the necropsy protocol, and in which post-mortem changes were eliminated as far as possible.

The sections were then surveyed and a series of measurements and observations made including size of follicles, amount of colloid, consistency of colloid, form and staining properties of the epithelial cells, type and changes in nuclei, detachment and degeneration of epithelial cells, degrees of vascularity, proportion of connective tissue, and state of the lymphatics. Only after this was recorded on a proforma were the case records scrutinized for age, maturity, and other data. This was then added and the data collated. While each thyroid showed minor variability of structure they were classified on their predominant picture.

The age and maturity of the thyroids studied are shown in the Table.

TABLE

Age at Death and Gestational Age at Birth of Material Studied

Age at Death	Total	Gestation at Birth (wk.)				
		→30	31-35	36-40	41 +	Uncertain
Stillbirths ..	21	2	6	6	2	5
→24 hr. ..	72	18	16	31	2	5
25-48 hr. ..	44	—	8	23	5	8
49 hr.-5 dy. ..	37	1	6	18	2	10
6-10 dy. ..	34	1	5	22	2	4
11-28 dy. ..	62	1	2	37	5	17
2-3 mth. ..	90	—	6	46	7	31
4-6 mth. ..	48	—	3	21	1	23
7-12 mth. ..	22	—	—	9	—	13
13 mth.-5 yr. ..	40	—	1	7	5	27
6-17 yr. ..	30	—	—	5	—	25
Total 500						

Results

The variety of histological patterns found are illustrated in Fig. 1-7 and the incidence of each is discussed in turn.

Colloid content. The proportion of thyroid, showing absence of colloid plentiful colloid, and intermediate quantities is indicated in Fig. 8 where the findings are related to postnatal age. Colloid was absent in 43% of the thyroids of stillborns, in 21% of children dying within 24 hours of birth, in 6% of those dying by the age of 10 days, while no thyroid with absent colloid was seen over the age of 3 months. On the other hand, all thyroids seen over the age of 7 months contained ample colloid. 14% only of stillborn thyroids showed uniform colloid-filled follicles, 33% by 24 hours and 55% by 10 days. There thus seems to be a rapid and progressive filling of the thyroid with colloid immediately after the neonatal period.

It must be remembered that we are not considering the size of the follicles but simply the presence of stainable colloid. For example, the size of the follicle in thyroids illustrated in Fig. 2 is not grossly different from that in Fig. 3. Those in Fig. 2 have their cells firmly attached to the basement membrane with a central colloid mass, while in Fig. 3 most of the cells appear to be floating free in a thin, watery fluid.

In about an equal number of stillborns and 45% of thyroids from children dying within 2 hours of births, traces of colloid can be seen. There appears to be loss of stainable colloid from the follicles though acini do not usually completely collapse. When stained with PAS, the acini show an apparent progressive loss of staining material. In the discharged follicles there are minute fragments of PAS-staining material between the detached cells.

FIG. 2.—Thyroid from a 40-week child with hydrocephalus, dying at 3 days. The follicles are round, lined by cuboid epithelium which is intact, and containing plenty of uniform colloid. ($\times 110$.)

FIG. 3.—Thyroid from a 34-week child dying at 5 days with intestinal obstruction. There is general detachment and desquamation of epithelial cells. No colloid is present. ($\times 200$.)

Vacuolation and detachment of cells. The occurrence of vacuolation of the cells and their detachment seems to bear a direct relation to the amount of staining colloid.

The vacuolation first becomes apparent in the area between the nucleus and the basement membrane and does not appear to affect all follicles uniformly (see Fig. 4). The vacuolation is related to a general swelling of the cell including the nuclei until the cell leaves the basement membrane.

FIG. 4.—Thyroid from a 31-week stillborn. The mother had hypertension. The picture shows two follicles with intact epithelium, others show detachment and desquamation. Little colloid is present. Note also the irregularity in size of the nuclei in the follicles with detachment. ($\times 417$.)

When that occurs the cytoplasm seems to fragment and the nucleus becomes pyknotic.

The incidence of cell vacuolation and detachment is indicated in Fig. 9 where it is seen that over 60% of stillborns show this feature, and between 20% and 30% of infants up to 3 days, after which age the

incidence falls to around 5%, to disappear completely over the age of 4 months.

Nuclear knots. As mentioned earlier, it was the presence of these irregular masses of haemotophilic material in the follicles and sometimes

(a)

(b)

FIG. 5.—Nuclear knots. (a) Thyroid from a child dying at 8 weeks. The child was born at 31 weeks' gestation, had a congenital intestinal obstruction, and died after operation. The thyroid shows some groups of vesicles with complete detachment of epithelium but in addition, large, dark masses of nuclei that appear to be total conglomeration of the nuclei of vesicles that have lost most of their fluid content. ($\times 560$.) (b) A higher power view of smaller groups of nuclear aggregates. The larger groups appear to be almost a chain of nuclei. ($\times 1263$.) This thyroid was from a term child, a forceps delivery, dying at 36 hours with gross intracranial haemorrhage.

apparently between follicles of neonatal thyroids that stimulated this survey (Fig. 1). The incidence of these structures is shown in Fig. 10. The knots are found in about 35% of stillborns and remain at this incidence until the third day. By day 6, and during the next 3 months, they can be found in about 15% of thyroids, but are not usually seen over the age of 4 months.

There is little doubt but that these masses are aggregates of thyroid cell nuclei. Their staining properties are those of nuclei and it is easy to trace a whole series of structures from a couple of shed cells that have apparently lost their cytoplasm, to large masses of 20 or more fused nuclei (see Fig. 5a and 5b). The apparent interstitial aggregations appear to be the end result of completely collapsed follicles.

Types of epithelium. The predominant appearance of the epithelium was fairly easily divisible into three types; the most common type in which the cells appear to be almost square in section (*cuboid*); those in which the cells are less tall than their basement membrane surface (*flattened*); and those where the cells are tall (*columnal*). Cuboid cells are to be seen in Fig. 2, and two glands are also shown with different degrees of columnal type cells, one from a child dying at 24 hours (Fig. 6) where some colloid is present, and the other from a child dying at 3 weeks (Fig. 7).

When the incidence of these different types of epithelium was plotted relative to postnatal age, a

FIG. 6.—Thyroid from a child born at 30 weeks' gestation (a breech delivery), and dying at 24 hours with hyaline membrane in lungs. The gland shows well-formed follicles lined by columnal epithelium containing colloid. Colloid shows vacuolation. A picture of mild hyperplasia. ($\times 240$.)

FIG. 7.—Thyroid from a child born at 36 weeks' gestation and dying 3 weeks later with hydrocephalus and multiple congenital abnormalities. The picture shows irregular follicles, lined by tall columnal epithelium and completely devoid of colloid. A picture of active hyperplasia. ($\times 116$.)

rather striking picture emerged (Fig. 11). The columnal type epithelium was not seen in stillborns but was seen in up to 5% of glands from 24 hours after birth to 2 months. At this time, no glands with flattened type epithelium was seen but, from 3 months onwards, flattened epithelium was seen with increasing frequency. Cuboid type epithelium predominated in 70% of the glands in the stillborns and up to 2 days, and appeared to diminish progressively in the older children as they more and more approached the adult picture.

Vascularity. The blood vessels in the thyroid of stillborns and neonates are much more prominent than is seen in both older children and adults, and it is not uncommon for the neonatal thyroid to appear as a dark red structure. The thyroid showing the most intense vascularity is usually that which, at first sight, most resembles post-mortem change, in that the follicles usually show advanced vacuolation with detachment and there is loss of colloid. In addition, such glands usually show collapse of the follicles. Such glands were seen in 30% of stillborns, in 12% in the group up to 24 hours, in 2% at 2 days, but were not seen at all in older glands.

Relation of lesion to maturity at birth. The lesions listed above were charted in relation to gestational age as distinct from postnatal age, and no definite pattern of changes (Fig. 8, 9, 10, and 11) emerged. We were therefore forced to conclude

FIG. 8.—The proportion of thyroids examined which showed absent or plentiful colloid, related to age after birth.

FIG. 9.—The incidence of thyroids showing gross vacuolation and detachment of epithelium as in Fig. 3; and also thyroids showing no such changes. (Intermediate grades as Fig. 4 have not been charted.)

that the changes studied were related to birth, rather than directly to maturity.

Relation of lesion to causes of death. The causes of death were grouped into categories—gastro-intestinal disease, asphyxia, 'cot death', Gram-negative infections, Gram-positive infections, cerebral diseases, cerebral oedema, congenital deformities, sclerema, and hyaline membrane, etc. Of these disease categories, two only showed any

FIG. 10.—The incidence of nuclear knots in the thyroid related to postnatal age at death.

FIG. 11.—The proportion of thyroids showing columnar cell, cuboid, and flattened epithelium related to age.

pattern that might be of significance. One group included 'cot deaths' in which minimal changes were seen, but these children all died outside the neonatal period. A more significant group was children with sclerema neonatorum. Of 15 children with sclerema, none showed the presence of either a severe degree of cell vacuolation or of nuclear knots. These findings are more important as these children died at the age when vacuolation and nuclear knots are most prominent. After this we examined a further 24 thyroids from children dying with sclerema neonatorum and dying between 5 and 10 days after birth, and of these one only showed nuclear knots.

Discussion

If we accept that the changes that we have discussed are related to postnatal age and thus reflect some happening related to birth, then what significance, if any, do the changes have?

As has been mentioned above, the histological appearance of colloid depletion, cell vacuolation, and detachment in neonatal thyroids have been seen and described by a number of workers over the past 100 years (Biondi, 1892; Hesselberg, 1910; Norris, 1916; Murray, 1927; Sclaire, 1956; Nicod, 1961; Müller and Rämisch, 1966). Some consider it to be post-mortem autolysis, others have suggested that birth trauma may be a factor, but the majority feel that the changes are specific for the age and of some significance.

In this study we have made every attempt that we thought practical to eliminate changes due to post-mortem autolysis. We did this on histological criteria rather than time after death, for several reasons. First, that in many recent infants, with the use of resuscitative machinery the actual time of death is a little arbitrary. Second, that we were dealing with many stillborns in whom the moment of death is not known, and third, that we had no knowledge of the rapidity of the refrigeration of different infants—a factor that seems to be at least as great an influence on postnatal change as the number of hours after death.

The histological state of the thyroid in the neonate must be related to the physiological findings. The fetal thyroid starts trapping iodine about the 12th week of gestation. Studies on experimental animals and human fetal thyroids show that the capacity of the fetal thyroid to concentrate iodine increases as gestation progresses (Chapman *et al.*, 1948; Hodges *et al.*, 1955; Aboul-Khair *et al.*, 1966). Radioactive iodine is discharged more rapidly by the fetal thyroid than that of the adult, and this may be due to increased rate of thyroxine excretion. The values of uptake of ^{131}I in normal newborn infants are as high as in adults with hyperthyroidism.

Fisher and Oddie (1964) studied the thyroïdal hyperactivity in newborn infants during the first few hours of postnatal life. Serum hormone iodine values and tri-iodothyronine ^{131}I erythrocytic uptake increase significantly. This increase occurs in association with a high clearance rate of ^{131}I , suggesting that a neonatal thyroïdal hyperactivity is due to stimulation by the TSH during the early hours of postnatal life. Raud and Odell (1969), using radio-immuno-assay of human thyrotropin, found no difference in the serum concentration of TSH in men, women, and children over 1 year of age, the mean values being 4.4, 5.4, and 4.8 μ

unit/ml., respectively: in newborn infants, however, the value is 8.9 while in the corresponding mother's serum it is 4.3. Fisher *et al.* (1969) estimated the serum TSH levels in infants. Maternal TSH levels do not change during or after delivery, whereas in infants the concentration rises significantly within 10 minutes of birth and reaches a peak at 30 minutes, after which the level falls progressively over 48 hours. In response to this TSH, PBI concentrations rise progressively but at a slower rate during the 24 to 48 hours. Incubation of infants to between 37°C.–39°C. during the first 4 hours after birth fail to affect the release of TSH. However, if the infants are cooled to room temperature at 3–4 hours of age, the TSH concentration rises compared with that of infants maintained in incubators. Fisher and Oddie (1964) had previously shown that prevention of neonatal cooling minimized the usual marked postnatal increase in the PBI levels. They also showed no significant rise in PBI in steroid-treated infants.

In Fig. 12 we have combined the incidence of changes in the thyroid that are probably related to over stimulation and these are related to birth. There is a phase of intense vascularity lasting little more than 24 hours after birth; the absence, presumably due to complete discharge, of colloid follows a parallel course 24 hours later, and the disappearance of nuclear aggregates follows 4 to 5 days later. These histological findings have a direct relation to the TSH levels, PBI levels, and values for radio-active iodine uptake and discharge found by other workers. The question of dyshormono-

FIG. 12.—Features regarded as indicative of over-stimulation of the thyroid and related to birth—massive congestion, columnal epithelium, absent colloid, and, later, nuclear knots.

genesis also arises, the early fragmentation of the colloid is not unlike that described (Kennedy, 1969) as associated with iodoprotein defect, but other features are dissimilar.

Since these findings are most prevalent at birth and occur in stillborns, it seems impossible for them to be initiated by postnatal cold stress; they must be due to something related to labour.

The question that arises is whether or not the 'over stimulation' of the neonatal thyroid is a pathological state or whether it falls into the same category as the involution of the fetal adrenal cortex (X zone) which is almost certainly physiological. Within our series of cases, the 'stimulation' features with complete absence of colloid were seen in up to 45% of stillborns and in 25% of children dying at 24 hours (see Fig. 8). In stillborns, 14% only showed no colloid discharge, and in infants 33% did so by 24 hours. It must be remembered that in selecting our material we deliberately excluded any thyroids that showed any suspicion of post-mortem change. Thus, we must have retained the majority of thyroids that were non-reactive, but quite certainly discarded many with reactions that would be almost indistinguishable from post-mortem autolysis, and this applied particularly to the neonates.

To obtain our 500 thyroids, we surveyed 1,225 thyroids. It is not possible to give precise numbers for incidence, but it is certain that the actual incidence of the non-reactive glands (14% in stillborns and 33% in infants at 24 hours) is much lower, probably in the range of 5 and 10%. Sclare (1956) found 23 of 100 thyroids to be of his category 'A' which consisted of glands whose general appearance was similar to that seen in adults. His cases range from stillborn to 11 days. He noted no difference in incidence with the gestation age, but that at 3 to 11 days, type 'A' thyroids 'became predominant'. It will be obvious from our Fig. 8 how much the thyroid picture is related to the day of death, and there are no published data available to compare with our own.

Sclare found no disease relation in any of the thyroid changes he described. His series was small and for the purposes of case correlation, our own material of 500 thyroids is barely sufficient. The only neonatal disease that showed any possible significant association was sclerema neonatorum of which there were 15 cases in the series. None of these showed the presence of nuclear knots or cell vacuolation and detachment of severe degree. When we increased the number of thyroids from children with sclerema from our files to 39, we found one only with nuclear knots. The cause of sclerema

neonatorum is not known, but it is certainly related to intracellular fat. It is an obvious speculation that the condition be due to an absence of 'normal' thyroid neonatal discharge. The work of Jost and his colleagues indicates that the thyroid at this age is intimately related to fat metabolism (Jost and Picon, 1958; Geloso *et al.*, 1968). Before speculating further on this, a study of the thyroid function of children with sclerema is needed.

The columnal cell change in the acini appears to fall into a different category. This change is not seen in stillborns, it comes on after birth. The total range that we have seen it in is from 24 hours to 28 days and occurs in about 1 in 25 infants. These changes, if seen in older persons, would be interpreted as suggestive of thyrotoxicosis. They could be possible effects of LATS produced by the mother and acting on the child. It seems justifiable to check the thyroid state of the mothers of such children.

We feel that the perinatal thyroid discharge is probably a labour-related physiological state and forms a definable entity. Neonatal thyroids at necropsy can be assessed on fairly definite criteria and these can be related to time after birth. It will only be after this is done that we can attempt to relate neonatal diseases to thyroid histology. The features of perinatal thyroid discharge are (1) reduction and loss of colloid, (2) vacuolation and detachment of cells, (3) irregular and pyknotic nuclei, and (4) the presence of nuclear knots.

This study carries all the limitations inherent in a random post-mortem survey, but the recognition of nuclear knots and their implications confirms that there is a definite thyroid picture which we think best described as 'perinatal thyroid discharge'.

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Correspondence to Dr. J. L. Emery, Department of Pathology, The Children's Hospital, Western Bank, Sheffield 10.