

Thyroid status in the newborn infant

Effective thyroxine ratio and free thyroxine index

T. G. BRIEN, J. A. FAY, and E. A. GRIFFIN*

From the Radioisotope Department, St. Vincent's Hospital, Dublin

Brien, T. G., Fay, J. A., and Griffin, E. A. (1974). *Archives of Disease in Childhood*, 49, 225. **Thyroid status in the newborn infant: effective thyroxine ratio and free thyroxine index.** The effective thyroxine ratio (ETR) was determined in 28 term and 17 premature infants at birth and in 17 infants aged 0 to 6 weeks. The mean values found were significantly higher than those in 20 adult euthyroid controls. Serum thyroxine (T_4), T_3 resin uptake ratio (T_3 RUR), free thyroxine index (FTI), and ETR were determined in 14 term infants at birth. It was concluded that the raised T_4 was partly due to an increase in thyroxine binding globulin but that there was also a degree of true thyroid hyperactivity. Serum thyroxine alone was not considered a suitable index of thyroid function in infants and the free thyroxine index or the effective thyroxine ratio was preferred instead.

The diagnosis of hypothyroidism in the newborn is a matter of some clinical importance since treatment is simple and the consequences of delay so severe (Lancet, 1971).

The measurement of serum thyroxine (T_4) and the T_3 resin uptake ratio test (T_3 RUR) are now used extensively in the diagnosis of thyroid disease in the adult but relatively few studies have been undertaken in newborn children (O'Halloran and Webster, 1972; Murray, Joasoo, and Parkin, 1971). Combination of the T_4 and T_3 RUR tests to produce a free thyroxine index (FTI) has been shown to improve diagnostic accuracy (Howorth and Ward, 1972), and the FTI has been shown to be directly related to the measured concentration of free or metabolically available thyroxine (Stein and Price, 1972).

Recently a new test of thyroid function, the effective thyroxine ratio (ETR), has been introduced (Mincey, Thorson, and Brown, 1971; Mincey *et al.*, 1972). The basis of this test is that serum thyroxine is estimated in the presence of thyroxine binding proteins from the same serum and is expressed as a ratio of serum thyroxine similarly determined in normal serum. This compensates for variations in T_4 due to differences in the thyroxine binding protein content of serum. The ETR has been

shown to have a diagnostic accuracy similar to the FTI (Toft *et al.*, 1973) and to be related to the free thyroxine content of serum (Mincey *et al.*, 1972). Since it is a single laboratory procedure and somewhat easier to carry out than the combined T_4 and T_3 RUR tests, we thought it worth while to investigate the ETR levels in newborn infants and to establish normal values for this test in infancy, as adult normal values have already been established (Mincey *et al.*, 1972).

Materials and methods

Cord blood samples were obtained from infants delivered at the Coombe Hospital, Dublin. The blood samples were allowed to clot and the serum separated and stored at -20°C until assayed. Infants were regarded as premature if they were born 14 days or more before the expected date of delivery, otherwise they were categorized as term. The average date of delivery of the premature infants was 25 days before term and their average weight was 2.73 kg. There were 28 infants in the term group and 17 in the premature. Blood samples were also obtained from 17 children either in the immediate postnatal period or while attending a follow-up clinic at 6 weeks when blood was being sampled for other purposes. In addition, 20 euthyroid adults were measured for comparison.

ETR, T_4 , and T_3 RUR were measured using commercially available kits.* FTI was calculated as T_4/T_3 RUR. Normal values for ETR by this method

Received 12 September 1973.

*Present address: Paediatric Department, Coombe Hospital, Dublin.

*Res-o-Mat, Mallinckrodt Chemical Works, St. Louis, Mo., U.S.A.

are given as 0.86–1.13 for adults, and this range has been confirmed in our laboratory. Normal T_4 values are 5.0–13.7 $\mu\text{g}/100\text{ ml}$ and normal T_3 RUR values 0.87–1.13, hypothyroid values being >1.13 and hyperthyroid values <0.87 .

Statistical comparisons were carried out using Student's 't' test.

Results

Results are shown in the Table and Fig. ETR values for term infants were not significantly different from those in the premature group, but were significantly higher than those in the adult group and significantly lower than those in the 0 to 6 week group ($P < 0.001$ in each case). Similar results were found for the premature group. The 0 to 6 week group was significantly higher than each other category ($P < 0.001$).

Despite these differences between means, only

TABLE

Effective thyroxine ratio values on cord bloods from term and premature infants, and peripheral blood samples from children aged 0 to 6 weeks and euthyroid adults

	Mean \pm SD	Number	Range
Term	1.015 \pm 0.056	28	0.90–1.22
Premature	1.019 \pm 0.049	17	0.92–1.11
0 to 6 weeks	1.086 \pm 0.068	17	0.98–1.20
Adults	0.956 \pm 0.066	20	0.86–1.13

one of the term group and none of the premature group had ETR values outside the normal adult range. However, 6 out of 17 of the 0 to 6 week group had values greater than the upper adult normal limit.

In the Fig. T_3 RUR, T_4 , FTI, and ETR values are shown for cord blood samples from 14 term infants. While again most values lie within the adult normal range, the T_3 RUR values are inclined towards the upper or hypothyroid limit and the T_4 values towards the hyperthyroid limit. Both FTI and ETR values are grouped more closely around the normal mean, the FTI values showing a somewhat greater spread than the ETR.

Discussion

The effective thyroxine ratio is a single-step laboratory procedure which provides a measure of the metabolically-available thyroxine in the circulating blood and which has a high diagnostic accuracy in clinical situations. In the present study we have shown a raised ETR at birth that rises further in the immediate postnatal period. This confirms the findings of O'Halloran and Webster (1972) who found FTI levels raised at birth, rising even higher during the next 14 days, and returning to the (raised) birth level only after 3 months.

Similar results were found by Ryness (1972) who found raised T_4 values at birth, rising in the immediate postnatal period and declining thereafter throughout childhood and adolescence. Chadd,

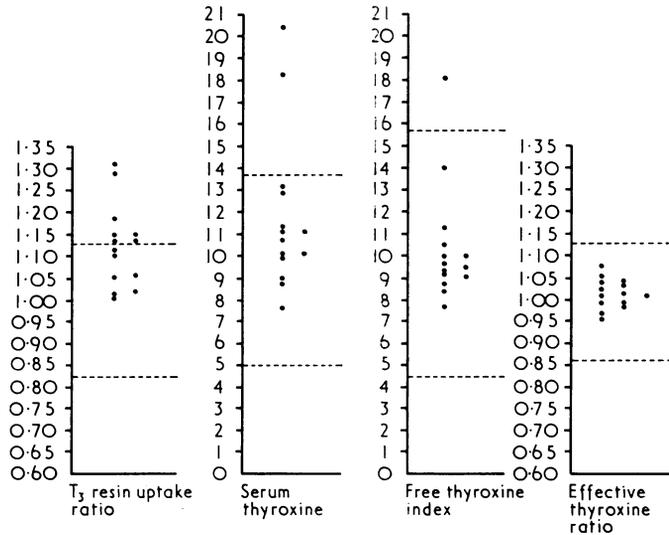


FIG.— T_3 resin uptake ratio, serum thyroxine, free thyroxine index, and effective thyroxine ratio values in 14 cord blood samples from term infants. Broken lines show normal adult ranges.

Gray, and Davies (1970) estimated protein-bound iodine and T_3 uptake at birth and at 8 days in term and premature infants and found raised values of protein-bound iodine at birth, rising even further on the eighth day. T_3 uptake was raised in the premature group at birth, but was otherwise normal.

It is evident, therefore, that total serum thyroxine is raised at birth and increases further over the next few weeks after which there is a gradual decline to adult values until adolescence. This decline has also been documented by Murray *et al.* (1971).

An increase in total thyroxine could normally be explained in either of two ways. There is an increase in free or unbound thyroxine due to thyroid hyperactivity or there is an increase in thyroxine binding globulin, as occurs in pregnancy, leading to an increase in the bound fraction alone.

The results of the present study, together with those of O'Halloran and Webster (1972), suggest that there is a true increase in free thyroxine at birth and during the postnatal period. Nevertheless, the T_3 resin uptake results suggest that there is also an increase in serum binding proteins during this period so that the increase in total serum thyroxine is probably due to both mechanisms acting together.

This study was originally planned to establish a laboratory procedure for the diagnosis of neonatal hypothyroidism. It is now evident that the T_4 alone is not a wholly reliable indication of thyroid status for this purpose and that the FTI or ETR are best relied upon. While we are not yet in a position

to assign definite limits for these test values, we consider that values lying at the lower end of the normal adult range should be regarded with suspicion, e.g. below about 0.92 for the ETR and below about 6.0 for FTI.

REFERENCES

- Chadd, M. A., Gray, O. P., and Davies, D. F. (1970). Thyroid function tests in the newborn. *Archives of Disease in Childhood*, **45**, 374.
- Howorth, P. J. N., and Ward, R. L. (1972). The T_4 -free thyroxine index as a test of thyroid function of first choice. *Journal of Clinical Pathology*, **25**, 259.
- Lancet* (1971). Editorial. Prevention of mental subnormality due to hypothyroidism, **2**, 1363.
- Mincey, E. K., Thorson, S. C., and Brown, J. L. (1971). A new in-vitro blood test for determining thyroid status—the effective thyroxine ratio. *Clinical Biochemistry*, **4**, 216.
- Mincey, E. K., Thorson, S. C., Brown, J. L., Morrison, R. T., and McIntosh, H. W. (1972). A new parameter of thyroid function—the effective thyroxine ratio. *Journal of Nuclear Medicine*, **13**, 165.
- Murray, I. P. C., Joasoo, A., and Parkin, J. (1971). In-vitro thyroid tests in children. *Medical Journal of Australia*, **1**, 77.
- O'Halloran, M. T., and Webster, H. L. (1972). Thyroid function assays in infants. *Journal of Pediatrics*, **81**, 916.
- Ryness, J. (1972). The measurement of serum thyroxine in children. *Journal of Clinical Pathology*, **25**, 726.
- Stein, R. B., and Price, L. (1972). Evaluation of adjusted total thyroxine (free thyroxine index) as a measure of thyroid function. *Journal of Clinical Endocrinology and Metabolism*, **34**, 225.
- Toft, A. D., Seth, J., Kirkham, K. E., Marshall, A., and Irvine, W. J. (1973). Assessment of *in vitro* thyroid function tests in 100 consecutive patients referred to a thyroid clinic. *Clinical Endocrinology*, **2**, 127.

Correspondence to Mr. T. G. Brien, Radioisotope Department, St. Vincent's Hospital, Elm Park, Dublin 4, Eire.