Circulating thyroid hormone levels in children

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SUMMARY Extensive use of radioimmunoassay for routine measurement of serum thyroid hormones in paediatric thyroid disorders showed inconsistencies between laboratory results based upon adult criteria and clinical observation. To resolve this disparity, serum triiodothyronine (T3) and thyroxine (T4) levels were measured by radioimmunoassay in 354 healthy children aged between 3 weeks and 17 years.

The mean serum T3 concentration in children up to 10 years of age was 1.94 ± 0.35 ng/ml (SD) which was higher than the mean serum T3 of 1.37 ± 0.25 ng/ml in healthy adults. Similarly, the mean serum T4 of 10 ± 2.5 μ g/100 ml was higher than the adult mean serum T4 of 8.5 ± 1.5 μ g/100 ml. Neither concentration changed significantly from 3 weeks to 10 years of age, nor was there any sex difference. In girls serum T3 and T4 concentrations declined gradually from age 10 to maturity. A perimenarcheal nadir observed in the T4 data was thought to reflect the joint effects of the age-dependent fall in circulating T4 and the concomitant oestrogen-dependent rise in thyroxine-binding globulin. In boys the decline in serum T3 occurred approximately 2 years later than in the girls. These observations show that the normal ranges for serum T3 and T4 in children are higher than those in adults and that reference to normal adult ranges may lead to misclassification in diagnosis and monitoring of paediatric thyroid disorders.

Simple and rapid radioimmunoassays for measurement of serum thyroxine (T4) and triiodothyronine (T3) are now readily available for assessment of thyroid function in children, yet the criteria for normal thyroid function are mostly derived from adult data (Fisher, 1973). Using a competitive protein binding assay, O'Halloran and Webster (1972) reported that after the neonatal surge in thyroid hormone concentration, serum T4 declined till the age of one year to stabilize at a mean level of 9.2 μ g/100 ml. Murray *et al.* (1971) showed higher serum T4 and T3 resin uptake levels in childhood which declined slowly with age until late adolescence. Published information on circulating T3 levels is, however, sparse and conflicting. AvRuskin *et al.* (1973) found no significant change in six groups of children aged between 1 and 18 years, the mean serum T3 levels being within the normal adult range. By contrast, Rubenstein *et al.* (1973) reported higher serum T3 levels in young children with a fall of approximately 0.05 ng/ml per decade.

After extensive routine use of serum T3 estimations, it has become apparent that circulating T3 levels in children are higher than in adults, and that many clinically hypothyroid children with raised serum thyroid-stimulating hormone (TSH) levels

have T3 levels within the normal adult range. This study was undertaken to determine serum T3 and T4 levels in normal children from 3 weeks to 17 years of age.

Subjects and methods

Sera were obtained for estimation of T3, T4, and TSH concentrations in the following groups of children.

- (1) 112 children between the ages of 3 weeks and 9 years who were in hospital for elective surgery or minor nonendocrine illnesses. Blood samples were obtained for routine investigations and subsequently donated for this study.
- (2) 196 normal schoolgirls aged 9 to 17 years who were participating in a study of endocrine and pubertal relationships conducted by the Garvan Institute of Medical Research in collaboration with the Sydney Human Performance Laboratory. All sera from this group were randomly assayed in two batches at the same time, using the same reagents.
- (3) 46 normal schoolboys of three ages, 10, 14, and 16 years, also participating in the above study on whose sera T3 estimations were

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Table 1 Mean serum triiodothyronine (T3) and thyroxine (T4) levels in group 1, children aged 3 weeks to 9 years

	Age (years)									
	<1	1	2	3	4	5	6	7	8	9
T3 ng/ml $\pm$ SD	1.99 $\pm$ 0.32	2.00 $\pm$ 0.36	1.82 $\pm$ 0.28	2.05 $\pm$ 0.30	1.86 $\pm$ 0.25	2.06 $\pm$ 0.38	1.97 $\pm$ 0.38	1.87 $\pm$ 0.33	1.96 $\pm$ 0.36	1.92 $\pm$ 0.31
n	22	18	9	9	10	10	11	15	16	11
T4 μ g/100 ml $\pm$ SD	10.5 $\pm$ 2.2	10.2 $\pm$ 1.8	10.3 $\pm$ 1.8	10.6 $\pm$ 3.3	9.3 $\pm$ 1.8	9.0 $\pm$ 2.1	10.7 $\pm$ 3.0	9.6 $\pm$ 1.4	9.1 $\pm$ 1.7	9.4 $\pm$ 0.3
n	20	17	8	6	8	5	10	13	10	6

Conversion: Traditional units to SI—T3: 1 ng/ml $\approx$ 1.536 nmol/l. T4: 1 μ g/100 ml $\approx$ 12.87 nmol/l.

performed in the same assay as a pair-matched subgroup from group 2.

Serum T4 and T3 were measured by specific radioimmunoassays (Corcoran *et al.*, 1973; Eastman *et al.*, 1975). Serum TSH was measured by radioimmunoassay using reagents kindly supplied by the NIAMDD with MRC human TSH 68/38 as standard. Sensitivities of the assays were 0.3–1.0 μ U/ml serum TSH, 0.08 ng/ml serum T3, and 0.25 μ g/100 ml serum T4. Intra-assay variation for T3 and T4 was 3%, and for TSH 6%. Inter-assay variation was between 11% and 13% for all three systems.

Results

Results are reported as mean $\pm$ 1 SD unless otherwise stated. Statistical analyses were performed using Student's *t* test. Serum TSH measurements were performed to exclude possible undetected primary hypothyroidism. Values ranged from below assay sensitivity to 7 μ U/ml and are not reported in detail.

Group 1: children up to 9 years of age. Results are

shown in Table 1, where the mean serum T3 and T4 levels are arranged in single-year sets. There was no significant difference in either mean T3 or T4 levels between any age group, nor was there any sex difference. The mean T3 over the whole group, however, was 1.94 ± 0.35 ng/ml, range 1.2–3.54 ng/ml. This is significantly higher ($P < 0.001$) than the adult mean of 1.37 ± 0.25 ng/ml previously reported by this laboratory (Carter *et al.*, 1974). Serum T4 levels ranged from 5.5 to 16 μ g/100 ml with a mean of 10.2 ± 2.5 μ g/100 ml. Compared with the normal adult mean serum T4 of 8.5 ± 1.5 μ g/100 ml, the difference was highly significant ($P < 0.001$). Individual serum T3 and T4 determinations are shown in Figs. 1 and 2 with reference to the normal adult range. Whereas the majority of T4 determinations fall within the normal adult range, the majority of T3 determinations are above the normal adult range.

Group 2: girls aged 9 to 17 years. Since there were only 2 girls in the 9-year age group, the data have been supplemented by inclusion of results of girls of the same age in group 1, and thus are subject to inter-assay variation. The decline in mean serum T3

Fig. 1 Individual serum T3 levels in children aged between 3 weeks and 10 years (mean $\pm$ 2 SD is shown on the right). Normal adult range is hatched area. See Table 1 for conversion from traditional units to SI.

Fig. 2 Individual serum T4 levels in children aged between 3 weeks and 10 years (mean $\pm$ 2 SD is shown on the right). Normal adult range is hatched area.

from 1.92 ng/ml at age 9 to 1.61 ng/ml at age 17 is shown in Fig. 3. The fall in serum T3 is significant ($P < 0.05$) by age 14 when compared with the mean T3 levels at age 10. When the data were assessed according to pubertal development there was a highly significant ($P < 0.0001$) difference between the mean premenarcheal T3 levels of 1.91 ± 0.26 ng/ml

Fig. 3 Mean serum T3 levels showing the decline in values from the age of 9 to 17 years. Bars are 1 SEM.

Table 2 Mean circulating T4:T3 ratios in girls in group 2

	Age (years)								
	9	10	11	12	13	14	15	16	17
T4:T3	46.9 (50.0)	42.9	42.0	42.3	39.0	43.0	43.8	48.5	52.8

and the mean postmenarcheal T3 level of 1.73 ± 0.21 ng/ml.

The mean serum T4 levels are shown in Fig. 4. The nadir in serum T4 of $7.3 \mu\text{g}/100 \text{ ml}$ corresponds with the average age of menarche (13.1 years) in the girls examined. The decline in serum T4 at age 13 is significant ($P < 0.0001$) when compared with the 10-year age group. By the age of 17 years the mean T4 level had risen to the normal adult level of $8.5 \mu\text{g}/100 \text{ ml}$.

Fig. 4 Mean serum T4 levels in girls aged between 9 and 17 years, showing the premenarcheal nadir. Bars are 1 SEM.

The T4/T3 ratios were calculated individually and the mean values for each age group are shown in Table 2. The normal Australian adult ratio in this laboratory is 67 ± 10 .

Group 3: schoolboys and pair-matched girls. Since male and female levels of T3 are the same both in early childhood and adulthood, a smaller study was carried out to check that the fall in serum T3 in boys followed the same trend to adult values as in pair-matched girls. The results are shown in Table 3.

Table 3 Comparison of circulating T3 levels (ng/ml $\pm$ SD) in pair-matched girls and boys in group 3

	10 years	14 years	16 years
Girls	1.95 ± 0.19	1.81 ± 0.15	1.56 ± 0.22
Boys	1.94 ± 0.28	2.00 ± 0.18	1.85 ± 0.27

Early in adolescence mean levels were the same (age 10, 1.94 ng/ml). At age 16, however, the mean T3 for boys ($1.85 \pm 0.27 \text{ ng/ml}$) was still maintained at the same level as for 14-year-old girls ($1.81 \pm 0.15 \text{ ng/ml}$), while the mean serum T3 in the corresponding female age group had fallen to $1.56 \pm 0.22 \text{ ng/ml}$. The decrease in circulating T3 to adult levels therefore appeared approximately 2 years later in boys than in girls.

Discussion

This study clearly shows that serum T3 and T4 levels are significantly higher in prepubertal children when compared with normal adults. Serum T3 levels decline steadily from around the onset of puberty to normal adult levels sometime after the age of 17 years. Serum T4 levels show a similar but less marked decline and reach a nadir in girls at the time of menarche. Although the relative changes in T3 are small, they are statistically significant and unless estimated in the one assay, may pass unnoticed. Thus, a similar decline may exist in the younger age groups as suggested by Rubenstein *et al.* (1973), but it was not detected in this study. The marked fall in T3 compared with the smaller fall in T4 is shown by the rise in T4/T3 ratios with age.

Serum T4 levels were approximately 10 to 15% higher than those previously reported by other workers and tabulated in the review of Fisher (1973). As the serum T4 concentration estimated by radioimmunoassay is approximately 15% higher than that obtained by competitive protein binding analysis (Chopra, 1972), these results are consistent with previous reports. Our absolute values for serum T3 in children are higher than those reported by Rubenstein *et al.* (1973) and AvRuskin *et al.* (1973), though the mean serum T3 levels in adults obtained by these workers and ourselves are comparable. Apart from the considerable differences in the numbers of children studied, which may have influenced mean serum T3 levels, there is no obvious explanation for this disparity. Thyroid disease, alterations in circulating thyroid hormone binding proteins, iodine intake, nutrition, and associated nonthyroidal illness are potent determinants of circulating T3 levels. As T3 is derived mainly from extrathyroidal monodeiodination of T4, factors inhibiting conversion of T4 to T3, such as nonthyroidal illness (Carter *et al.*, 1974) and decreased caloric intake (Spaulding *et al.*, 1976), result in decreased circulating T3 levels. In our experience, children hospitalized for minor illnesses, and who

are not eating normally, may exhibit decreased serum T3 levels characteristic of the sick euthyroid state. Although care was taken to exclude such children from group 1 in this study, some of the children with lower T3 levels may reflect this problem. Whether associated illness and differences in nutrition and iodine intake account for the differences between serum T3 levels reported in this and other studies remains speculative.

Thyroxine degradation rates, when measured per unit body weight, are increased in children compared with adults (Haddad, 1960; Hung *et al.*, 1965). It follows that higher serum T4 levels are consistent with higher production rates, and hence increased thyroidal secretion rates in children. The kinetics of T3 metabolism in children are not known. Assuming the degradation rate for T3 in children is not less than that in adults, it is probable that thyroidal T3 secretion is also increased. Furthermore, since T3 and T4 are secreted in the same proportions as they occur in the thyroid gland and as the thyroidal T3:T4 ratios are similar in the fetus and adult (Fisher *et al.*, 1973), increased T4 output should be accompanied by increased T3 secretion. In our study the serum T3 levels were increased to a greater extent than T4, as evidenced by the T4/T3 ratios, suggesting a relative increase in T3 production compared with T4. As T3 is derived mainly from T4 it is highly likely that T4 to T3 conversion is enhanced in the well nourished, healthy child.

The profile of mean T4 levels of perimenarcheal girls as shown in Fig. 4 is difficult to explain. Since oestrogens have a profound effect in raising thyroxine binding globulin and thus circulating T4 levels, it is possible that the profile reported is the outcome of an age-dependent fall in serum T4 and an oestrogen-dependent rise after menarche.

This study has confirmed our impressions, based upon large numbers of serum thyroid hormone estimations in children, that serum T3 and T4 levels are higher in children compared with adults. These results complement published studies of serum thyroid hormone concentrations in the fetus at term (Lieblich and Utiger 1973; Eastman *et al.*, 1973; Fisher *et al.*, 1973), during early neonatal life and infancy (Montalvo *et al.*, 1973; Erenberg *et al.*, 1974), and provide a basis for definition of normal ranges for thyroid function tests from birth to maturity. This is of great importance in the assessment of thyroid function in children with suspected thyroid disease. Unless laboratories are aware of the higher normal range in children, erroneous diagnoses of hyperthyroidism in clinically suspect but euthyroid children, and of euthyroidism in mildly hypothyroid children, whether treated or untreated, will occur.

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