

CHAPTER IV

DISCUSSION

Normal range of serum T_4 and serum T_3 among Thai subjects

The normal range of serum thyroxine and serum triiodothyronine among Thai subjects are comparable to those of the Caucasian subjects (Table 5).

Table 5 indicates that there is no difference in the normal range of serum T_4 and serum T_3 between Thai people and subjects of Caucasian extraction. The slight variation from study to study should be attributed to variation of method and technique of the individual laboratory. Therefore each laboratory should have its own range of normal values. Moreover, laboratory values can only help in the diagnosis of the majority of the subjects but the final word still depends on the diagnostic acumen of the clinician.

Serum T_4 and serum T_3 in Graves' disease patients

Before therapy serum T_3 was elevated in all 48 subjects (see page 11) diagnosed as having Graves' disease. However serum T_4 of 6 patients were not elevated. These patients therefore had T_3 toxicosis, a new entity described only recently (Hollander 1972). In this study the incidence of T_3 toxicosis was 12.5 percent. This is very close to the figure found by Marsden (1975). In 39 Graves' disease patients Marsden found five with T_3 toxicosis, an incidence of 12.8%. This high incidence of T_3 toxicosis confirmed the opinion of many authors, that serum T_3 level is a better indication for thyrotoxicosis than serum T_4 . This is

Table 5 Comparison of the normal ranges of serum T_4 and serum T_3 in Thai subjects with those of Caucasian subjects

Subjects	Normal range	
	Serum T_4	Serum T_3
Present study (Thai subjects)	3-11 $\mu\text{g}\%$	70-200 $\text{ng}\%$
Hesch and Huefner (1974)	4.8-11.9 $\mu\text{g}\%$	90-150 $\text{ng}\%$
Marsden and McKerren (1975)	4-11 $\mu\text{g}\%$	60-200 $\text{ng}\%$
Larsen (1972)	-	85-160 $\text{ng}\%$
Liebich and Utiger (1971,1972)	-	95-195 $\text{ng}\%$
Hollander (1972)	-	96-172 $\text{ng}\%$

particularly true in toxic thyroid nodules in which the incidence of high T_3 and normal T_4 was found to be higher than in Graves' disease (Hollander 1972 and Marsden 1975). Elevation of serum T_3 alone may be an early manifestation of thyrotoxicosis while a full blown elevations of both T_3 and T_4 are to follow later. Hesch and Huefner (1974) found that all the so-called euthyroid Graves' disease (that is patients with exophthalmic goiter, no symptom of thyrotoxicosis but whose thyroid glands are not suppressible and serum T_4 are normal) had elevated serum T_3 . They also advocated that euthyroid exophthalmic patients are only patients with early thyrotoxicosis and sooner or later patients will develop full blown disease; but in some, the disease may burn out and never develop any symptoms and signs of thyrotoxicosis. This is therefore another disease entity that only serum T_3 will be useful for finding the abnormality.

Serum T_3 however is inferior to serum T_4 in the detection of hypothyroidism. This is amply demonstrated in this study. Only 11 out of 29 patients with low serum T_4 had serum T_3 below normal range. Moreover only three of the eight patients who developed signs and symptoms of hypothyroidism had serum T_3 below normal range.

Effect of antithyroid drug on serum T_4 and T_3

The acute changes of serum T_4 and T_3 in the first five days after initiation of propylthiouracil medication was studied by Abuid and Larsen (1974). Their significant finding was that the drop of T_3 level in the serum was much more rapid than T_4 making the T_4/T_3 ratio markedly elevated from the level before treatment. The mean T_4/T_3 ratio before therapy was

43±3. This ratio rose up to 88±7 on day two and plateaued at that level to day 5. In this study the mean T_4/T_3 ratio of 39±15 in hyperthyroid subjects was comparable to 43±3 found by Abuid and Larsen (1974). Seven days after initiation of antithyroid drug the T_4/T_3 ratio only rose to 50±21. Therefore at seven days after therapy, the T_4/T_3 ratio may already be on a downward trend. This is confirmed by a further decrease in T_4/T_3 ratio in the following weeks. The rise in T_4/T_3 ratio was interpreted by Larsen as a result of more rapid metabolism of circulating T_3 while the new production was inhibited by the antithyroid drug. Since propylthiouracil (PTU) was used in the study by Abuid and Larsen and PTU was demonstrated to have peripheral action on conversion of T_4 to T_3 , this peripheral effect of PTU also may contribute to the rapid rise of T_4/T_3 ratio in Abuid and Larsen's study. In the present study methimazole was used instead of PTU. Since methimazole has never been demonstrated to have any peripheral action, this therefore may explain a slower drop of serum T_3 in this study and consequently lower T_4/T_3 ratio. However by seventh day of therapy levels of serum thyroxine also dropped significantly making the T_4/T_3 ratio lower than the values found by Abuid and Larsen who followed only up to the fifth day after therapy.

In 29 patients who developed hypothyroid state T_4/T_3 ratio became very low, 24±15, as compared to 39±15 for hyperthyroid subjects. Figs. 11 and 12 show that in hypothyroid state T_4/T_3 ratio correlates better with T_4 than with T_3 indicating that T_4 is a better indicator of hypothyroid state than serum T_3 . In contrast, in hyperthyroid state T_4/T_3 ratio correlates significantly with T_3 but not with T_4 indicating that

T_3 is a better indicator of hyperthyroid state than T_4 .

Side effects of methimazole

No serious side effect of agranulocytosis was found in this study. The 9.8% incidence of skin rashes is comparable to the findings of others. This only confirms that it is the most common side effect found with anti-thyroid drug therapy excluding the incidence of hypothyroidism which was found in up to three quarters of the patients in this study during the course of therapy.

The incidence of low serum T_4 is quite large with antithyroid therapy in the conventional dose used in Thailand which is already half of the dose recommended in the western countries. The incidence rose rapidly in the first 4 months of therapy and plateaued off during the next few months. However serum T_3 was found to be low in only one third of these patients and only in 37% (3 out of 8) of patients who already developed signs and symptoms of hypothyroidism. This may indicate that in the presence of blocking drug the thyroid gland produces T_3 in preference to T_4 for economy of the thyroid gland. This is supported by the markedly decreased T_4/T_3 ratio in the hypothyroid subjects.

There is a lag period of many weeks between the onset of low serum T_4 and signs and symptoms of hypothyroidism (Table 4). The same lag period was found between the onset of elevation of T_4 and T_3 , particularly the latter and the onset of signs and symptoms of hyperthyroidism (Hollander, 1971). This probably indicates a prolonged effect of thyroid hormone intracellularly.