Tohoku J. exp. Med., 1979, 127, 85-95

Changes in Thyroid Hormones by Treatment with Aspirin and Prednisolone in Subacute Thyroiditis with Hyperthyroidism

MAKIKO YAMAMOTO, SHINTARO SAITO, KAZUO KAISE, NOBUKO KAISE, KATSUMI YOSHIDA and KAORU YOSHINAGA

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980

YAMAMOTO, M., SAITO, S., KAISE, K., KAISE, N., YOSHIDA, K. and YOSHINAGA, K. *Changes in Thyroid Hormones by Treatment with Aspirin and Prednisolone in Subacute Thyroiditis with Hyperthyroidism.* Tohoku J. exp. Med., 1979, **127** (1), 85-95 —— Thyroid functions were studied in 11 patients with subacute thyroiditis accompanied by signs and symptoms of hyperthyroidism, and were compared with 13 patients with untreated thyrotoxicosis in which serum T4 was elevated to the identical level. Serum T3 was also elevated in subacute thyroiditis but to a significantly lower extent than in thyrotoxicosis. Therefore the ratio of T4/T3 was significantly higher in subacute thyroiditis than in thyrotoxicosis. Although duration of thyroid swelling was shorter in the group treated by prednisolone than by aspirin, the accelerated ESR, thyroid tenderness and fever subsided almost similarly in the two groups. Serum T4 and T3 levels declined more rapidly in treatment with prednisolone compared with aspirin. In patients treated by aspirin initial increase in T3 level occurred transiently with simultaneous decrease in the T4/T3 ratio. These changes suggest the increase in peripheral conversion of T4 to T3. Even in severe cases of subacute thyroiditis associated with hyperthyroidism, aspirin treatment is an effective therapy and there is no recurrence following withdrawal of the medication. ——— subacute thyroiditis; serum thyroxine; serum triiodothyronine; prednisolone; aspirin

Subacute thyroiditis is characterized by an acute onset with fever, malaise, sore throat and pain in the neck. The thyroid is enlarged and tender. In the acute stage some patients, in addition to the typical symptoms of acute infection, may show signs and symptoms of hyperthyroidism. Simultaneously, the thyroid hormone levels measured as PBI or total thyroxine (T4) are elevated (Czernick and Harrell-Steinberg 1957; Volpé et al. 1958; Christiansen et al. 1970). These changes are explained by the destruction of the thyroid parenchyma releasing the hormones into the circulation. Serum triiodothyronine (T3), as well as T4 (Ogihara et al. 1973; Larsen 1974), is elevated in the initial hyperthyroid phase. Mild cases of this disease are generally treated by aspirin (Torikai and Kumaoka 1958) but in severe cases the use of corticosteroids has been advocated (Greene 1971).

In this report, the thyroid functions in initial hyperthyroid phase of subacute thyroiditis were compared with those of untreated thyrotoxicosis. Serum T4, T3, TSH and erythrocyte sedimentasion rate (ESR) were measured during the coruse

Received for publication, April 26, 1978.

of the illness and the effects of aspirin on the changes in such varients were compared with those of prednisolone.

Materials and Methods

Eleven patients with severe subacute thyroiditis accompanied by signs and symptoms of hyperthyroidism in the acute stage were seen in our Thyroid Clinic between 1973 and 1975, and were subjected to the present study. The clinical and laboratory findings at the first examination are presented in Table 1. The diagnosis of subacute thyroiditis was made by the typical symptoms, accelerated ESR and marked depression of thyroidal radioiodine (^{131}I) uptake. Thirteen patients with untreated thyrotoxicosis in which serum levels of T4 were similar as those in the group of subacute thyroiditis, were selected and their thyroid functions were compared with those of the patients with subacute thyroiditis. BMR and thyroidal ^{131}I uptake were determined by standard procedures. Serum T4 was assessed by a competetive protein binding assay with Tetrasorb-125 kit (Dinabbot Co.). The normal range was 5–15 μg/100 ml. For the ^{131}I-T3 resin sponge uptake (RSU), Triosorb kit (Dinabbot Co.) was used. Its normal range was 25–39%. Serum T3 was measured by radioimmunoassay (Sakurada et al. 1973) and normal range was 70–180 ng/100 ml. TSH was measured by radioimmunoassay with H-TSH kit (Daiichi RI Lab.). The antithyroglobulin and antimicrosomal antibodies were detected by the tanned-red blood cell-hemagglutination test (Thyroid Test and Microsome Test, Fujizoki Co.).

Five patients (Cases 4, 5, 6, 7, 8) treated by aspirin and 3 patients (Cases 1, 2, 3) by prednisolone were followed during the treatments.

Table 1. *Clinical data in patients with subacute thyroiditis*

Case	Sex	Age	Period before treatment	ESR (mm/hr)	Fever (°C)	Heart rate (/min)	Thyrotoxic signs
1	F	45	1 M	65	36.8	90	pal., wt. loss (2 kg)
2	F	37	1 M	126	37.2	120	per., wt. loss (2 kg)
3	F	38	1 M	126	37.1	108	wt. loss (5 kg)
4	F	45	3 W	42	36.7	112	per., wt. loss (4 kg)
5	F	57	1 W	120	38.0	106	pal., per., wt. loss (5 kg)
6	F	55	2 W	100	36.4	118	per.
7	F	38	2 M	110	39.0	120	per., wt. loss (5 kg)
8	F	51	2 W	72	36.9	106	pal., wt. loss (2 kg)
9	M	35	1 M	108	36.1	96	pal., per., wt. loss (5 kg)
10	F	25	2 W	93	36.1	125	wt. loss (5 kg)
11	F	43	1 M	77	36.0	100	pal.

pal., palpitation; per., perspiration; wt., weight.

Results

The 11 patients with subacute thyroiditis showed signs of weight loss, palpitation, perspiration and tachycardia at the first examination as shown in Table 1. At the second examination, usually within 10 days, these signs became almost obscure. In Table 2, thyroid functions and antithyroidal antibodies in acute stage of subacute thyroiditis with hyperthyroidism are shown. Table 3 shows the comparisons between the cases with subacute thyroiditis and those of untreated patients with thyrotoxicosis. Ten patients with subacute thyroiditis had a very low ^{131}I-uptake in the thyroid gland. The mean value of serum T3 was elevated in subacute thyroiditis but was significantly lower than the mean value

TABLE 2. *Thyroid function tests and thyroidal antibodies in patients with subacute thyroiditis*

Case No.	BMR (%)	Serum T4 (μg/100ml)	Serum T3 (ng/100ml)	T4/T3	RSU (%)	TSH (μU/ml)	24 hr ^{131}I uptake (%)	Titers of thyroidal antibodies	
								TGA	MSA
1	+23	35	483	72.4	34	1.9	——	−	−
2	——	35	330	106.0	40	2.7	0.3	−	−
3	——	24	550	43.6	41	n.d.	0.15	−	−
4	+32	27	430	62.7	34	2.6	0.4	−	−
5	+31	22.6	330	68.4	50	1.8	0.8	−	−
6	+40	20.8	220	94.5	50	n.d.	0.7	−	−
7	+28	20.6	300	68.6	33	n.d.	0.36	−	−
8	+35	19.6	380	51.5	34	1.3	0	−	1:100
9	+14	23.3	295	78.9	40	n.d.	0	1:1,600	−
10	+41	27.1	——	——	47	——	0	−	−
11	——	30	500	60.0	40	2.3	0.55	−	−

TGA, antithyroglobulin antibody; MSA, antimicrosomal antibody; −, lower than 1:100.

TABLE 3. *Thyroid function tests and thyroidal antibodies in a group of patients with subacute thyroiditis compared with a group of patients with untreated thyrotoxicosis*

	Subacute thyroiditis Mean±S.E. (*n*)	Thyrotoxicosis Mean±S.E. *n*=13	Comparison between groups (*p* value)
Serum T 4 (μg/100 ml) (5–15)†	25.3 ± 1.65(11)	28.7± 2.27	n.s.
BMR (%) (+15–−15)†	+30.5 ± 3.1 (8)	+43.1± 4.3	n.s.
Serum T3 (ng/100 ml) (70–180)†	381.8 ±33.4 (10)	806 ±27.6	$p<0.001$
T4/T3	70.6 ± 5.9 (10)	36.1± 2.9	$p<0.001$
RSU (%) (25–39)†	46.2 ± 1.3 (11)	52.6± 1.6	$p<0.001$
TSH (μU/ml) (8>)†	1.2 ± 0.3 (10)	n.d.	$p<0.01$
24 hr ^{131}I uptake (%) (10–40)†	0.32± 0.03(10)	70 ± 2.5	$p<0.001$
Thyroidal antibodies			
TGA	1/11*	2/13*	
MSA	1/11*	12/13*	

* Incidence of positive cases in thyroidal antibodies=positive cases / total cases.
† Normal range.

in thyrotoxicosis ($p<0.001$). The ratio of T4/T3 in subacute thyroiditis was higher than that in thyrotoxicosis ($p<0.001$). The mean value of TSH was normal in subacute thyroiditis and was not detectable in patients with thyrotoxicosis ($p<0.01$). The mean value of RSU in patients with subacute thyroiditis was elevated but was significantly lower than those in thyrotoxicosis ($p<0.001$).

Antithyroidal antibodies were positive in one out of 11 patients with subacute thyroiditis, but in thyrotoxicosis antimicrosomal antibodies were positive in 12 out of 13 patients.

Figs. 1 to 8 show the changes in serum T4, T3, TSH, ESR, duration of fever, thyroid tenderness and thyroid swelling during the clinical course of subacute

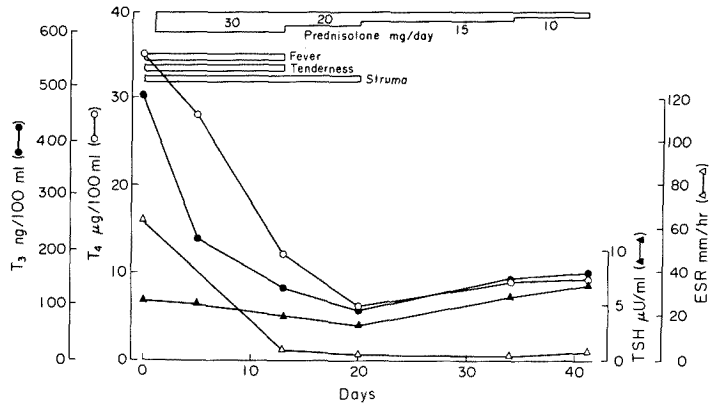

Fig. 1. Patient No. 1. Changes in serum T4, T3, TSH, ESR and clinical signs after treatment with prednisolone in the patient with subacute thyroiditis accompanied with hyperthyroidism in early stage.

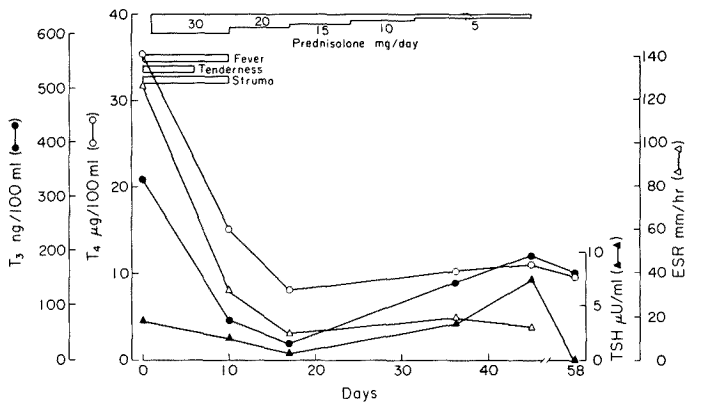

Fig. 2. Patient No. 2. See the legend in Fig. 1.

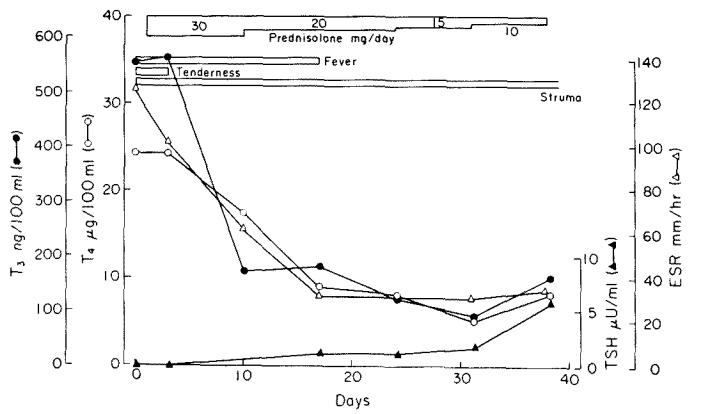

Fig. 3. Patient No. 3. See the legend in Fig. 1.

thyroiditis with hyperthyroidism at the early stage.

ESR returned to normal range accompanied with decrease in thyroid hormones. In two patients treated by prednisolone, on days 13 and 17, respectively, (Figs. 1, 2) ESR returned to be below 20 mm/hr. In Case 3 (Fig. 3) ESR did not decrease to normal range and there was an exacerbation of symptoms following prednisolone withdrawal. In patients treated by aspirin (Figs. 4, 5, 7, 8), four cases excluding Case 6 in which administration of aspirin was interrupted because of gastrointestinal side effects, on days 27, 43, 43 and 71, respectively (mean 46) ESR returned to normal. Thyroid tenderness disappeared within 2–12 days (mean 6.3 days) after treatment with prednisolone (Figs. 1–3) and within 7–15 days (mean 12.2 days) after aspirin (Figs. 4–8). Struma disappeared on days 19 and 9, respectively (Figs. 1, 2) after prednisolone and within 35–63 days (mean 46 days) after aspirin (Figs. 5–8). In cases 3 and 4 (Figs. 3, 4) thyroid swelling greatly reduced but did not completely

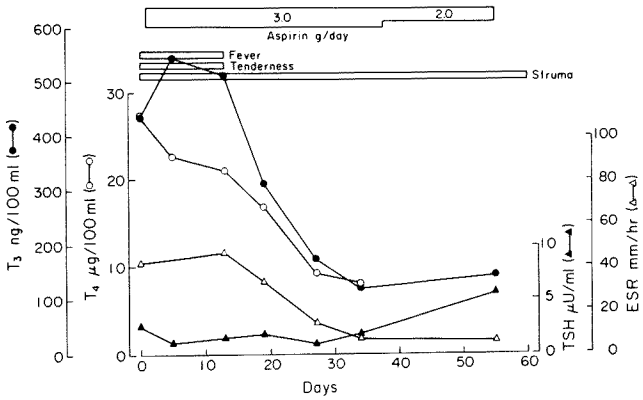

Fig. 4. Patient No. 4. Changes in serum T4, T3, TSH, ESR and clinical signs after treatment with aspirin in the patient with subacute thyroiditis accompanied with hyperthyroidism in early stage.

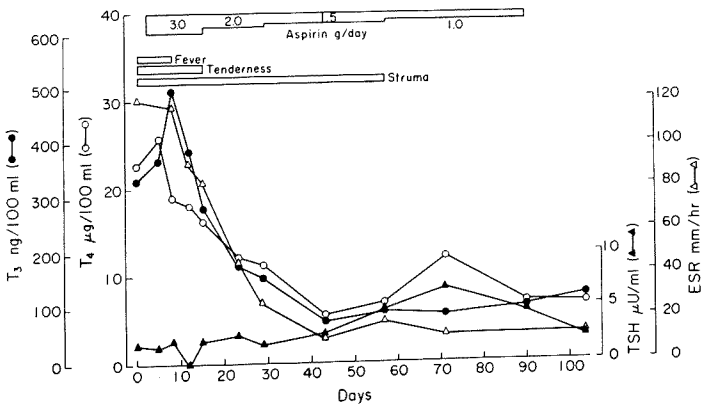

Fig. 5. Patient No. 5. See the legend in Fig. 4.

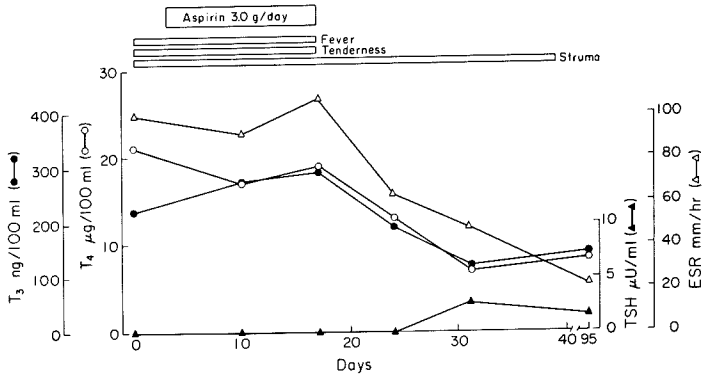

Fig. 6. Patient No. 6. See the legend in Fig. 4.

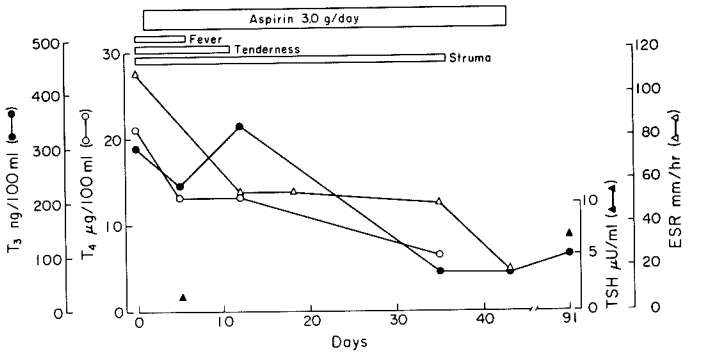

Fig. 7. Patient No. 7. See the legend in Fig. 4.

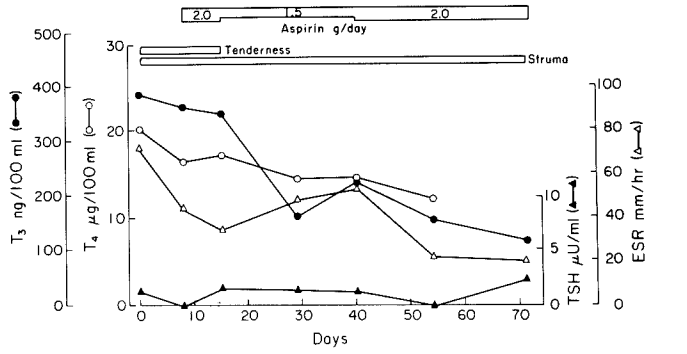

Fig. 8. Patient No. 8. See the legend in Fig. 4.

disappear during observation period. Fever subsided completely 9–16 days (mean 12.3 days) after the administration of prednisolone (Figs. 1–3) and 5–14 days (mean 9.3 days) after aspirin (Figs. 4–7). In Case 8, the initial body temperature was 36.9°C and the temperature was not elevated at all. Concerning

the clinical signs, no significant differences were found between two groups in relation to duration of accelerated ESR, thyroidal tenderness and fever. However, the duration of thyroid swelling was significantly shorter in the group treated by prednisolone ($p<0.05$).

Serum level of T4 and T3 declined more rapidly in patients treated by prednisolone. Serum level of T3 elevated transiently in 4 patients out of 5 treated by aspirin. Despite of transient increase in serum T3 concentration observed in patients treated by aspirin, there was not any exacerbation of thyrotoxic signs. Only slight changes within the normal range in TSH were observed during this periods.

The percentage of changes in the initial value in serum T4 and T3 induced by prednisolone and aspirin were plotted as shown in Fig. 9. Subsequently the areas circumscribed by plotted lines during the respective 30 days treatments were measured. In Fig. 10, the areas of T4 and T3 were shown in patients treated by prednisolone and aspirin respectively. The areas of T4 and T3 in the group treated by aspirin were significantly greater than those in the group treated by prednisolone ($p<0.05$, $p<0.001$, respectively). In the group treated by prednisolone the difference between the areas of T3 and T4 was not significant. However, in the group treated by aspirin, the area of T3 was significantly greater than that of T4 ($p<0.05$).

Then in the group treated by prednisolone T4 and T3 simultaneously declined and more rapidly than in group treated by aspirin. In the aspirin treated group, the transient increase in the serum level of T3 caused the increase of the T3 area in comparison to that of T4.

In Fig. 11, the changes of serum T4/T3 ratio is shown. The ratio was decreased transiently in 4 cases treated by aspirin. On the other hand, the ratio

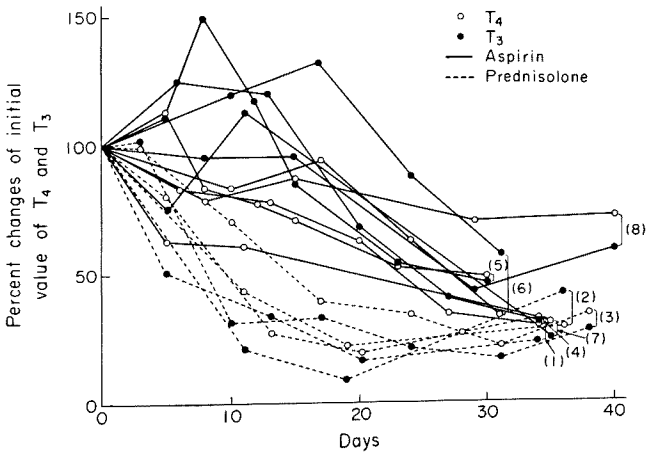

Fig. 9. Changes of T4 and T3 during the treatment with prednisolone and aspirin respectively in patients with subacute thyroiditis accompanied with hyperthyroidism. Case number of the patients was shown in the parenthesis.

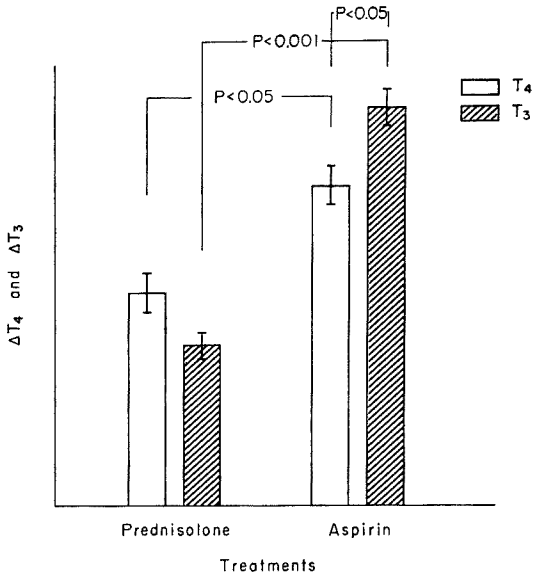

Fig. 10. Comparisons of the areas of T4 and T3. The areas were measured as the percentage of changes in thyroid hormones during the 30 days treatments. See Fig. 9.

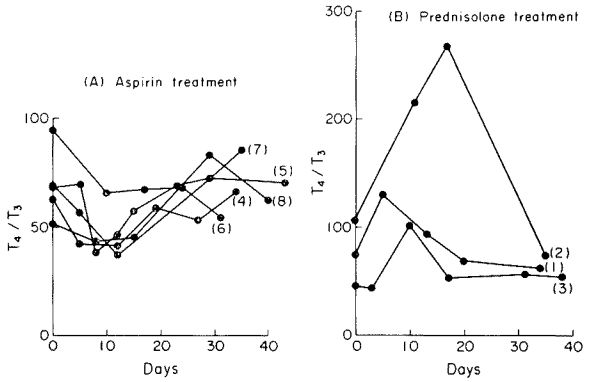

Fig. 11. Changes in serum T4/T3 ratio in treatment with prednisolone and aspirin in patients with subacute thyroiditis accompanied with hyperthyroidism in early phase. Case number of the patients was shown in the parenthesis.

increased within about two weeks in all of 3 cases treated by prednisolone.

Discussion

In patients with severe subacute thyroiditis showing serum T4 levels as high as in thyrotoxicosis, revealed common characteristic of lower levels of serum T3 and higher T4/T3 ratios than those in thyrotoxicosis. Recent studies on circulating T3 and T4 concentrations in patients with untreated thyrotoxicosis have indicated

that in 39 patients with untreated thyrotoxicosis the T4/T3 ratio was 53±3 (mean ±S.E.), while in 42 normal subjects it was 71±3. This overproduction of T3 relative to T4 is typical of the disease (Larsen 1972). In the present study, the T4/T3 ratio (70.6±5.9) in patients with subacute thyroiditis was almost similar to the value of normal subjects, and the ratio was significantly higher than that in thyrotoxicosis (36.1±2.9).

In accordance with our results, lower value of resin T3 test in subacute thyroiditis than those in patients with thyrotoxicosis was reported by Christiansen et al. (1970). It was explained that the binding capacity of TBP was decreased in thyrotoxicosis.

Serum TSH was not detectable in thyrotoxicosis and was normal in subacute thyroiditis in our study. These difference may in part reflect that the duration of increase in thyroid hormones is shorter and that the inhibitory effect of TSH secretion is weaker in subacute thyroiditis compared to thyrotoxicosis.

Antimicrosomal antibody was negative in 10 out of 11 patients with subacute thyroiditis but positive in 12 out of 13 patients with thyrotoxicosis. This indicates a possibility that hyperthyroidism due to subacute thyroiditis can be distinguished from thyrotoxicosis by measuring antithyroidal antibodies.

The decline of both serum T4 and T3 in patients with subacute thyroiditis by treatment of betamethasone (Ogihara et al. 1973) and during its course without any medication (Larsen 1974) have been reported. But the change of thyroid hormones in the patients with subacute thyroiditis treated with aspirin has not been observed. Although we were unable to perform a controlled trial unfortunately, in our study, both serum T4 and T3 of group treated by prednisolone simultaneously declined more rapidly than that of the group treated by aspirin. Transient increase in serum T3 occurred initialy in the group treated by aspirin, hence the decline of serum T3 is more gradual than T4. Since both increase in serum T3 concentration and decrease in T4/T3 ratio were observed in initial phase after administration of aspirin, the increase in T3 may be attributed to increase in the conversion of T4 to T3. Several recent studies have reported significantly decreased levels of serum total T3 in the presence of normal T4 concentration in a variety of systemic illness including fever, and it was explained by the decreased peripheral conversion of T4 to T3 (Chopra et al. 1975b). The rise in T3 and decrease in T4/T3 ratio occurred about two weeks after the start of aspirin administration and at that time the fever returned to normal range and thyroidal tenderness disappeared. However, ESR even increased in all 5 cases. It was suggested that the reduction in fever and thyroidal inflammatory changes subsequently increased in peripheral T3 formation to a degree commensurate with the amount of T4 present.

Corticosteroids have been reported to inhibit the conversion of T4 to T3 and result in decrease in T3 and increase in rT3 (3,3′,5′-triiodothyronine) (Chopra et al. 1975a). The transient increase in T3 was not observed in prednisolone treated patients and in turn increase in T4/T3 ratio occurred initially. This phenomenon

may be explained by the inhibitory effect of prednisolone on the conversion of T4 to T3.

It has been reported that steroids decrease the binding capacity of thyroxine-binding-globulin (TBG) and increase that of thyroxin-binding-prealbumin (TBPA) and the partitioning of T4 in serum between the bound and free states reflect the alteration in TBG rather than the alteration in TBPA (Woeber and Ingbar 1974).

More rapid decline in T4 of patients treated by prednisolone may be partly influenced by the effect of prednisolone on TBG binding.

The administration of cortisone or its derivatives has been recommended as the most efficacious mode of therapy when improvement of signs and symptoms is desired quickly. The major problem with cortisone administration has been the high incidence of recurrence after withdrawal of the medication (Vagenakis et al. 1970). Aspirin treatment, despite of initial increase in T3, had satisfactory effects on clinical signs and symptoms in subacute thyroiditis with no recurrence after withdrawal of the drug. It is concluded that aspirin treatment should be advocated not only in moderate but also in more severe cases of subacute thyroiditis.

References

1) Chopra, I.J., Williams, D.E., Orgiazzi, J. & Solomon, D.H. (1975a) Opposite effects of dexamethasone on serum concentrations of 3,3′,5′-triiodothyronine (reverse T3) and 3,3',5-triiodothyronine (T3). *J. clin. Endocr.*, **41**, 911–920.
2) Chopra, I.J., Chopra, U., Smith, S.R., Reza, M. & Solomon, D.H. (1975b) Reciprocal changes in serum concentration of 3,3',5'-triiodothyronine (reverse T3) and 3,3',5-triiodothyronine (T3) in systemic illness. *J. clin. Endocr.*, **41**, 1043–1049.
3) Christiansen, N.J.B., Siersbaek-Nielsen, K., Hansen, J.E.M. & Korsgaard Chirstensen, L. (1970) Serum thyroxine in the early phase of subacute thyroiditis. *Acta endocr. (Kbh.)*, **64**, 359–363.
4) Czernick, P. & Harrell-Steinberg, A. (1957) The chronology of events in the development of subacute thyroiditis, studied by radioactive iodine. *J. clin. Endocr.*, **17**, 1448–1453.
5) Greene, J.N. (1971) Subacute thyroiditis. *Amer. J. Med.*, **51**, 97–108.
6) Larsen, P.R. (1972) Triiodothyronine: Review of recent studies of its physiology and pathophysiology in man. *Metabolism*, **21**, 1073–1092.
7) Larsen, P.R. (1974) Serum triiodothyronine, thyroxine, and thyrotropin during hyperthyroid, hypothyroid, and recovery phases of subacute nonsuppurative thyroiditis. *Metabolism*, **23**, 467–471.
8) Ogihara, T., Yamamoto, T., Azukizawa, M., Miyai, K. & Kumahara, Y. (1973) Serum thyrotropin and thyroid hormones in the course of subacute thyroiditis. *J. clin. Endocr.*, **37**, 602–606.
9) Sakurada, T., Saito, S., Yamaguchi, T., Yamamoto, M., Demura, H., Demura, R., Fukuchi, S., Yoshinaga, K. & Torikai, T. (1973) Radioimmunoassay of triiodothyronine. *Tohoku J. exp. Med.*, **110**, 329–340.
10) Torikai, T. & Kumaoka, S. (1958) Subacute thyroiditis treated with salicylate: report of 5 cases. *New Engl. J. Med.*, **259**, 1265–1267.
11) Vagenakis, A.G., Abreau, C.M. & Braverman, L.E. (1970) Prevention of recurrence in acute thyroiditis following corticosteroid withdrawal. *J. clin. Endocr.*, **31**, 705–708.
12) Volpé, R., Johnston, M.W. & Huber, N. (1958) Thyroid function in subacute thyroiditis. *J. clin. Endocr.*, **18**, 65–78.

13) Woeber K.A. & Ingbar, S.H. (1974) Interactions of thyroid hormones with binding proteins. In: *Handbook of Physiology*, edited by R.O. Greep & E.B. Astwood, Williams & Wilkins Co., Baltimore, pp. 187–196.