*Clinical Endocrinology* (1985), **22**, 489–496

# COMPARATIVE EFFECTS OF SODIUM IPODATE AND IODIDE ON SERUM THYROID HORMONE CONCENTRATIONS IN PATIENTS WITH GRAVES' DISEASE

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*(Received 16 July 1984; revised 10 October 1984; accepted 22 October 1984)*

SUMMARY

Patients with thyrotoxic Graves' disease were treated daily for 10 d with 1 g sodium ipodate, an iodine rich X-ray contrast agent which impairs outer ring (5'-) deiodination of T4 to T3, or with 12 drops of a saturated solution of potassium iodide (SSKI). T4, T3 and reverse T3 (rT3) concentrations were measured before, during, and 5 and 10 d after the administration of each drug. SSKI therapy induced a decrease in the serum T4 concentration from $14{\cdot}7 \pm 1{\cdot}3$ $\mu$g/dl (mean $\pm$ SE) to a nadir of $7{\cdot}9 \pm 0{\cdot}9$ on days 9 and 10 of therapy, all values reaching the normal range by day 9; a decrease in the serum T3 concentration from $402 \pm 43$ ng/dl to a nadir of $143 \pm 20$ on day 10, remaining elevated in all patients until day 5 and decreasing into the normal range in all except one patient on days 9 and 10; and no change in the serum rT3 concentration. Serum T4 and T3 concentrations returned to baseline values 10 d after withdrawal of SSKI. In contrast sodium ipodate therapy induced only a modest decrease in the serum T4 concentration from $15{\cdot}1 \pm 0{\cdot}7$ $\mu$g/dl to a nadir on day 9 of $11{\cdot}3 \pm 1{\cdot}0$ and serum T4 remained above the normal range in most patients until day 8; a striking and rapid decrease (within 12 h) in the serum T3 concentration from $340 \pm 36$ ng/dl to mean values ranging from 79 to 85 during the last 5 d of therapy, with most values below the normal range during the last 3 d; and a marked increase in the serum rT3 concentration from $111 \pm 15$ ng/dl to a peak value of $376 \pm 59$ on day 5. A significant rebound increase in serum T4 ($18{\cdot}7 \pm 1{\cdot}7$ $\mu$g/dl; $P < 0{\cdot}01$) and serum T3 ($512 \pm 72$; $P < 0{\cdot}01$) concentrations as compared to pretreatment values occurred 10 days after sodium ipodate was discontinued. We conclude that although treatment of hyperthyroidism with

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sodium ipodate induced a more rapid and more profound decrease in the serum T3 concentration than did SSKI, a marked rebound increase in serum T4 and T3 concentrations occurred after withdrawal of sodium ipodate but not after SSKI was discontinued.

Iodine containing oral cholecystographic X-ray contrast agents have been reported to be useful in the treatment of hyperthyroid patients (Brown *et al.*, 1978). Their administration induces a marked and rapid decrease in the serum T3 concentration, a slight decrease in the serum T4 concentration and a striking increase in the serum reverse T3 (rT3) concentration (Wu *et al.*, 1978 a, b, 1982). Their efficacy in treatment is primarily due to their rapid inhibitory effect on outer ring, 5′-deiodination of T4 to the more active iodothyronine, T3 (Burgi *et al.*, 1976; Kleinmann *et al.*, 1980; Beng *et al.*, 1980; Suzuki *et al.*, 1979, 1981), and the effect of iodine itself on blocking the release of thyroid hormones from the thyroid (Wartofsky *et al.*, 1970). Stable iodine may be employed in the treatment of mild Graves' hyperthyroidism (Hamburger, 1981) and is often used as adjunctive therapy before thyroidectomy (Braverman, 1981; Feek *et al.*, 1980), after therapy with $^{131}I$ (Ross *et al.*, 1983), and in the treatment of thyroid storm (Braverman, 1983).

Comparative studies on the effects of cholecystographic contrast media and stable iodine as the sole treatment of hyperthyroidism are not available. In the present study we have evaluated the effects of one of these X-ray agents, sodium ipodate, and of stable iodine on serum thyroid hormone concentrations in patients with thyrotoxic Graves' disease.

## SUBJECTS AND METHODS

Sixteen patients with active Graves' disease were studied. Informed consent was obtained in all patients. The diagnosis of Graves' disease was established by clinical and laboratory evaluation. Nine patients, eight females and one male, with a mean age of $35{\cdot}7 \pm 6{\cdot}1$ years (mean $\pm$ SE) were treated with 1 g sodium ipodate (Biloptin, Schering, AG Berlin; 616 mg iodine) administered orally each day. Seven patients, six females and one male with a mean age of $38{\cdot}4 \pm 6{\cdot}3$ years were treated with 12 drops of saturated solution of potassium iodide (SSKI) (456 mg iodine) administered orally each day. The quantity of iodine in both preparations is far in excess of that needed to treat Graves' disease. It is not known how much free iodine is released from the metabolism of sodium ipodate. Sodium ipodate and SSKI were each administered as a single dose at 0800 h for 10 d. All patients were hospitalized during the study and no other medications were administered.

Blood samples were obtained before treatment (baseline) and 6 and 12 h after the administration of the first dose of each drug and daily thereafter until the 10th day of treatment and 5 d (day 15) and 10 d (day 20) after stopping therapy. Blood was obtained in the morning before drug administration.

Serum samples were kept frozen at $-20^{\circ}$C. T4 was measured by radioimmunoassay (RIA) with materials obtained from Biodata (Milan, Italy). Serum T3 and rT3 concentrations were measured by methods previously described (Bandini *et al.*, 1975; Roti *et al.*, 1979). Serum TSH was measured with materials kindly obtained from the National Pituitary Agency, NIAMDDK (Bethesda, MD). Except for a few specimens with insufficient volume, assays were performed in duplicate with all samples for each subject included in the assay for that hormone. All values are reported as the mean $\pm$ SE.

Statistical analysis of the data was conducted using the one way analysis of variance (ANOVA) to compare hormone variation in each study group of patients. For each treatment group, Duncan's multiple range test, corrected for an unequal number of observations, was employed to compare hormone concentrations during and after treatment to baseline values (Kramer, 1956). Comparison of hormone values during the treatment period (days 1 to 10) between the two groups of patients was carried out by ANOVA.

## RESULTS

### *Serum T4 concentration*

Basal serum T4 concentration in the patients treated with sodium ipodate was $15{\cdot}1 \pm 0{\cdot}7$ $\mu$g/dl. During treatment, a significant decrease ($F$-test; $P < 0{\cdot}01$) in serum T4 concentration was observed and the lowest value was reached on the ninth day of therapy. Values on day 7 were significantly lower than basal values (Duncan's test; $P < 0{\cdot}005$). The serum T4 concentration remained above normal in most of the patients until day 8 and in four of the patients on days 9 and 10. No values were below the normal range. Ten days after treatment was discontinued, a significant rebound increase above baseline values was observed (Duncan's test; $P < 0{\cdot}01$) (Table 1).

SSKI treatment also resulted in a significant decrease ($F$-test; $P < 0{\cdot}01$) in serum T4 concentrations from $14{\cdot}7 \pm 1{\cdot}3$ $\mu$g/dl to $7{\cdot}9 \pm 0{\cdot}9$ and $7{\cdot}9 \pm 0{\cdot}8$ on days 9 and 10 of therapy. Values on day 4 were significantly lower than basal values (Duncan's test; $P < 0{\cdot}05$). Serum T4 values decreased into the normal range, but not below, in all patients by days 9 and 10 of SSKI therapy. No significant increase in the serum T4 concentration, as compared to baseline values, was observed after withdrawal of SSKI therapy (Table 1).

Variations in the serum T4 concentration in the sodium ipodate and SSKI treatment groups, compared by ANOVA, were significantly different ($P < 0{\cdot}001$) (Fig. 1). The progressive decrease in serum T4 concentration was greater in the patients treated with SSKI.

Table 1. Iodothyronine concentrations before and after therapy with sodium ipodate or SSKI

| Therapy | Before therapy | Days off therapy | |
|---|---|---|---|
| | | 5 | 10 |
| Sodium ipodate (1 gm daily) | | | |
| T4 ($\mu$g/dl) | $15{\cdot}1 \pm 0{\cdot}7$ (9)* | $11{\cdot}9 \pm 1{\cdot}4$ (9) | $18{\cdot}7 \pm 1{\cdot}7$ (8)† |
| T3 (ng/dl) | $40 \pm 36$ (9) | $219 \pm 31$ (9) | $512 \pm 72$ (8)† |
| rT3 (ng/dl) | $111 \pm 15$ (9) | $94 \pm 14$ (9) | $110 \pm 12$ (8) |
| SSKI (12 drops daily) | | | |
| T4 ($\mu$g/dl) | $14{\cdot}7 \pm 1{\cdot}3$ (7) | $10{\cdot}1 \pm 1{\cdot}7$ (6) | $14{\cdot}8 \pm 2{\cdot}8$ (6) |
| T3 (ng/dl) | $402 \pm 43$ (7) | $284 \pm 71$ (6) | $396 \pm 93$ (6) |
| rT3 (ng/dl) | $93 \pm 18$ (7) | $57 \pm 8$ (6) | $86 \pm 19$ (6) |

* Mean $\pm$ SE; numbers in parentheses represent the number of patients in each group.

† $P < 0{\cdot}01$ vs before therapy values (Duncan's test).

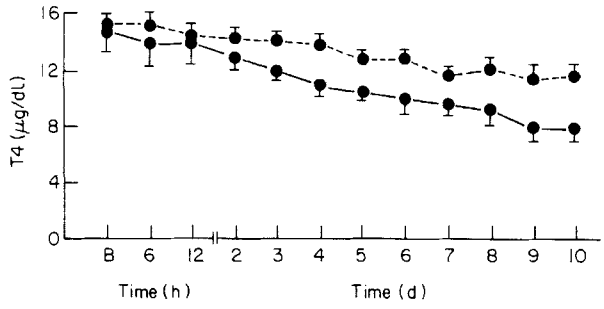


Fig. 1. The effects of sodium ipodate (● - - - ●) and SSKI (●—●) administration on the serum T4 concentration in patients with thyrotoxic Graves' disease. Bars show SE. $F$-test, $P < 0{\cdot}001$.

*Serum T3 concentration*

Basal serum T3 concentration in the patients treated with sodium ipodate was $340 \pm 36$ ng/dl. During treatment, a highly significant decrease ($F$-test; $P < 0{\cdot}01$) in serum T3 concentration was observed as early as 12 h after the administration of the first dose of sodium ipodate (Duncan's test; $P < 0{\cdot}01$). Serum T3 concentration reached a nadir on the last 5 d of treatment, ranging between $79 \pm 7$ and $85 \pm 10$. By the fourth day, all values were either normal ($n = 6$) or below normal ($n = 3$), and during the last 3 d of therapy, most values were subnormal. After therapy was discontinued, a significant rebound increase in the serum T3 concentration was observed 10 d later (day 20) ($512 \pm 72$; Duncan's test; $P < 0{\cdot}01$) (Table 1).

In patients treated with SSKI, the basal serum T3 concentration was $402 \pm 43$ ng/dl. A significant decrease was observed during SSKI therapy ($F$-test; $P < 0{\cdot}01$), reaching a nadir on day 10 ($143 \pm 20$). In contrast to the findings with sodium ipodate, serum T3 values did not fall below the normal range in any of the patients treated with SSKI. Serum T3 concentrations remained elevated in all patients until day 5 and became normal in all but one patient on the last 2 d of therapy. No significant rebound increase in the serum T3 concentration was observed after SSKI was discontinued (Table 1).

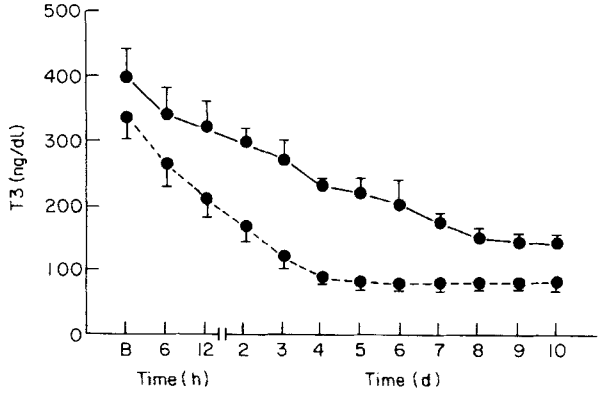


Fig. 2. The effects of sodium ipodate (● - - - ●) and SSKI (●— ●) administration on the serum T3 concentration in patients with thyrotoxic Graves' disease. Bars show SE. $F$-test, $P < 0{\cdot}001$.

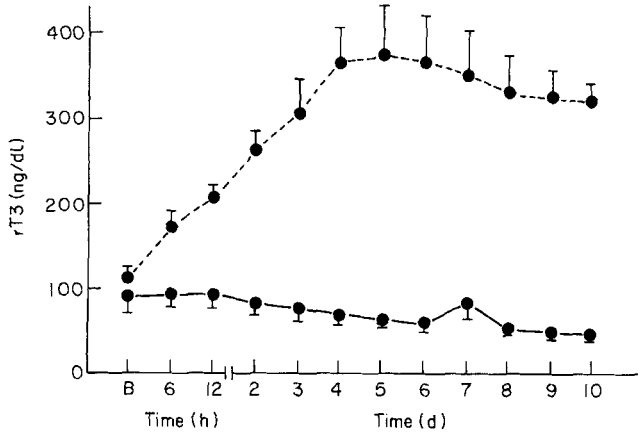


Fig. 3. The effects of sodium ipodate (● - - - ●) and SSKI (●—●) administration on the serum rT3 concentration in patients with thyrotoxic Graves' disease. Bars show SE. *F*-test, $P < 0{\cdot}001$.

When analysed by ANOVA, serum T3 concentrations during treatment with sodium ipodate or SSKI were significantly different ($P < 0{\cdot}001$) (Fig. 2). The progressive decrease in serum T3 concentrations was greater in the patients treated with sodium ipodate.

### *Serum rT3 concentration*

The serum rT3 concentration increased during sodium ipodate therapy (*F*-test; $P < 0{\cdot}01$), from a basal value of $111 \pm 15$ ng/dl to a peak value of $376 \pm 59$ on day 5 (Duncan's test; $P < 0{\cdot}01$). After withdrawal of sodium ipodate, the serum rT3 concentration returned to baseline values (Table 1).

In the patients treated with SSKI, serum rT3 concentrations did not vary from baseline values (*F*-test).

The different patterns of response of the serum rT3 concentration associated with sodium ipodate and SSKI therapy are evident in Fig. 3. Variations in the serum rT3 concentration in the sodium ipodate and SSKI treatment groups were significantly different (ANOVA; $P < 0{\cdot}01$).

### *Serum TSH concentration*

Serum TSH concentration was below the limit of detectability (0·6 μU/ml) in all subjects throughout.

## DISCUSSION

The administration of iodide as sole therapy in patients with hyperthyroid Graves' disease is usually not recommended unless the hyperthyroidism is mild and the thyroid gland is only slightly enlarged, in which case iodides can be used with caution (Hamburger, 1981; Braverman, 1981). Pharmacologic doses of iodide do rapidly block release of T4 and T3 from the hyperfunctioning thyroid (Wartofsky *et al.*, 1970). However, Emerson *et al.* (1975) have reported that iodide therapy of active Graves' disease rarely restores the

serum T4 and T3 concentrations to normal and that escape from the blocking effects frequently occurs. Feek *et al.* (1980) have reported that the administration of SSKI for 10 d in patients with thyrotoxic Graves' disease receiving propranolol therapy did restore both serum T4 and T3 concentrations to normal. Iodine treatment in combination with antithyroid drug therapy is occasionally employed in the early treatment of hyperthyroidism, especially in those patients in whom a rapid response is desired; this usually induces a rapid fall in the serum T3 concentration (Croxson *et al.*, 1977).

Oral cholecystographic contrast media when administered to normal subjects result in a decrease in the serum T3 concentration and an increase in serum T4 and rT3 concentrations (Burgi *et al.*, 1976; Kleinmann *et al.*, 1980; Beng *et al.*, 1980; Suzuki *et al.*, 1979, 1981). In hyperthyroid patients, the administration of sodium ipodate alone or in combination with PTU and propranolol resulted in a more pronounced decrease in the serum T3 concentration than that observed employing PTU alone or PTU and propranolol (Wu *et al.*, 1978 a, b, 1982; Sharp *et al.*, 1981). The marked decrease in the serum T3 concentration following sodium ipodate administration is most likely due to the inhibition of 5′-deiodinase, decreasing the peripheral conversion of T4 to T3 (Chopra *et al.*, 1978; Kaplan & Utiger, 1978; Silva *et al.*, 1978), and a drug induced inhibition of the flux of T4 from plasma into liver (Felicetta *et al.*, 1980). These effects are more likely to be related to the chemical structure of the X-ray contrast compounds rather than their iodine content since other X-ray contrast agents, such as diatrizoate, have little if any effect on serum iodothyronine concentrations in euthyroid subjects (Kleinmann *et al.*, 1982). However, it is likely that the changes induced by sodium ipodate might be due, in part, to iodine released from the drug by deiodination in peripheral tissues. The consistent decrease in the thyroid radioiodine uptake associated with the administration of X-ray contrast media strongly suggests that deiodination of these compounds does occur *in vivo* (Grayson, 1960).

There are few if any data available comparing the effects of iodide and sodium ipodate administered separately on serum iodothyronine concentrations during and after the short-term therapy of patients with hyperthyroid Graves' disease. The present study did reveal some differences in the serum thyroid hormone responses to these two drugs. The decrease in serum T4 concentrations was greater in the patients receiving SSKI than in those treated with sodium ipodate. It is probable that the decrease in serum T4 induced by the iodide released from the deiodination of sodium ipodate was partially offset by the inhibitory effect of the drug on the peripheral conversion of T4 to T3 and on influx of T4 from serum to liver. In contrast, the decrease in serum T3 concentration was more rapid and far greater in the patients treated with sodium ipodate, primarily due to the reduction of T3 generation from T4 induced by the drug. The marked elevation in serum rT3 concentration during soldium ipodate therapy is also due to impaired outer ring 5′-deiodination of rT3 resulting in impaired clearance of this iodothyronine.

A major difference between SSKI and sodium ipodate therapy which might be of clinical importance is the response of the serum T4 and T3 concentrations following the abrupt withdrawal of therapy. Serum T4 and T3 concentrations returned to their elevated basal values following cessation of therapy with SSKI. In contrast, a highly significant rebound increase in serum T4 and T3 concentrations above basal, pretreatment values was observed 10 days after withdrawal of sodium ipodate. This suggests that sodium ipodate therapy should be used with caution as sole therapy for thyrotoxic Graves' disease, a problem discussed by Costa (1979). Although Wu *et al.* (1978b) suggested that

such a rebound increase in serum T4 and T3 concentrations would not occur, no supporting data was given. When antithyroid drug therapy is administered with sodium ipodate, this rebound phenomenon would probably not occur. However, it has been suggested that the recurrence rate of hyperthyroidism in patients treated with antithyroid drugs is increased when iodine intake is high (Wartofsky, 1973). Since the iodine content in adipose tissue of patients given cholecystographic dyes for X-ray studies 1 year earlier was 15 times normal (Costa *et al.*, 1978), it is possible that the recurrence rate in patients receiving antithyroid drugs and sodium ipodate would be increased.

ACKNOWLEDGEMENT

The authors would like to thank Linda Desai for her assistance in the preparation of this manuscript. This work was supported in part by Grant no. 83.00471.04 of Consiglio Nazionale della Ricerche, Rome, Italy, and by Grant AM-18919 from the NIAMDDK, NIH, Bethesda, MD.

REFERENCES

BANDINI, P., ROBUSCHI, G., EMANUELE, R., GNUDI, A. & ROTI, E. (1975) Dosaggio radioimmunologica della triiodotironina (T3) nel siero. *Lab J Res Lab Med*, **6**, 495–500.

BENG, C.G., WELLBY, M.L., SYMONS R.G., STUART, S. & MARSHALL, J. (1980) The effect of iopodate on the serum iodothyronine pattern in normal subjects. *Acta Endocrinologica (Kbh)*, **93**, 175–178.

BROWN, J., SOLOMON, D.H., BEALL, G.N., TERASAKI, P.I., CHOPRA, I.J., VAN HERLE, A.J. & WU, S.Y. (1978) Autoimmune thyroid diseases. Graves' and Hashimoto's. *Annals of Internal Medicine*, **88**, 379–391.

BURGI, H., WIMPFHEIMER, C., BURGER, A., ZAUNBAUER, W., ROSLER, H. & LEMARCHAND-BERAUD, T. (1976) Changes of circulating thyroxine, triiodothyronine and reverse triiodothyronine after radiographic contrast agents. *Journal of Clinical Endocrinology and Metabolism*, **43**, 1203–1210.

BRAVERMAN, L.E. (1981) Is there a place for long-term stable iodine in the treatment of Graves' disease, In *Controversies in Clinical Thyroidology* (eds. J.I. Hamburger & J.M. Miller). Springer-Verlag, New York.

BRAVERMAN, L.E. (1983) Thyroid storm. In *Current Endocrinologic Therapy* (eds. D.T. Krieger & C.W. Bardin) pp. 65–69. B.C. Decker, Inc., Trenton, NJ.

CHOPRA, I.J., SOLOMON, D.H., CHOPRA, U., WU, S.Y., FISHER, D.A. & NAKAMURA, Y. (1978) Pathways of metabolism of thyroid hormones. *Recent Progress in Hormone Research*, **34**, 521–567.

COSTA, A., BRAMBATI-TESTORI, O., CENDERELLI, C., GIRIBONE, G. & MIGLIARDI, M. (1978) Iodine content of human tissues after administration of iodine containing drugs or contrast media. *Journal of Endocrinological Investigation*, **1**, 221–226.

COSTA, A. (1979) The use of X-ray contrast media in the treatment of hyperthyroidism. *Journal of Endocrinological Investigation*, **2**, 461–462 (letter).

CROXSON, M.S., HALL, T.D. & NICOLOFF, J.T. (1977) Combination drug therapy for treatment of hyperthyroid Graves' disease. *Journal of Clinical Endocrinology and and Metabolism*, **45**, 623–630.

EMERSON, C.H., ANDERSON, A.J., HOWARD, W.J. & UTIGER, R.D. (1975) Serum thyroxine and triiodothyronine concentrations during iodide treatment of hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **40**, 33–36.

FEEK, C.M., SAWERS, J.S., IRVINE, W.J., BECKETT, G.J., RATCLIFFE, W.A. & TOFF, A.D. (1980) Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. *New England Journal of Medicine*, **302**, 883–885.

FELICETTA, J.V., GREEN, W.L. & NELP, W.B. (1980) Inhibition of hepatic binding of thyroxine by cholecystographic agents. *Journal of Clinical Investigation*, **65**, 1032–1040.

GRAYSON, R.R. (1960) Factors which influence the radioactive iodine thyroidal uptake test. *American Journal of Medicine*, **28**, 397–415.

HAMBURGER, J.I. (1981) Is there a place for long-term stable iodine in the treatment of Graves' disease, In *Controversies in Clinical Thyroidology* (eds. J.I. Hamburger & J.M. Miller). Springer-Verlag, New York.

KAPLAN, M.M. & UTIGER R.D. (1978) Iodothyronine metabolism in rat liver homogenate. *Journal of Clinical Investigation*, **61**, 459–471.

KLEINMANN, R.E., VAGENAKIS, A.G. & BRAVERMAN, L.E. (1980) The effect of iopanoic acid on the regulation of thyrotropin secretion in euthyroid subjects. *Journal of Clinical Endocrinology and Metabolism*, **51,** 339–403.

KLEINMANN, R.E., STERNTHAL, E., STAROBIN, O. & BRAVERMAN, L.E. (1982) Cardiac catheterization dye does not affect serum thyroid hormone concentrations or TSH secretion. *Catheterization and Cardiovascular Diagnosis*, **8,** 261–265.

KRAMER, C.Y. (1956) Extension of multiple range tests to group means with unequal number of replication. *Biometrics*, **12,** 307–310.

ROSS, D.S., DANIELS, G.H., DESTEFANO, P., MALOOF, F. & RIDGWAY, E.C. (1983) Use of adjunctive potassium iodide after radioactive iodide ($^{131}$I) treatment of Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **57,** 250–253.

ROTI, E., ROBUSCHI, G., BANDINI, P., EMANUELE, R. & GNUDI, A. (1979) Radioimmunoassay of 3,3′,5′ triiodothyronine (reverse T3) in unextracted serum: concentration in peripheral vein in normal, altered thyroid economy, after TRH injection and in thyroid vein. *Journal of Nuclear Medicine and Allied Sciences*, **23,** 25–30.

SHARP, B., REED, A.W., TAMAGNA, E.I., GEFFNER, D.L. & HERSHMAN, J.M. (1981) Treatment of hyperthyroidism with sodium ipodate (oragrafin) in addition to propylthiouracil and propranolol. *Journal of Clinical Endocrinology and Metabolism*, **53,** 622–625.

SILVA, J.E., DICK, T.E. & LARSEN, P.R. (1978) The contribution of local tissue thyroxine monodeiodination to the nuclear 3.5,3′-triiodothyronine in pituitary, liver and kidney of euthyroid rats. *Endocrinology*, **103,** 1196–1207.

SUZUKI, H., KADENA, N., TAKENCHI, K. & NAKAGAWA S. (1979) Effects of three-day oral cholecystography on serum iodothyronines and TSH concentrations: comparison of the effect among some cholecystographic agents and the effects of iopanoic acid on the pituitary-axis. *Acta Endocrinologica (Kbh)*, **92,** 477–488.

SUZUKI, H., NOGUCHI, K., NAKAHATA, M., NAKAGAWA, S. & KADENA N. (1981) Effect of iopanoic acid on the pituitary-thyroid axis: time sequence of changes in serum iodothyronines, thyrotropin, and prolactin concentrations and responses to thyroid hormones. *Journal of Clinical Endocrinology and Metabolism*, **53,** 779–783.

WARTOFSKY, L., RANSIL, B.J. & INGBAR, S.H. (1970) Inhibition by iodine of the release of thyroxine from the thyroid glands of patients with thyrotoxicosis. *Journal of Clinical Investigation*, **49,** 78–86.

WARTOFSKY, L. (1973) Low remission after therapy for Graves' disease: possible relation of dietary iodine with antithyroid therapy results. *Journal of the American Medical Association*, **226,** 1083–1088.

WU, S.Y., CHOPRA, I.J., SOLOMON, D.H. & BENNETT, L.R. (1978a) Changes in circulating iodothyronines in euthyroid and hyperthyroid subjects given ipodate (oragrafin), an agent for oral cholecystography. *Journal of Clinical Endocrinology and Metabolism*, **46,** 691–697.

WU, S.Y., CHOPRA, I.J., SOLOMON, D.H. & JOHNSON, D.E. (1978b) The effect of repeated administration of ipodate (oragrafin) in hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **47,** 1358–1362.

WU, S.Y., SHYH, T.P., CHOPRA, I.J., SOLOMON, D.H., HUANG, H.W. & CHU, P.C. (1982) Comparison of sodium ipodate (oragrafin) and propylthiouracil in early treatment of hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **54,** 630–634.