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# HYPOTHYROIDISM FOLLOWING $^{131}I$ THERAPY FOR HYPERTHYROIDISM IN RELATION TO IMMUNOLOGIC PARAMETERS

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Immunologic reactions are known to be of importance in the development of hypothyroidism after treatment for hyperthyroidism. Postoperative hypothyroidism is more frequent when the surgical thyroid specimens reveal marked lymphoid infiltration (WHITESELL JR & BLACK 1949, HARGREAVES & GARNER 1968). A higher incidence of postoperative hypothyroidism was found in patients who before treatment had demonstrable antibodies to thyroid antigens (HJORT & MOGENSEN 1962). $^{131}I$ treatment for hyperthyroidism is followed by hypothyroidism in a considerable proportion of the cases (LARSSON 1955, WERNER et coll. 1957, BELING & EINHORN 1961, BECKER et coll. 1971). A correlation between thyroid autoantibodies after $^{131}I$ treatment and hypothyroidism developing early after the therapy has been found (BLAGG 1960, SKANSE & NILSSON 1961, EINHORN et coll. 1965) as well as a correlation between the presence of thyroid antibodies before $^{131}I$ therapy and the development of hypothyroidism following such therapy (LUNDELL & JONSSON 1973). Whether this correlation found by LUNDELL & JONSSON still existed after a longer follow-up period of the same patient group has now been investigated.

## Material and Methods

The original series (LUNDELL & JONSSON ) comprised 188 patients (144 females, 44 males) with confirmed hyperthyroidism and in whom sera for determination of antibodies to thyroid antigens had been collected before and after $^{131}I$ therapy during the period 1963 to 1969. A further 3 patients also treated at this hospital during the same period and where sera had been collected in the same manner could be added to the group of 188 patients. The median age of the 191 patients was 55 years (range 23–83 years).

Fourteen per cent of the patients (n=27) had no clinically demonstrable goiter, 46 per cent (n=88) a diffuse goiter and 40 per cent (n=76) a nodular goiter. The goiters were assessed on the basis of palpation as being moderately or markedly enlarged. None of the patients had previously received a therapeutic dose of $^{131}I$, but 37 patients had been operated upon.

The principles of $^{131}I$ therapy have been reported elsewhere (LARSSON, BELING & EINHORN). The amount of $^{131}I$ administered at each treatment varied between 74 MBq (2 mCi) for patients without demonstrable goiter and 1 295 MBq (35 mCi) for patients with large nodular goiters and the dose was calculated without knowledge of the thyroid antibody titers. When the initial $^{131}I$ dose was insufficient to control the hyperthyroidism further doses were given, usually at a 3-month interval. Sixty-one per cent of the patients received one dose, 25 per cent two doses, 8 per cent three doses, and 3 per cent of the patients received between five and seven

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doses. The mean initial dose administered was 270 MBq (7.3 mCi) and the mean total dose 470 MBq (12.7 mCi; range 74–3 700 MBq).

The patients were examined regularly after treatment at intervals of 2 to 4 months during the first year, and subsequently at longer invervals, usually 6 months to one year, until they developed hypothyroidism or up till 31 December 1978. For patients who received more than one $^{131}I$ treatment, the follow-up period always dated from the time of the initial treatment. Classified as hypothyroid were all patients requiring permanent thyroid replacement therapy. The diagnosis of hypothyroidism was based on the clinical condition of the patient, supported by laboratory analyses of sera and radioiodine tracer tests. If permitted on clinical grounds, thyroid replacement therapy was generally avoided during the first 4 months after the $^{131}I$ therapy since transient hypothyroidism may occur within the first months of such therapy.

Sera were collected from each patient before therapy and at intervals thereafter during the first year afterwards. Antibodies to thyroid cytoplasmic antigen were determined by Coons' direct immunofluorescence technique (ROITT & DONIACH 1958, HOLBOROW et coll. 1959). Antibodies to thyroglobulin were determined by the Boyden passive hemagglutination test with tanned red cells (DERRIEN et coll. 1948, BOYDEN 1951, WITEBSKY & ROSE 1956). Patients with titers of less than 1/20 of antibodies to thyroglobulin were classified as negative, and those with titers of 1/20 or more as positive.

The cumulative incidence of hypothyroidism was calculated using standard life-table techniques. The statistical methods used were the log-rank test and the Student's t-test.

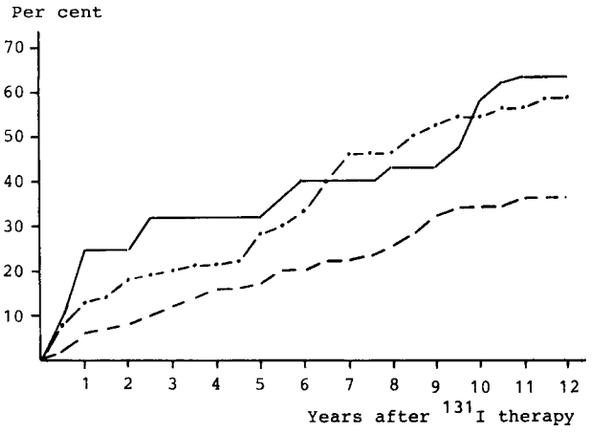


Fig. 1. Cumulative incidence of hypothyroidism after $^{131}I$ therapy for hyperthyroidism. — No demonstrable goiter (n=27). –·– Diffuse goiter (n=88). – – Nodular goiter (n=76).

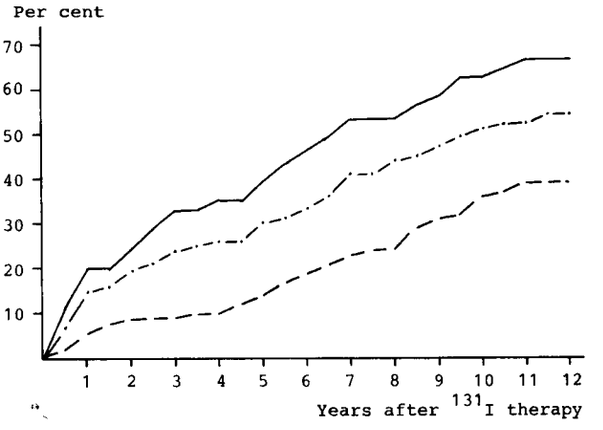


Fig. 2. Cumulative incidence of hypothyroidism after $^{131}I$ therapy in patients with or without thyroid antibodies before therapy. Patients with antibodies to both cytoplasmic antigen and thyroglobulin are included in both seropositive groups. — With antibodies to cytoplasmic antigen. –·– With antibodies to thyroglobulin. – – Without antibodies.

## Results

The cumulative incidence of hypothyroidism after $^{131}I$ treatment for hyperthyroidism is shown in Fig. 1. After one year 25 per cent of the patients without demonstrable goiter, 13 per cent of those with diffuse goiter, and 5 per cent of the patients with nodular goiter were hypothyroid. At the end of the follow-up the cumulative incidence of hypothyroidism was 63 per cent for patients without goiter, 57 per cent for those with diffuse goiter and 36 per cent for patients with nodular goiter. The differences were statistically significant ($p<0.01$) between the group with nodular goiter and each of the two other groups, but not between the group with diffuse goiter and that without goiter.

The incidence of hypothyroidism in the 37 patients operated upon before $^{131}I$ treatment was similar to that of the other 154 patients.

Of the 75 patients who before treatment had demonstrable antibodies to thyroid cytoplasmic antigen, 20 per cent were hypothyroid within one year and 66 per cent within 12 years of the treatment, as compared with somewhat lower figures for those with demonstrable antibodies to thyroglobulin (n=88; Fig. 2). Patients who lacked both antibodies (n=81) exhibited a lower cumulative incidence than

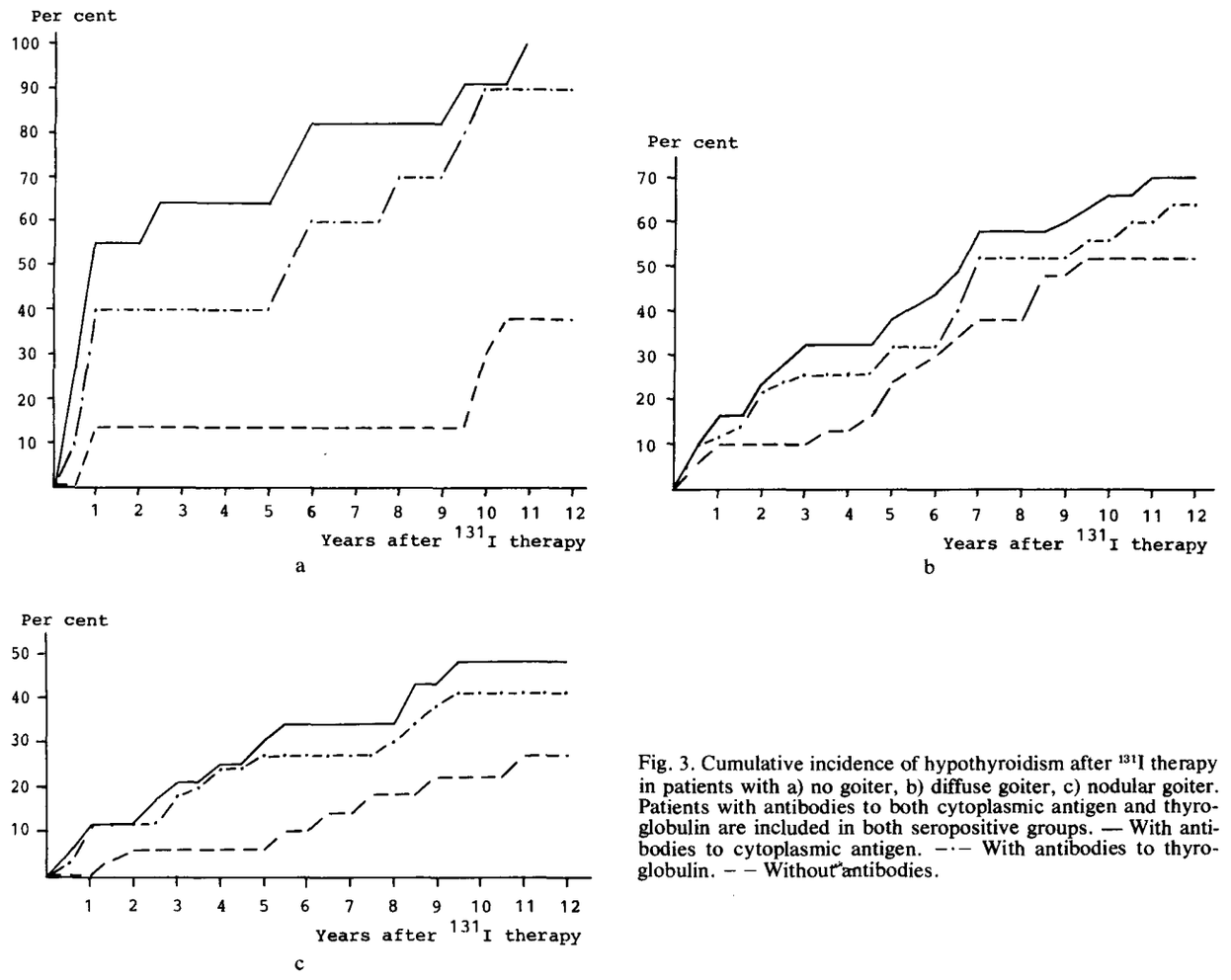


Fig. 3. Cumulative incidence of hypothyroidism after $^{131}$I therapy in patients with a) no goiter, b) diffuse goiter, c) nodular goiter. Patients with antibodies to both cytoplasmic antigen and thyroglobulin are included in both seropositive groups. — With antibodies to cytoplasmic antigen. –·– With antibodies to thyroglobulin. – – Without antibodies.

patients with antibodies to cytoplasmic antigen or thyroglobulin, or both ($p<0.05$); 6 per cent within one year as compared with 39 per cent within 12 years of therapy.

Fig. 3 demonstrates the significance of the presence of thyroid antibodies before treatment in the development of hypothyroidism in relation to the type of goiter. Six of the 11 patients without demonstrable goiter (Fig. 3 a) and who displayed antibodies to thyroid cytoplasmic antigen became hypothyroid within one year and all the cases were hypothyroid within 12 years of the treatment. Patients with demonstrable antibodies to thyroglobulin ($n=10$) had an incidence of hypothyroidism that was similar to that of patients with demonstrable antibodies to thyroid cytoplasmic antigen although somewhat delayed. In those patients without detectable antibodies before treatment ($n=14$), 14 per cent were hypothyroid within one year and 38 per cent within 12 years of treatment. The difference between the seropositive (cytoplasmic antigen or thyroglobulin, or both) and seronegative groups was statistically significant ($p<0.01$).

In the group of patients with diffuse goiter (Fig. 3 b) and presence of antibodies to thyroid cytoplasmic antigen before therapy, 14 per cent of the cases were hypothyroid within one year and 63 per cent within 12 years. Patients who before treatment had antibodies to thyroglobulin had a similar but somewhat lower cumulative incidence of hypothyroidism. Thirty-three patients had no detectable antibodies before treatment, and they had a slightly lower cumulative incidence than the seropositive patients. However, the differences between the three curves were not statistically significant.

Seventy-six patients had a nodular goiter (Fig. 3 c) and the cumulative incidence of hypothyroidism was lower for patients without demonstrable antibodies

before therapy (n=34), but the differences were not statistically significant.

Fig. 4 shows the cumulative incidence of hypothyroidism in patients with demonstrable antibodies to thyroid cytoplasmic antigen or thyroglobulin, or both, before therapy in relation to the type of goiter. It seems evident that the presence of these antibodies sooner or later results in hypothyroidism in almost all patients without goiter. The group of diffuse goiter had a similar progressive hypothyroidism although at a slower rate. A longer follow-up period is needed to ascertain whether the group with nodular goiter reaches a plateau, as is suggested in the figure.

Of the 119 patients without demonstrable antibodies to thyroid cytoplasmic antigen before the $^{131}$I therapy (Fig. 5), 52 developed such antibodies afterwards, while 67 remained seronegative with respect to cytoplasmic antigen titers for at least one year. A significantly higher incidence of hypothyroidism was found in the group becoming seropositive ($p<0.01$). Of 104 patients without demonstrable antibodies to thyroglobulin before therapy, 33 developed such antibodies within one year. No correlation was found between the incidence of hypothyroidism and the presence of antibodies to thyroglobulin developing after the therapy in comparison with those remaining seronegative for that antibody. Patients with diffuse goiter or not palpable thyroid glands more often developed antibodies to thyroid cytoplasmic antigen following therapy than patients with nodular goiter.

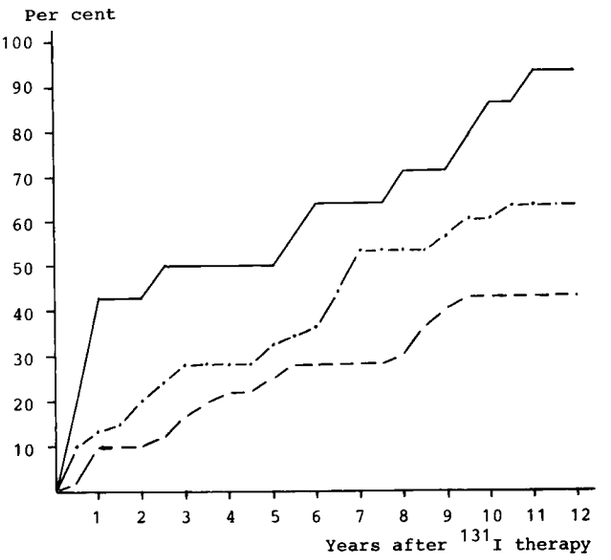


Fig. 4. Cumulative incidence of hypothyroidism after $^{131}$I therapy in patients with thyroid antibodies to cytoplasmic antigen or thyroglobulin, or both, before therapy. — No goiter. -·- Diffuse goiter. – – Nodular goiter.

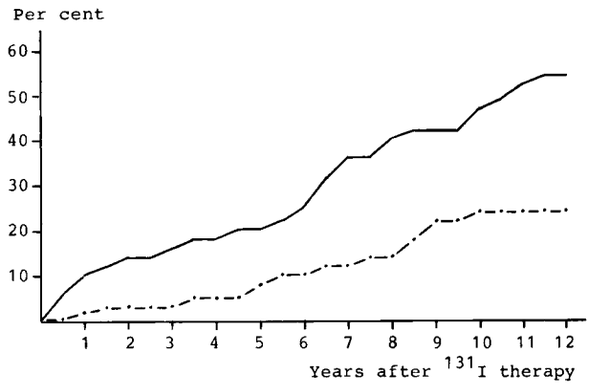


Fig. 5. Cumulative incidence of hypothyroidism after $^{131}$I therapy in patients without antibodies to cytoplasmic antigen before therapy. — Seropositive to cytoplasmic antigen after therapy. -·- Seronegative to cytoplasmic antigen after therapy.

## Discussion

$^{131}$I therapy for hyperthyroidism is followed by hypothyroidism in a considerable number of patients. Between 7 and 20 per cent of the patients become hypothyroid during the first year after therapy, and the cumulative incidence increases to 25 to 30 per cent within 7 to 12 years of treatment (BELING & EINHORN). At present all patients treated with $^{131}$I for hyperthyroidism between 1951 and 1977 at Radiumhemmet are analysed. The results after the analysis of the first 3 000 of these cases show that the cumulative incidence of hypothyroidism increases steadily to 70 per cent within 25 years after such therapy.

$^{131}$I therapy for hyperthyroidism may trigger an autoimmune reaction manifested as an increase in humoral thyroid antibodies (EINHORN et coll. 1965, O'GORMAN et coll. 1964). This also occurred after $^{131}$I therapy in euthyroid subjects (EINHORN et coll. 1966). Previously it was shown that patients, who had demonstrable antibodies before $^{131}$I treatment, developed hypothyroidism to a greater extent than those without such antibodies (LUNDELL & JONSSON). The present results show that this difference persists as long as 12 years after treatment. In the previous series, hypothyroidism developing within one year after the $^{131}$I therapy also occurred significantly more often in patients without demonstrable antibodies to thyroid cytoplasmic antigen before

treatment, but who developed such antibodies after treatment, than in those who remained seronegative (LUNDELL & JONSSON). With the prolonged observation period of the present series, a significant difference was found also for hypothyroidism developing more than one year after the therapy.

The increase in thyroid antibodies after $^{131}$I therapy is temporary and lasts about one year, and at the time of hypothyroidism the level of humoral antibodies usually is at pre-treatment or lower levels (EINHORN et coll. 1965, 1966). It is thus not likely that this humoral autoimmune reaction caused by the $^{131}$I therapy can alone account for the continued increase in the cumulative incidence of hypothyroidism many years after treatment. It is not known whether $^{131}$I therapy also triggers an autoimmune cell-mediated response. If so, such a response could contribute to the progressive development of hypothyroidism. Another explanation could be a progressive atrophy similar to that which has been observed after external irradiation (EINHORN et coll. 1965).

The present analysis shows that the results previously reported at an early stage of the same group of patients (LUNDELL & JONSSON) are valid also for a longer follow-up period. It is evident that thyroid antibodies—and mainly those to thyroid cytoplasmic antigen—as well as the type of goiter, are of importance in the development of hypothyroidism after $^{131}$I therapy for hyperthyroidism. Immunologic factors must therefore be taken into account when comparing the results of different $^{131}$I treatment schedules for hyperthyroidism.

The level of thyroid antibodies before treatment could be a valuable factor when determining the dose of $^{131}$I administered for the treatment of hyperthyroidism. Patients with a high risk of developing hypothyroidism could possibly be treated with higher doses, thereby curing them without unnecessary delay, but also bringing about the onset of hypothyroidism more rapidly. Some of the problems arising in the follow-up of these patients would then be diminished.

## SUMMARY

A series of 191 patients with hyperthyroidism treated with $^{131}$I was examined for the presence of antibodies to thyroid cytoplasmic antigen and to thyroglobulin before and after therapy, and followed up for 12 years. Patients with thyroid antibodies before therapy had a significantly higher incidence of hypothyroidism than those without demonstrable antibodies ($p<0.01$). A higher incidence of hypothyroidism occurred in the presence of antibodies to thyroid cytoplasmic antigen than to thyroglobulin. Patients without demonstrable antibodies to thyroid cytoplasmic antigen before the therapy and who afterwards developed such antibodies had a significantly higher incidence of hypothyroidism than those who remained seronegative ($p<0.01$).

## ACKNOWLEDGEMENTS

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