# Subsequent Fertility and Birth Histories of Children and Adolescents Treated with $^{131}I$ for Thyroid Cancer

Salil D. Sarkar, William H. Beierwaltes, Satinder P. Gill, and Betty J. Cowley

*University of Michigan Medical Center, Ann Arbor, Michigan*

***Forty patients aged 20 years or less who had been treated with $^{131}I$ after surgery for papillary–follicular thyroid carcinoma were contacted for followup study. Five had died and two were unmarried; the remaining 33 were studied with respect to their subsequent reproductive histories and the health of the offspring. The mean age at the time of the first $^{131}I$ therapeutic dose was 14.6 years (range 6–20), and the average followup interval, from that first dose until followup, was 18.7 years (range 14–25). The mean total dose of $^{131}I$ was 196 mCi (range 80–691). The incidences of infertility (12%), miscarriage (1.4%), prematurity (8%), and major congenital anomaly (1.4%) found in this series are not significantly different from those in the general population. Thus, our study offers no overt evidence of genetic damage in children and adolescents treated with high doses of $^{131}I$ for thyroid carcinoma.***

**J Nucl Med 17: 460–464, 1976**

Numerous reports (*1–5*) have shown that $^{131}I$ therapy in conjunction with surgery improves the survival rate in selected cases of papillary–follicular carcinoma of the thyroid. Fear of possible genetic mutation, however, has restricted the use of $^{131}I$ therapy in younger patients. Studies by Starr et al (*6*) and Safa et al (*7*) on hyperthyroid children and adolescents treated with $^{131}I$ (mean dose below 10 mCi) have not shown any difference in reproductive capacity or health of offspring of these patients compared with the general population. However, we have seen no similar study of young patients with thyroid carcinoma, which is treated with much higher doses of $^{131}I$. The present report concerns the fertility and birth histories of 33 such patients.

## MATERIALS AND METHODS

**Patient selection.** A review of hospital records disclosed that 40 young patients (aged 20 years or less) had had surgery and subsequent radioiodine therapy for papillary–follicular carcinoma of the thyroid between 1947 and 1960. Of these, five had died: three of thyroid cancer, one of embryonal carcinoma of the testis, and another of hepatocellular carcinoma. A sixth was not married, and a seventh had been widowed shortly after marriage, thus leaving 33 patients for this study.

**Collection of data.** The patients (13 males and 20 females*) were contacted by telephone in 1974 and standard fertility and birth histories were obtained, including reproductive capacity, miscarriages, premature births, stillbirths, neonatal mortality, and congenital defects. Infertility was assumed if conception had not occurred after more than a year of marriage and no contraceptives were used. Additional information, where necessary, was obtained from hospital records and from the patients' personal physicians.

Received July 29, 1975; revision accepted Jan. 20, 1976.

For reprints contact: William H. Beierwaltes, Sect. of Nuclear Medicine, University of Michigan Medical Center, Ann Arbor, Mich. 48109.

* This female-to-male ratio (1.5) parallels the ratio of 1.4 reported by Hempelman for thyroid carcinoma, including neoplasms treated with x-ray in infancy (*J Natl Cancer Inst* 38: 317–341, 1967).

**Age distribution.** At the time of the first $^{131}I$ therapy, six patients were aged 6–10 years, 11 were aged 11–15, and 16 were aged 16–20; the mean age for all 33 patients was 14.6 ± 4.1 (1 s.d.). Their ages at the time of followup ranged over 25–43 years, with a mean of 32.2 ± 5.0. The time interval between the first therapy and the present study was 14–25 years, with a mean of 18.7 ± 3.4.

**Dose.** The total dose of $^{131}I$ was 80–691 mCi, with a mean of 196 ± 133 mCi. The dose was 80–100 mCi in four patients, 101–150 mCi in 15, 151–250 mCi in seven, 251–350 in three, and 351–450 mCi in two. The other patients (Nos. 25 and 40 in Table 1) received 454 and 691 mCi, respectively. Eighteen patients had received a single dose of $^{131}I$, 13 received two doses, one received three, and one received four. In those patients receiving more than one dose, the $^{131}I$ therapy was completed within 3 years, except for two patients (Nos. 13 and 25) who received two doses, 16 and 4 years apart, respectively.

Although the absorbed radiation dose from $^{131}I$ in these patients could not be calculated directly, a rough estimate may be obtained from MIRD Dose Estimate Report No. 5 (*8*). Thus, for a total administered dose of 80–691 mCi, the cumulative total-body radiation dose (0.24 rad/mCi) would range over 20–166 rads and the gonadal dose (0.1 rad/mCi) would be 8–69 rads, with variations due to differences in body and organ masses.

## RESULTS

Tables 1 and 2 give the details of each patient's therapy, reproductive history, and offspring com-

**TABLE 1. REPRODUCTIVE HISTORY OF PATIENTS TREATED WITH $^{131}I$ FOR THYROID CANCER**

| Patient No. | Sex | Age at 1st dose (years) | Doses (mCi) | Age at study (years) | Fertility | No. of live births |
|---|---|---|---|---|---|---|
| 1 | F | 3 | 40 | Deceased at age 4 | — | — |
| 2 | M | 3 | 4 | Deceased at age 4 | — | — |
| 3 | M | 9 | 60, 60 | Deceased at age 29 | Unmarried | — |
| 4 | M | 12 | 60, 172, 208, 166 | Deceased at age 22 | Unmarried | — |
| 5 | F | 12 | 95 | 33 | Unmarried | — |
| 6 | F | 20 | 205 | Deceased at age 21 | Unmarried | — |
| 7 | F | 20 | 125 | 38 | Widowed soon after marriage | — |
| 8 | M | 6 | 50, 60 | 28 | Fertile | 1 |
| 9 | M | 7 | 60, 60 | 28 | Fertile | 2 |
| 10 | M | 8 | 119 | 26 | Fertile | 3 |
| 11 | M | 9 | 50, 80, 130 | 32 | Fertile | 3 |
| 12 | F | 10 | 177 | 25 | Fertile | 3 |
| 13 | F | 10 | 180 | 32 | Fertile | 3 |
| 14 | M | 11 | 80 | 32 | Fertile | 4 |
| 15 | F | 12 | 80, 70, 80 | 32 | Fertile | 5 |
| 16 | F | 12 | 153, 102 | 29 | Fertile | 3 |
| 17 | F | 12 | 95, 146, 206 | 26 | Fertile | 1 |
| 18 | M | 13 | 125 | 30 | Fertile | 1 |
| 19 | F | 13 | 95 | 27 | Fertile | 1 |
| 20 | M | 13 | 40, 72 | 39 | Fertile | 3 |
| 21 | F | 13 | 195 | 28 | Fertile | Pregnant with 1st child |
| 22 | F | 14 | 121 | 29 | Infertile for 3 years before 1st pregnancy* | 1 |
| 23 | F | 14 | 122 | 30 | Fertile | 2 |
| 24 | F | 14 | 80, 80, 92, 150 | 36 | Fertile | 2 |
| 25 | F | 16 | 50, 100, 100, 204 | 30 | Fertile | 3 |
| 26 | M | 16 | 123 | 33 | Fertile | 5 |
| 27 | M | 17 | 60, 125 | 43 | Fertile | 3 |
| 28 | M | 17 | 126 | 35 | Fertile | 2 |
| 29 | M | 17 | 50, 80, 80 | 39 | Infertile (married 14 years) | — |
| 30 | M | 18 | 97 | 41 | ? Infertile† (married 3 years) | — |
| 31 | F | 18 | 130 | 36 | Fertile | 3 |
| 32 | F | 18 | 125 | 35 | Fertile | 2 |
| 33 | F | 18 | 122 | 34 | Fertile | 2 |
| 34 | F | 18 | 100 | 40 | Fertile | 1 |
| 35 | F | 19 | 120 | 36 | Fertile | 4 |
| 36 | F | 19 | 125 | 35 | Fertile | 1 |
| 37 | F | 20 | 146 | 36 | Fertile | 2 |
| 38 | F | 20 | 217 | 35 | Infertile (married 14 years) | — |
| 39 | F | 20 | 60, 90, 82, 100 | 44 | Fertile | 3 |
| 40 | M | 20 | 226, 230, 235 | 34 | Fertile | 2 |

Incidence of infertility in study, 12%
Prevalence in normal population, 12%
* First pregnancy terminated in miscarriage at 3.5 months. Incidence for miscarriage in study was 1.4%, whereas normal prevalence is 15%.
† Spends most of his time in mental institution.

**TABLE 2. BIRTH HISTORY OF PATIENTS TREATED FOR THYROID CANCER**

| Parent (Pt. No.) | Sex of offspring | Age at study (years) | Perinatal complications |
|---|---|---|---|
| 8 | M | 1 week | None |
| 9 | M | 5 | None |
| | F | 2 | None |
| 10 | M | 6 | None |
| | M | 4 | None |
| | F | 2 | None |
| 11 | M | 6 | 2 months premature: healthy |
| | M | 2 | None |
| 12 | M | 7 | None |
| | F | 3 | None |
| | M | 2 | None |
| 13 | M | 11 | None |
| | F | 9 | None |
| | M | 2 | None |
| 14 | F | 9 | 6 weeks premature: healthy twins |
| | F | 9 | |
| | M | 4 | None |
| | F | 2 | None |
| 15 | F | 14 | None |
| | F | 13 | None |
| | F | 6 | None |
| | F | 3 | None |
| | M | 1 | None |
| 16 | F | 10 | None |
| | M | 8 | None |
| | M | 2 weeks | None |
| 17 | M | 1 month | None |
| 18 | M | 2 | None |
| 19 | F | 1 | None |
| 20 | M | 14 | None |
| | M | 11 | None |
| | F | 5 | 1 month premature: healthy |
| 22 | M | 1 | Cesarian birth: healthy |
| 23 | F | 11 | None |
| | M | 8 | None |
| 24 | F | 16 | None |
| | F | 15 | None |
| 25 | M | 9 | None |
| | F | 8 | None |
| | M | 5 | None |
| 26 | M | 12 | None |
| | F | Deceased* | None |
| | F | Deceased† | None |
| | F | 10 | None |
| | F | 5 | None |
| 27 | M | 10 | None |
| | M | Deceased‡ | 1 month premature |
| | M | 8 | None |
| 28 | M | 13 | None |
| | M | 10 | None |
| 31 | F | 13 | None |
| | F | 11 | None |
| | F | 7 | None |
| 32 | F | 13 | None |
| | M | 10 | None |
| 33 | F | 7 | None |
| | F | 5 | None |
| 34 | M | 18 | None |
| 35 | M | Deceased‡‖ | None |
| | M | 10 | None |
| | M | 9 | None |
| | F | 6 | None |
| 36 | F | 13 | None |
| 37 | M | 9 | None |
| | F | 6 | None |
| 39 | F | 20 | None |
| | M | 18 | None |
| | M | 14 | None |
| 40 | M | 8 | 3 weeks premature: healthy |
| | M | 2 | None |

Incidence of premature offspring, 8%
Prevalence in normal population, 7–14%
* Died at age 8 months of meningitis.
† Died at age 4 in auto accident.
‡ Died within 24 hr of birth.
‖ Had congenital cardiac anomaly (1.4% incidence); normal prevalence of significant congenital anomaly is 1–2%.

plications, along with the incidence of complications in our series and the published normal incidences of infertility (*9*), miscarriage (*10,11*), prematurity (*12,13*), and congenital anomalies (*12*).

Of the 13 men, two (15%) are childless. One of them (No. 29) has been married for 14 years. Although the other (No. 30) has been married for 3 years, he has had a psychiatric disorder since childhood and spent most of his time in a mental institution. If this latter patient is excluded, the incidence of infertility would be 8%. The wives of the remaining 11 have had 28 live births, six of which (21%) were premature. However, two of these children (patient No. 14) were twins and, if these two are excluded, the incidence of prematurity would be 15%. Of the other premature children, one died in the neonatal period; this child had two healthy siblings.

Of the 20 women in the series, two (10%) have a history of infertility. One of them (No. 38) is childless after 14 years of marriage. Another (No. 22) was infertile for 3 years before a fruitful pregnancy; this patient had a spontaneous abortion 10 months prior to the first childbirth. One patient (No. 21) was pregnant at the time of followup. Thus, 18 of the 20 women have had 43 live births. Patient No. 35 had one infant with a congenital cardiac anomaly and it died soon after birth; she has had three other children, all healthy.

Altogether, our 33 patients (or their wives) had 71 live births. Four patients (12%) were infertile

(normal published incidence, 12%), and there were six (8%) cases of prematurity (7–14%), one (1.4%) miscarriage (15%), and one (1.4%) birth with a significant congenital anomaly (1–2%). In those four patients with infertility, workup for an etiology either was not done or was inconclusive.

Although the time interval between the last dose and conception is important, it is hazardous to comment on this factor because of the variable period between dose and marriage. We note, nevertheless, that there were successful pregnancies in two female patients (Nos. 24 and 39) as early as 2.3 years after the dose, and in three other female patients (Nos. 32, 34, and 36), within 2.5–3.0 years after the last dose of $^{131}$I.

We also studied the relationship of reproductive history to such known factors as age at first therapy, total dose, and interval before followup. At the time of the first therapy, the mean age of the nine patients with complications was 16.3 ± 3.7 years, which is not significantly different from the mean age (14.0 ± 4.1) of the 24 patients with no complications ($p > 0.10$). The mean total dose in patients with complications was 224 ± 184 mCi as opposed to 186 ± 112 mCi in those without complications; this difference is not statistically significant ($p > 0.40$). An incidental finding was that five (56%) of the patients with complications, compared to 29% of those without, had received x-ray therapy either before or after radioiodine treatment. Three of these patients received a mean dose of 3,767 rads; in the two others the doses are not known. The mean durations of followup in the groups with and without complications were 19.6 ± 4.2 years and 18.4 ± 3.1 years, respectively.

## DISCUSSION

Although the demonstration that no harmful genetic effects have been observed in children and adolescents (and their offspring) treated for hyperthyroidism with $^{131}$I (*7*) has elicited considerable interest, we have seen no similar studies of children and adolescents treated for thyroid carcinoma, which involves $^{131}$I doses 10–68 times greater than those used to treat Graves' disease.

Our studies show no overt evidence of genetic damage in the children and adolescents of the latter group. Even following estimated cumulative radiation doses ranging from 20–166 rads to the whole body and 8–69 rads to the gonads, the incidence of infertility, miscarriage, prematurity, and congenital anomaly is not significantly different from that seen in the general population. Furthermore, where these occurred, there was no relationship to age at first therapy, total dose of $^{131}$I, or duration of followup. However, patients reporting complications had a higher incidence of added x-ray therapy.

Although theoretical estimates of genetic risks in humans exposed to ionizing radiation have been published (*14*), they are based on animal data, and we lack conclusive clinical evidence of genetic damage in humans exposed to therapeutic radiation. Genetic changes have been extensively investigated in the heavily irradiated survivors of the atomic bombings (*15,16*), and no increases in major congenital anomalies, stillbirths, or infant mortality were found. The only positive finding was an alteration of the sex ratio in the offspring.

Radioiodine therapy of metastatic thyroid carcinoma after surgery is a simple procedure that can be life-saving in certain situations (*1,2*). Nevertheless, its use may be denied patients, especially in the younger age groups, for fear of genetic damage. This report of our limited experience should encourage others to publish their results so that a significant body of data can be accumulated, similar to that already accumulated on the reproductive histories of children treated with $^{131}$I for hyperthyroidism. Meanwhile, it may be reassuring to parents of children about to be treated with $^{131}$I for metastatic thyroid carcinoma to know that our experience to date provides no cause for alarm.

## REFERENCES


1. VARMA VM, BEIERWALTES WH, NOFAL M, et al: Treatment of thyroid cancer: Death rates after surgery and after surgery followed by sodium iodide I-131. *JAMA* 214: 1437–1442, 1970

2. HARNESS JK, THOMPSON NW, SISSON JC, et al: Differentiated thyroid carcinoma—Treatment of distant metastases. *Arch Surg* 108: 410–419, 1974

3. LEEPER RD: The effect of $^{131}$I therapy on survival of patients with metastatic papillary or follicular thyroid carcinoma. *J Clin Endocrinol Metab* 36: 1143–1152, 1973

4. POCHIN EE: Radioiodine therapy of thyroid cancer. *Semin Nucl Med* 1: 503–515, 1971

5. CASSANO C, BASCHIERI I, BASCHIERI L: Follow-up of 188 cases of thyroid carcinoma after combined surgical and radioiodine treatment. In *Thyroid Neoplasia*. London, Academic, 1968, pp 143–155

6. STARR P, JAFFE HL, OETTINGER L: Later results of $^{131}$I treatment of hyperthyroidism in 73 children and adolescents: 1967 follow-up. *J Nucl Med* 10: 586–590, 1969

7. SAFA AM, SCHUMACHER OP, RODRIGUEZ-ANTUNEZ A: Long-term followup results in children and adolescents treated with radioactive iodine ($^{131}$I) for hyperthyroidism. *N Engl J Med* 292: 167–171, 1975

8. MIRD Dose Estimate Report No. 5: Summary of current radiation dose estimates to humans from $^{123}$I, $^{124}$I, $^{125}$I, $^{126}$I, $^{130}$I, $^{131}$I, and $^{132}$I as sodium iodide. *J Nucl Med* 16: 857–860, 1975

9. GUTTMACHER AF: Fertility of man. *Fertil Steril* 3: 281–289, 1952

*10.* WARBURTON D, FRASER FC: Spontaneous abortion risks in man—Data from reproductive histories collected in a medical genetics unit. *Am J Hum Genet* 16: 1–25, 1964

*11.* ERHARDT CL: Pregnancy losses in New York City, 1960. *Am J Public Health* 53: 1337–1352, 1963

*12.* HELLMAN LM, PRITCHARD JA, WYNN RM: *Williams' Obstetrics.* 14th ed. New York, Appleton–Century, 1971, pp 529, 1063–1065

*13.* NISWANDER KR, GORDON M: *The Collaborative Perinatal Study of the National Institutes of Neurological Diseases and Stroke. The Women and Their Pregnancies.* Philadelphia, Pa., W. B. Saunders, 1972

*14.* International Commission on Radiological Protection, Committee I: The evaluation of risks from radiation. ICRP Report. *Health Phys* 12: 239–302, 1966

*15.* NEEL JV, SCHULL WJ (National Academy of Sciences, National Research Council): The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki. III. Washington, D.C., Government Printing Office, 1956, Publ. No. 461

*16.* SCHULL WJ, NEEL JV: Radiation and the sex ratio in man—Sex ratio among children of survivors of atomic bombings suggests induced sex-linked lethal mutations. *Science* 128: 343–348, 1958

## NOTICE OF NEXT ABNM CERTIFYING EXAMINATION

The American Board of Nuclear Medicine announces that its Fourth Certifying Examination in Nuclear Medicine will be held on Saturday, September 18, 1976.

The 1976 examination will be the last given under the present requirements of a combination of training and experience. Beginning with the 1977 examination, it will be necessary for candidates to have had two years of creditable performance in an accredited nuclear medicine residency.

Applications for the 1976 examination are available from:

**The American Board of Nuclear Medicine**
**475 Park Avenue South**
**New York, New York 10016**
**Telephone (212) 889-0717**

Applications should be accompanied by an application fee of $400 and submitted by the deadline of June 1st, 1976.

## SNM GREATER NEW YORK AREA CHAPTER SECOND ANNUAL SCIENTIFIC MEETING

**September 10–12, 1976** **New York Hilton** **New York, New York**

The 2nd Annual Scientific Meeting of the Greater New York Area Chapter of the Society of Nuclear Medicine will be held Friday through Sunday, September 10–12, 1976, at the New York Hilton at Sixth Avenue and 53rd Street in New York City.

In addition to selected scientific papers and commercial exhibits, the meeting will feature survey papers and workshops conducted by invited faculty. There will be a Business Meeting on September 11 at 4:00 p.m.

Submitted papers should be sent no later than July 15, 1976, to:

**Richard S. Benua, M.D., Program Chairman**
**Nuclear Medicine Service, Memorial Hospital**
**1275 York Avenue**
**New York, N.Y. 10021**