Gonadal Radiation Dose and Its Genetic Significance in Radioiodine Therapy of Hyperthyroidism

James S. Robertson and Colum A. Gorman

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Published estimates of radiation dose to the gonads from ^{131}I therapy of Graves' disease vary widely, largely because of differences in assumptions regarding the details of iodine kinetics. The calculations described in this paper show that hyperthyroid patients treated with 10 mCi of ^{131}I will usually receive a total radiation dose to the ovaries or testes of less than 3 rad. Several common roentgenographic diagnostic procedures may involve a greater radiation dose and a greater genetic hazard than does the usual ^{131}I treatment for hyperthyroidism. It is important to minimize total exposure to radiation, but it seems unreasonable to deny ^{131}I treatment for hyperthyroidism to young men and nonpregnant young women on the grounds of genetic hazard alone.

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Conflicting views are expressed in the literature and in various endocrinology textbooks on the absorbed dose of radiation that the ovaries or testes receive during radioiodine treatment for thyrotoxicosis and on the correct clinical advice to give young persons regarding such treatment. There is a 100-fold divergence among published estimates of ovarian exposure to ^{131}I radiation (Table 1). For these reasons, we decided (A) to recalculate the gonadal radiation dose from radioiodine; (B) to compare this radiation dosage with that from common roentgenographic procedures; and (C) to attempt an assessment of the genetic hazard that such radiation doses involve. While there are other hazards associated with all ionizing radiation, only the genetic effects will be considered here. Specific problems related to radioiodine therapy have been reviewed by Greig (*21*) and by Becker and Hurley (*22*).

Gonadal radiation dose estimates in the literature. Table 1 compares published estimates of the ovarian radiation dose from ^{131}I. The higher estimates usually result from the use of assumptions that originated as a basis for health physics rules for the protection of radiation workers and the general public. Such results are valid for their stated purpose, but they lose meaning when extrapolated to patients being treated for hyperthyroidism, because in this disease the iodine metabolism and excretion patterns do not correspond to the basic assumptions. Moreover, the destructiveness of the therapeutic radiation still further distorts the patient's iodine metabolism, which invalidates even the dose estimates extrapolated from diagnostic quantities of radioiodine.

At least one ovarian dose estimate, that given by Trunnell et al. (*13*), appears to involve a decimal-point error in the calculation. A recalculation, using their data (*13*) and method (*23*), leads to a revised estimate of 0.48 rad/mCi.

MODEL OF IODINE KINETICS

The absorbed radiation dose received by the gonads is not uniquely determined by the amount of radioactivity administered. It depends on the concentration of radioiodine as a function of time not only in the gonads themselves, but also in the other tissues from which γ radiation can reach the gonads.

The metabolism of iodine is complicated, involving not only uptake of iodide and secretion of iodi-

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For reprints contact: James Robertson, Dept. of Laboratory Medicine, Mayo Clinic, Rochester, MN 55901.

nated hormones by the thyroid, but also absorption from the intestinal tract, excretion by the kidneys, and secretion by the gastric and salivary glands. The kinetic aspects of the physiology of the thyroid gland and the metabolism of iodine and the thyroid hormone have recently been reviewed in detail (*24*).

TABLE 1. ESTIMATES OF OVARIAN* RADIATION DOSE FROM IODINE-131

Dose (rad/mCi)	Method†	Comment	Reference
0.05	CT	Compares other radioiodines	Wellman & Anger (1)
0.11	N	From 0.4 rad/3.6 mCi	Dillon (2)
0.14	CT	For euthyroid patients	MIRD Committee (3)
0.2	CT,L	Cites reported range 0.056–8.5 mrad/μCi	Roedler et al. (4)
0.037–0.242	CD	Measured ^{131}I in 100 ovaries	Weijer (5)
0.335	CT	For 35% thyroid uptake	Ellett (6)
0.4	N		Means et al. (7)
0.4	L	From 2 mrad/5 μCi whole-body dose	Blahd (8)
0.45	CT		Seltzer et al. (9)
0.13–1.17	CD	Measured ^{131}I in blood and thyroid in 20 cases	Weijer et al. (10)
0.3–1.5	L		ICRP (11)
1.5	CT		Myant (12)
1.65	CD,L	Excluding data from Ref. 13	Comas & Brucer (14)
1.7	CD	Integral dose, 130 kg-rad/mCi	Green et al. (15)
0.18–2	CT	Blood dose; average, 0.55 rad/mCi	Quimby et al. (16)
2.6	CD,L	Average including data from Ref. 13	Comas & Brucer (14)
2–2.7	L	Gonads	Garby (17)
2.7	CD	From 134 mrad/50 μCi	Irie et al. (18)
3.5	CT	Whole body	Vennart & Minski (19)
4	N	From 0.2 rad/0.05 mCi whole body	PDR (20)
5.37	CD	From 6.47 e.r./mCi × 0.83 rad/e.r.; see text	Trunnell et al. (13)

* If ovarian dose is not cited in reference, another approximation is given as indicated in comment.

† CD, calculated from new data given in reference; CT, calculated from theory and data in literature; L, literature cited; N, source not indicated.

Even among tissues that are not actively involved in iodine metabolism, the iodine concentration at a given time is not uniform (*13,25–27*). Nevertheless, in euthyroid and hyperthyroid patients the kinetics of iodine distribution are so strongly dominated by three rate-determining processes (renal excretion, thyroid uptake, and thyroid hormone production) that a greatly simplified model may be used in calculating the radiation dose. In the model used in the present work (Fig. 1), the rate constants of these three dominant processes are labeled r_1, r_2, and r_3, respectively. Basically similar models have been used by Singh et al. (*28*), Berman et al. (*29*), DeGroot (*30*), and Colard et al. (*31*). The rates of exchange between blood and all other tissues are assumed to be sufficiently rapid as to be negligible in affecting the overall kinetics. In particular, this assumption applies to the ovaries or testes and to the three sections of the intestine indicated in Fig. 1, for which special calculations are made for their contributions to the radiation dose.

In the calculations of radiation dose to the gonads during radioiodine treatment, the following sources will be treated explicitly: (A) β^- and γ radiation from radioiodine within the gonad itself and γ radiation from radioiodine in (B) the urinary system (in particular, from the bladder), (C) the thyroid, (D) the intestine, and (E) all other tissues (whole body). To calculate the whole-body contribution, a dispersion mass of 70 kg is assumed. For gonadal self-irradiation, however, the higher concentrations present in the blood are used, because for β irradiation the local concentration is the determining parameter. The ^{131}I concentration in blood is obtained by assuming an apparent dilution volume of 25 liters (*30,31*).

From a mathematical viewpoint, the radiation dose to the ovary could range from more than 7 rad/mCi (for the extreme condition of no renal excretion and no uptake in the thyroid) to a few millirads per millicurie (for the other extreme of 100% uptake and retention in the thyroid). Much of this range is not physiologically meaningful, and only a restricted portion applies to patients considered for radioiodine treatment. In particular, hyperthyroid patients generally do not have a thyroid uptake below 30%.

CALCULATIONS

Radiation dose. The calculations for absorbed radiation dose are based on the methods developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine (*32*). The basic expression for the total mean absorbed dose to a target organ, $\bar{D}(r_k)$, is

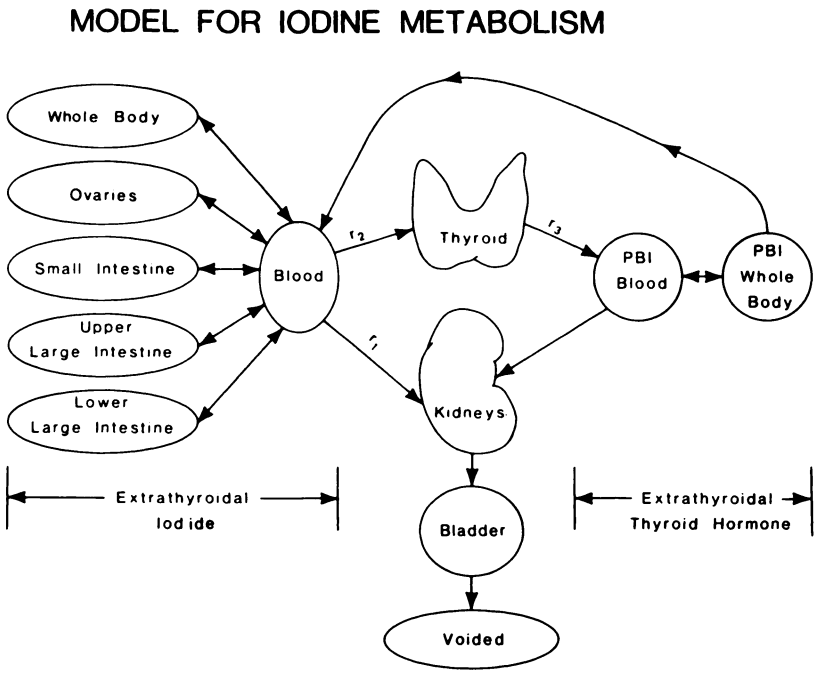

FIG. 1. Model of iodine metabolism as simplified for use in dose calculations. Extrathyroidal thyroid hormone is considered to be uniformly distributed throughout body.

$$\bar{D}(r_k) = \sum_h \bar{D}(r_k \leftarrow r_h),$$

$$\bar{D}(r_k) = \sum_h \tilde{A}_h(0,\infty)\frac{\sum_i \Delta_i \Phi_i(r_k \leftarrow r_h)}{m_k},$$

where $\bar{D}(r_k)$ is the total mean dose to the target organ r_k (rads); $\bar{D}(r_k \leftarrow r_h)$ is the dose to r_k from source organ r_h (rads); $\tilde{A}_h(0,\infty)$ is the cumulated activity in source organ r_h from $t = 0$ to $t = \infty$ (μCi-hr); m_k is the mass of the target organ r_k (gm); Δ_i is the mean energy emitted per nuclear transformation for i-type radiations (gm-rad/μCi-hr); $\Phi_i(r_k \leftarrow r_h)$ is the absorbed fraction of energy for the target organ r_k for i-type radiations emitted in source region r_h. Values for Δ_i for ^{131}I are available in *MIRD Pamphlet No. 10* (*33*). The Δ for nonpenetrating radiations from ^{131}I is 0.4165 gm-rad/μCi-hr. Since values for the mean dose per unit cumulated activity, S, have been tabulated (*36*), many of the tedious steps in the dose calculation can be eliminated:

$$S(r_k \leftarrow r_h) = \frac{\sum_i \Delta_i \Phi_i(r_k \leftarrow r_h)}{m_k},$$

where $S(r_k \leftarrow r_h)$ is the mean dose to r_k per unit cumulated activity in source organ r_h. Thus, we have

$$\bar{D}(r_k) = \sum_h \tilde{A}_h(0,\infty) S(r_k \leftarrow r_h).$$

When S values are used to calculate the dose, certain specific assumptions are implied, namely, the masses of target and source organs as specified in Ref. *36*, a uniform distribution of activity in the source organ, a bladder containing 200 ml of urine, and the nuclear data.

Table 2 gives the "S" values (in rad/μCi-hr) for ovaries and testes irradiated from ^{131}I. For the sources shown, note that the "S" values for the ovaries are larger than those for the testes. However, the emphasis here will be on ovarian irradiation.

Cumulated activity ($\tilde{A}$). Values for $\tilde{A}$ for ^{131}I are not yet available in the MIRD pamphlets and must be developed independently. To represent radioiodine distribution in the body, we use three compartments (whole body, thyroid, and urinary bladder) during the first 24 hr, and four compartments (the original three plus extrathyroid radioiodinated thyroid hormone) from then on. The other compartments indicated in Fig. 1 are given special attention.

TABLE 2. "S" FACTORS FOR ^{131}I RADIATION DOSE (rad/μCi-hr) TO GONADS FROM VARIOUS ORGANS*

Source organs	Ovaries†	Testes†
Bladder contents	1.9E-05	1.4E-05
Stomach contents	1.4E-06	1.3E-07
Small intestine plus contents	2.7E-05	1.0E-06
Upper large intestine contents	3.4E-05	1.2E-06
Lower large intestine contents	5.0E-05	5.7E-06
Ovaries	3.9E-02	—
Testes	—	1.3E-02
Thyroid	4.1E-08	7.2E-09
Total body	1.1E-05	1.0E-05

* Abstracted from Snyder et al. (36).
† In this table, the notations are abbreviated forms, e.g., 1.0E-06 represents 1.0×10^{-6}.

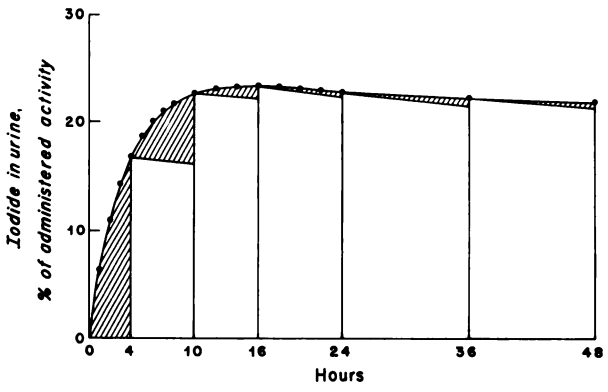

FIG. 2. Radioactivity excreted in urine. Curve is cumulative excreted activity, expressed as percentage of administered activity, without correction for radioactive decay. Activity present in bladder is indicated by shaded areas, and voided portion is represented by unshaded areas. Because of decay, voided activity decreases exponentially, as indicated by slanted tops of unshaded areas, except as additions to it are made when bladder is emptied. Curve was computed by assuming thyroid uptake of 75% of administered dose. Radiation dose to ovary from bladder is proportional to shaded areas, subject to corrections for changes in geometry as bladder size changes.

The kinetics of radioiodine is described by a system of differential equations, and integration of these expressions gives the desired values of $\tilde{A}$ for each compartment. This method accounts for the total activity administered A_0. That is, at any time t the sum of the activities in the various tissues and urine equals $A_0e^{-\lambda t}$. (For the present purposes, fecal excretion is included in urinary excretion.) An outline of the derivations is given in the Appendix.

Special calculations are needed for the urinary bladder in order to take the effects of voiding into account. This has been studied experimentally by Irie et al. (*18*) and by Comas and Brucer (*14*). The method we have used is illustrated in Fig. 2. In this example it is arbitrarily assumed that the bladder is emptied at 4, 10, 16, and 24 hr. Only the urine that enters the bladder during the 4–10-hr interval is used in calculating the dose to the ovary for the second period, and so on. The shaded areas in Fig. 2 indicate the portion of the integrated activity due to ^{131}I in the bladder.

Special calculations were also used for the radiation doses to the ovaries from activity in the intestinal tract and from ovarian self-irradiation, because these involve "S" factors greater than that for the whole body (Table 2). The activity in each section of the intestine is assumed to be proportional to its weight. In the calculation of the contribution to the radiation dose from the whole body, the activity assigned to the intestine is subtracted.

For ovarian self-irradiation, the genetically effective β^- dose is assumed to equal the average ovarian β^- dose (*5*) and the ovarian activity concentration is assumed not to exceed that in the blood (*5,13,25–27*).

The values of the rate constants r_1, r_2, and r_3 (Fig. 1) depend on the patient's physiologic status. Keating et al. (*37*) reported that the average renal excretion rate of iodide for euthyroid and hyperthyroid patients was $r_1 = 7.2\%/hr$, and their "collection rate" (chiefly thyroid uptake, but more broadly defined to include all nonrenal processes removing iodide from the blood) was $r_2 = 3.9\%/hr$ for normal subjects and $21.7\%/hr$ for hyperthyroid patients (*37*). The values chosen for r_3 will be discussed under the section on "Results." For predictive purposes, it would be convenient to relate the iodide excretion rate to the glomerular filtration rate, but the relationship is not simple and for a given patient a direct measurement of the radioiodide excretion rate is more reliable.

Computations. A prototype calculation is outlined in Table 3, using data representative of a hyperthyroid patient treated with ^{131}I. The values of $\tilde{A}/A_0$ were obtained by numerical evaluation of the equations given in the Appendix and the special calculations described in the foregoing section. The "S" values from Table 2 are multiplied by 1,000 to convert from rad/μCi-hr to rad/mCi-hr. The bladder dose was calculated by assuming voiding at 4, 10, 16, and 24 hr and at 12-hr intervals from 1 to 53 days (when 99% decay of ^{131}I is reached). For the

TABLE 3. PROTOTYPE CALCULATION OF RADIATION DOSE TO OVARIES FROM ^{131}I

($\lambda = 0.003588/hr$; $r_1 = 0.072/hr$; $r_2 = 0.217/hr$; and $r_3 = 0.0018/hr$)

Source organ	$\tilde{A}/A_0$ (μCi-hr/μCi)	"S" × 1,000 (rad/mCi-hr)	Radiation dose (rad/mCi)
Thyroid	142.6	0.000041	0.0058
Bladder	1.992	0.019	0.0378
Ovaries	0.0022	39	0.0864
Small intestine	0.0964	0.027	0.0026
Upper large intestine	0.0396	0.034	0.0013
Lower large intestine	0.0269	0.050	0.0013
Whole body (remaining)	6.297	0.011	0.0693*
Total	151.06		0.2045
Voided	127.67		
Total	278.73		

* This result overestimates the whole-body contribution to the ovarian dose because of partial duplication of the self-irradiation component (38). Also, the "S" factor for whole body has not been corrected for the deletion of the intestinal component.

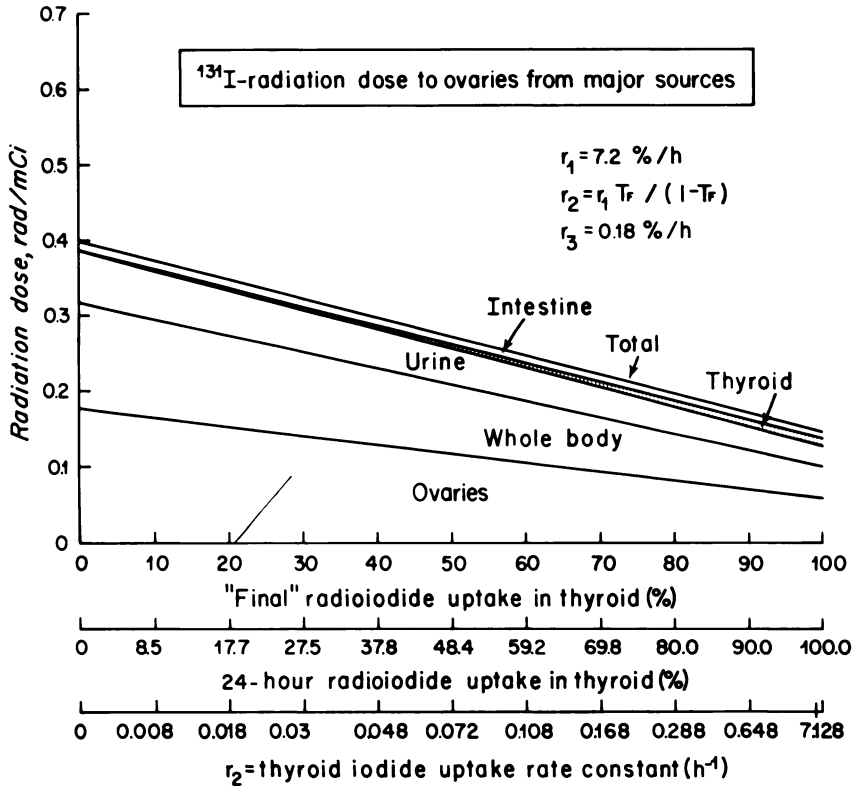

FIG. 3. Radiation dose to ovaries expressed as function of thyroid iodide uptake, separated into contributions from major sources. Area labeled "ovaries" represents self-irradiation. Contributions from other sources are indicated by vertical distances between upper and lower lines defining labeled space for each source. Basic abscissal scale used in these three figures measures "final" radioiodide uptake. This is closely related to 24-hr uptake, as shown by second abscissal scale, but relationship is affected by variations in r_1.

example used, the total radiation dose delivered to the ovary is 0.2 rad/mCi of administered ^{131}I.

RESULTS

The effects of the interplay among the dominant rate processes on the radiation dose to the ovaries are shown in Figs. 3, 4, and 5. It is simpler to plot the radiation dose as a function of the "final" or theoretical maximal thyroid uptake, defined as $T_F = r_2/(r_1 + r_2)$, rather than as a function of the more familiar 24-hr thyroid uptake T_{24}, which is related through the expression $T_{24} = T_F[1 - \exp(-24[r_1 + r_2])]$. For normal renal iodide excretion rates the numerical relationships between the "final" uptake

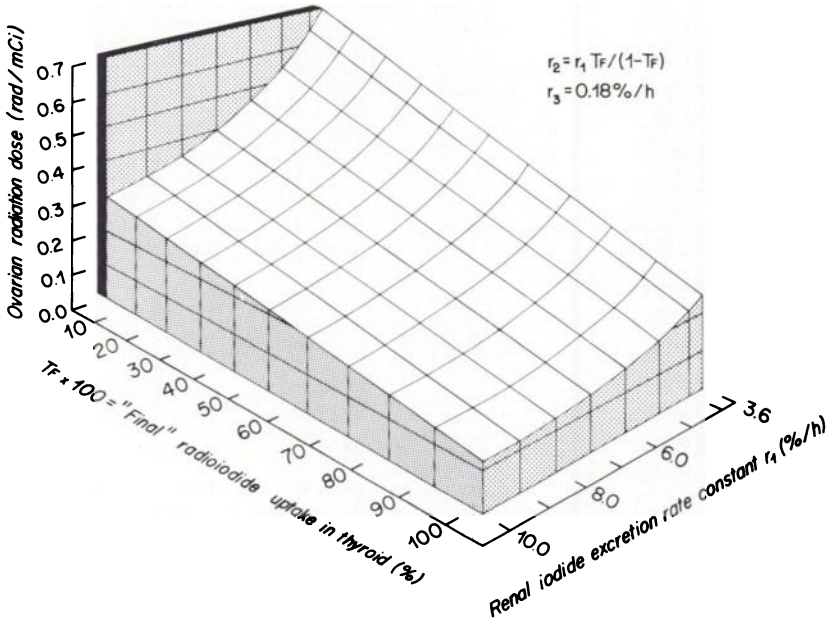

FIG. 4. Effect of variations in renal excretion rate constant r_1 on the ^{131}I radiation dose to ovary as function of thyroid radioiodide uptake. Note that, for given thyroid ^{131}I uptake, radiation dose to ovary increases if r_1 decreases.

and the 24-hr uptake are shown in the abscissal label of Fig. 3. This figure shows a breakdown of the radiation dose to the ovary into the contributions to the dose by the major organs considered. The total radiation dose is seen to be a nearly linear decreasing function of T_F. Figure 4 shows the effect of varying r_1 while keeping r_3 constant, and Fig. 5 shows the effect of varying r_3 for constant r_1.

The gonadal dose is seen to depend on r_1, r_2, and r_3 in a manner not simply expressed, and all of these variables should be evaluated for each patient to be treated. Note also that, due to radiation damage, the value of r_3 is progressively increased by radiation of the thyroid (*39*). Consequently, the value of r_3 obtained in a pretreatment tracer study usually will be lower than that for the therapeutic dose, and allowance for this difference should be made in calculating the radiation doses both to the thyroid and to the gonads.

The present results show how unreasonable it is to try to characterize the gonadal dose by a single number. Furthermore, the present calculations do not give full consideration to the effects of variations in weight and habitus of the patient. However, for comparison with the other estimates given in Table 1, we can conclude that under usual clinical conditions (a dose of less than 10 mCi of ^{131}I and a 24-hr thyroid uptake of more than 30%), the dose to the gonads would be unlikely to exceed 3.2 rad in a normal-sized patient.

Genetic effects. The genetic consequences of radiation are discussed in detail in the National Academy of Sciences' BEIR report (*40*) and the United Nations' UNSCEAR reports (*41,42*). In brief, radiation induces genetic effects either through gene mutations or through aberrations of chromosomal number or structure. The "spontaneous" mutation rate for humans is approximately 0.5×10^{-6} per gene per generation. Numerical estimates of the genetic risks of low doses of radiation are imprecise, but the dose that doubles the mutation rate is estimated to be 20–200 rem for humans (*40*). Although there is controversy about the applicability of the doubling-dose concept in human genetics, it has been widely used (*40,42*). In using radioiodine to treat hyperthyroidism, we deal with only 1–10% of the doubling dose. The genetic significance of such doses for the population at large has been discussed many times (*15,22,43,44*). For example, Quimby et al. (*16*) state: "If a relatively small group of prospective parents receives the doubling dose of radiation, no noticeable effects will be produced in the sum total of the first generation or of any subsequent one. For levels of radiation up to the doubling dose and even definitely beyond it, the genetic effects of radiation

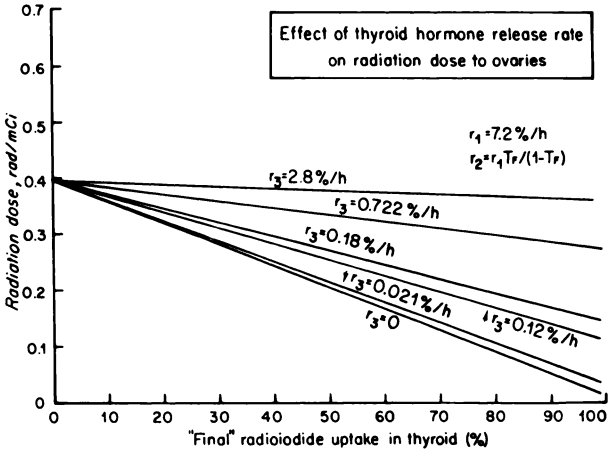

FIG. 5. Effect of variations in r_3 (rate constant for thyroid hormone release) on radiation dose to ovary as function of thyroid radioiodide uptake for $r_1 = 7.2\%/hr$. Similar families of curves are associated with other values of r_1. Dose to ovary increases with increase in r_3.

are only appreciable when reckoned over the population as a whole."

According to the ICRP report of 1966 (*43*), the increased risk of having a child with a harmful trait has been estimated at 1.6 per 100,000 live births for each rad of parental gonadal radiation above background. If the radiation dose to the ovary after a 10-mCi dose of ^{131}I in a patient assumed to have a 75% uptake is 2.0 rad, the maximal increased risk of having a child with a harmful trait would be 0.003% or less, whereas the spontaneous risk of such abnormalities is 0.8%.

Although it seems reasonably clear that radioiodine treatment for Graves' disease poses a very slight risk of gene mutation, it is important to ascertain that this is also true for chromosomal anomalies. The UNSCEAR report (*42*) indicates that reciprocal translocations may represent the predominant type of radiation-induced chromosomal anomalies and that the rate of induction varies from 0.6×10^{-4} per gamete per rad for acute high-dose radiation to 0.7×10^{-5} per gamete per rad at low doses. With the assumption that 6% of the unbalanced genomes survive to produce congenitally abnormal children, there will be about one such child per million births after low-dose acute radiation in which the cause can be attributed to reciprocal translocations. In the present state of our knowledge, it is not possible to give individual risk estimates for other categories of chromosomal change, including small deletions and duplications (*42*). The significance of the chromosomal changes in peripheral leukocytes (*45,46*) is unknown.

DISCUSSION

In selecting any form of treatment, one always tries to assess the alternatives available, the risks incurred, and the benefits to be expected. Surgical treatment, even in skilled hands, results in vocal cord paralysis or permanent hypoparathyroidism in about 1% of patients (*47*), and antithyroid drugs are associated with serious unfavorable reactions in 0.1–1% of patients (*48*). Radioiodine treatment provides rapid, effective, permanent, and inexpensive control of thyrotoxic Graves' disease. The disadvantages are the progressively increasing incidence of hypothyroidism (*49*), the still unsupported possibility of an increased incidence of thyroid carcinoma (*39,50–56*), and the possible genetic effects.

Table 4 shows the dose to the gonads from various commonly used diagnostic procedures. In most patients with Graves' disease treated with radioiodine, the gonad radiation dose will be in the same range as that from a barium enema, an excretory urogram, or a hysterosalpingogram. In our view, the evidence strongly supports the conclusion that ^{131}I therapy for Graves' disease poses such a slight genetic hazard that, solely on the grounds of genetic risk, it is unreasonable to withhold it from young men and nonpregnant young women. Whether any of the other drawbacks contraindicate its use is a matter to be decided for each individual patient.

APPENDIX

Formulas used for integrated activity, $\bar{A}/A_0$, in selected tissues. *Assumptions.* The simplified model of iodine metabolism diagrammed in Fig. 1 is used.

If radioiodine is administered orally, the kinetics of the first half hour or so depends on absorption from the gastrointestinal tract, but for simplicity we shall assume intravenous administration. A small correction for oral administration may be applied if desired.

Except for the initial delay in the intestine and a similar delay in the reabsorption of iodide secreted into the intestinal tract, it will be assumed that the exchange rates between blood and all nonthyroid organs are sufficiently rapid that the nonthyroid iodide may be treated as a single compartment. The two principal paths of removal of iodide from this compartment are indicated by r_1, the fractional rate of excretion by the kidneys into urine, and r_2, the fractional rate of uptake by the thyroid. A 24-hr delay in the secretion of radioactive thyroid hormone is assumed, after which the loss of radioiodine from the thyroid is indicated by r_3. This rate constant includes both the fractional rate of secretion of protein-bound iodine and any loss of free iodide from the thyroid.

The distribution of protein-bound iodine is known to differ from that of iodide (*57,58*), but this difference is neglected on the grounds that its effect on the gonadal dose is minor. The two iodine compartments are treated as being separate but coextensive, so that the two values of $\bar{A}(0,t)/A_0$ for a given organ are additive.

Degradation of the thyroid hormone introduces a feedback into the iodide compartment. The mathematical complications introduced by this lead to equations that, although readily handled by analog or digital computers, are too unwieldy for analytic solutions. For the present purposes it is assumed that the conversion to iodide is relatively rapid, so that the fractional rate of excretion of the degraded-thyroid-hormone iodine may be equated to that of iodide. This simplification leads to solutions that can be evaluated on a programmable desk calculator, and these equations are derived in the following sections. The symbols used are defined in Table A1.

Equations. With the simplifications discussed, the equations for the rates of change of activity in the four compartments are as follows:

$$dB/dt = -(\lambda + r_1 + r_2)B = -X_2B$$
$$dT/dt = r_2B - (\lambda + r_3)T = r_2B - X_3T$$
$$dP/dt = r_3T - (\lambda + r_1)P = r_3T - X_1P$$
$$dU/dt = r_1(B + P) - \lambda U.$$

The following solutions for this system of equations describe the fractional activities $A(t)/A_0$ in each of the designated sites:

$$B = B_0e^{-X_2t},$$

$$T = \left[\frac{r_2B_0}{r_1 + r_2 - r_3}\right][e^{-X_3t} - e^{-X_2t}] + T_0e^{-X_3t},$$

$$P = \left[\frac{r_2r_3B_0}{r_1 + r_2 - r_3}\right]\left[\frac{e^{-X_2t} - e^{-X_1t}}{r_2}\right] - \left[\frac{e^{-X_1t} - e^{-X_3t}}{r_1 - r_3}\right] + \left[\frac{r_3T_0}{r_1 - r_3}\right][e^{-X_2t} - e^{-X_1t}],$$

TABLE 4. GONAD DOSE (mrad) PER EXAMINATION WITH COMMON RADIODIAGNOSTIC PROCEDURES*

Procedures	Males		Females	
	Median	Range of means	Median	Range of means
Barium meal	30	5–230	340	60–830
Urography (descending)	430	15–2,090	590	270–1,160
Retrograde urography	580	150–2,090	520	85–1,390
Colon, barium enema	300	95–1,590	870	460–1,750
Upper femur	920	230–1,710	240	58–680
Obstetric, abdomen	—	—	300	110–1,600
Hysterosalpingography	—	—	1,270	275–2,700

* Abstracted from UNSCEAR report (*42*), p. 158.

TABLE A1. DEFINITIONS OF SYMBOLS

Symbol	Explanation	Units
t	Time	hr
λ	Radioactive decay constant (λ = ln 2/physical half-life)	hr^{-1}
r_1	Rate constant for urinary iodide excretion	hr^{-1}
r_2	Rate constant for thyroid iodide uptake	hr^{-1}
r_3	Rate constant for thyroid hormone release	hr^{-1}
A_0	Iodine-131 administered	μCi
$A(t)$	Fraction of administered activity at time t in designated organ or region, with the following substitutions for A: B = whole body (all organs not otherwise specified); T = thyroid (iodide + hormone); P = extrathyroid thyroid hormone; U = urine; I = total radioiodine	μCi/μCi
$\tilde{A}(t_1,t_2)$	$\int_{t_1}^{t_2} A\,dt$, the integrated fractional activity in designated organ between times t_1 and t_2	μCi-hr/μCi

$X_1 = \lambda + r_1$
$X_2 = \lambda + r_1 + r_2$
$X_3 = \lambda + r_3$

$$U = \left[\frac{r_1 B_0}{r_1 + r_2 - r_3}\right][e^{-\lambda t} - e^{-X_2 t}] - \left[\frac{r_3}{r_1 - r_3}\right](B_0 + T_0)[e^{-\lambda t} - e^{-X_1 t}] + \left[\frac{r_1}{r_1 - r_3}\right]\left[\frac{r_2 B_0}{r_1 + r_2 - r_3} - T_0\right][e^{-\lambda t} - e^{-X_3 t}] + U_0 e^{-\lambda t}.$$

Note that the decay factor $e^{-\lambda t}$ could be factored out of each of the above expressions, but the forms shown are convenient for computer program coding.

Values of $\tilde{A}(t_1,t_2)$ are obtained by substituting the expressions $(e^{-Xt_1} - e^{-Xt_2})/X$ for e^{-Xt} in the foregoing formulas, with $X = \lambda$, X_1, X_2, or X_3 as these expressions occur. This substitution has the effect of integrating the original expression between t_1 and t_2. For $\tilde{A}(0,\infty)$, the e^{-Xt} terms are replaced by $1/X$, which is the integral of e^{-Xt} for the time interval $t = 0$ to $t = \infty$.

A delay in the release of the radioactive thyroid hormone is allowed for by using a simplified set of equations, with $r_3 = 0$ for the first 24 hr. The A(24) values so calculated are substituted for the A_0 values in these formulas for calculation of $\tilde{A}(t)$ and $\tilde{A}(24,t)$, using $(t - 24)$ for t.

For calculations of $\Sigma\tilde{A}(0,\infty)$, except for the contribution from urine in the bladder, the values of A and $\tilde{A}$ for intermediate times are not needed. The considerations involved in obtaining the portion of $\tilde{U}$ attributable to the bladder are discussed in the main portion of the text. For the other sources, the $\tilde{A}(0,\infty)$ used in calculating the dose is the sum $\tilde{A}(0,24) + \tilde{A}(24,\infty)$. Simplified expressions for these values, assuming that $B_0 = 1$ and $T_0 = U_0 = P_0 = 0$, are as follows:

$$\tilde{B}(0,\infty) = \frac{1}{\lambda + r_1 + r_2},$$

$$\tilde{T}(0,\infty) = \left[\frac{r_2}{r_1 + r_2}\right][\tilde{I}(0,24) - \tilde{B}(0,24)] + \left[\frac{1}{\lambda + r_3}\right]\left[\frac{r_2 B(24)}{\lambda + r_1 + r_2} + T(24)\right],$$

$$\tilde{P}(24,\infty) = \left[\frac{r_3}{\lambda + r_1}\right]\tilde{T}(24,\infty),$$

$$\tilde{U}(0,\infty) = \frac{r_1}{r_2}\tilde{T}(0,24) + \frac{1}{\lambda}\{r_1[\tilde{B}(24,\infty) + \tilde{P}(24,\infty)] + U(24)\},$$

in which $\tilde{I}(0,24) = \frac{1}{\lambda}(1 - e^{-24\lambda})$.

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