RESPONSE OF THE OVERACTIVE THYROID TO RADIOIODINE THERAPY

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Although radioiodide has been employed in treatment of the overactive thyroid for more than 30 years, no analytic approaches have been presented which allow possible interlaboratory comparison or the testing of hypotheses against linearized data. Such approaches (some empirical, others based on biological models) are given here and applied to reported series of cases in which the amount of radioiodide administered was related to thyroid size.

ANALYSIS: DRINKS PER PATIENT

The discussion will be limited to the use of ^{131}I in the treatment of hyperthyroidism. Although ^{125}I has been employed, data are too limited to allow an analysis (*1,2*). Based on an attempt to deliver 7,000 rads to the thyroid, most dosage schedules require a value of about 80 μCi of ^{131}I/gm of thyroid (*3*). Multiple problems can be envisioned. Despite a number of schemes for calculating the weight of the thyroid based on its appearance on scintillation scans, this estimate can be in error. There is also little assurance of uniformity in the distribution of radioiodide within the thyroid. Perhaps most important, there are as yet no parameters for estimating the variable biological sensitivity to a given dose of radiation. Probably because of these factors, some patients do not respond to the dose of radioiodide calculated to render them euthyroid, while others respond "too well" and develop thyroid underactivity (hypothyroidism). Indeed, the incidence of hypothyroidism increases with time after either radioiodide therapy or surgery upon the overactive thyroid (*4*). Because of this variability, some groups have used a random scheme of doses or one fixed dose of radioiodide in therapy. Analyzing series of cases that report a dose based on efforts to consider thyroid size, iodide uptake, and turnover rate, we can demonstrate that there are consistent findings.

To examine the results of treating hyperthyroidism with radioiodide (^{131}I), two approaches will be used which differ from those usually employed.

1. The population will be divided into two classes: uncured hyperthyroids (H), and those who have been cured of their disease (C) by means of radioiodide therapy. By cured we mean rendered either normal (euthyroid) or hypothyroid.
2. The population will be followed successively from one radioiodide drink to another ("drink" is a colloquialism for treatments or doses; it is well enough entrenched to be retained). We will ask: what fraction of the uncured population has been cured by one drink, what fraction of the remaining *uncured* population has been cured by the second drink, and so on. When applied to the data of Silver (*3*), the analysis reveals that a mean of 51 $\pm$ 6% of the previously uncured patients are cured after each drink.

The fraction of uncured patients remaining changes only slightly from drink to drink. The decrease in the number of hyperthyroid patients can then be described in terms of an exponential function. Here H_0 is the original number of hyperthyroid patients, D is the number of radioiodide drinks given, and λ is a rate constant describing the therapeutic effect,

$$H = H_0 e^{-\lambda D}. \quad (1)$$

In other words, the number of patients not cured (still hyperthyroid, H) equals the original number (H_0) multiplied by an exponentially decreasing term. For Silver's data, the equation is (obtained by the method of least squares on the logarithmic transform):

$$H = H_0 e^{-0.676D}. \quad (2)$$

We can also note that the number of patients cured (C) must equal the original number of hyper-

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TABLE 1. COMPARISON OF RESPONSE OF THREE DIFFERENT PATIENT POPULATIONS TO RADIOIODIDE THERAPY*

Author	Rate constant	Correlation coefficient	No. drinks to cure ½ population (ln 2/rate constant)
Silver	0.676	0.99	1.03
Maynard	0.936	0.99	0.74
Nofal	1.121	0.99	0.62

* The difference between the slopes of the lines of the populations of Silver and Maynard is significant with $p < 0.001$. The difference between the slopes of the lines of the populations of Maynard and Nofal is significant, with p between 0.02 and 0.01.

thyroid individuals (H_0) minus those still hyperthyroid,

$$C = H_0 - H. \quad (3)$$

In addition to the report of Silver (*3*) mentioned above, there are two other series in the literature from which comparable data can be derived. These are the papers of Nofal and coworkers (*4*) and Maynard (*5*). Using the data handling discussed with Eq. 2, we can plot the logarithm of H/H_0 as a function of the number of drinks. This is shown in Fig. 1 for the three populations. The three patient groups are compared in Table 1 as to their rate constants, number of drinks to cure half the population, and the correlation coefficient.

There are two conclusions that can be drawn.

1. The proposed semilogarithmic plot is an adequate technique for linear comparisons of three different populations (the correlation coefficients are quite high).
2. If the patient populations were identical (age, sex, duration of disease, size of thyroid, turnover of iodide, previous therapy if any), then the rate constants would represent the differing vigorousness with which each group was treated with radioiodide. If the populations were not identical, then the rate constants would be the result of the interaction of both the population differences and the vigorousness of therapy.

Assuming for the moment that the populations were rather similar, we can try to equate the radiation dose delivered with the rate of decrease of hyperthyroidism (as a function of the number of drinks). Each of the reported treatment series was based on an effort to deliver a given radiation dose to the thyroid gland. This was done by giving a certain number of microcuries of radioiodide per estimated gram of thyroid tissue. Hence, we can attempt to relate the rate constant for the cure of hyperthyroidism to the quantity of radioiodide in the thyroid. The relationship would be of the form

$$MZ = \lambda. \quad (4)$$

Here M is the concentration of radioiodide in the thyroid (μCi/gm tissue), Z is a "constant" (gm/μCi-drink), and λ is the rate constant. Solving Eq. 4 in terms of Z for the three populations gives the mean value of 8.0×10^{-3} gm/μCi-drink. Using this value, we can construct Table 2. The prediction is

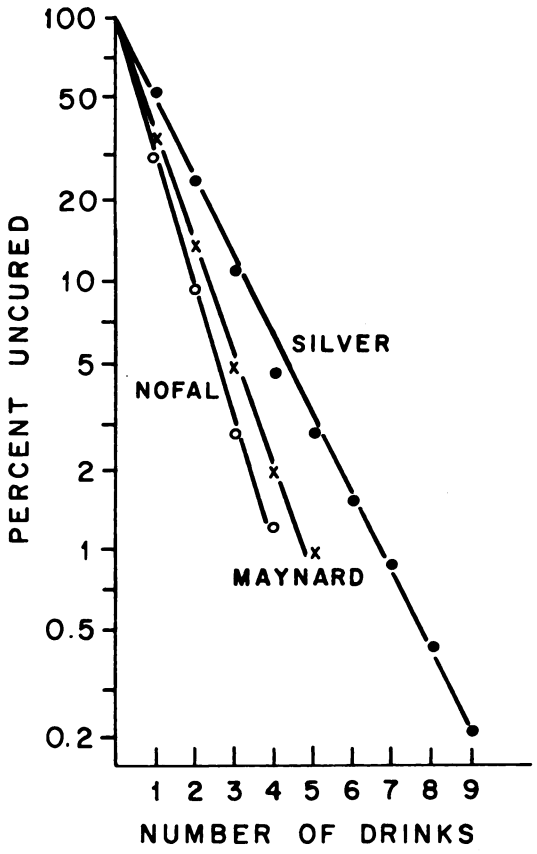

FIG. 1. Semilogarithmic plot of percent of patients still hyperthyroid as function of number of radioiodide drinks administered.

TABLE 2. ATTEMPT TO RELATE RATE CONSTANT FOR DECREASE IN HYPERTHYROIDISM IN ORIGINAL POPULATIONS TO QUANTITY OF RADIOIODIDE ESTIMATED TO BE IN THYROID*

	Dose (μCi) of radioiodide/gm thyroid	Z "constant"	λ rate per drink: calculated	λ rate per drink: observed
Silver	80	8.0×10^{-3}	0.640	0.676
Maynard	100*	8.0×10^{-3}	0.800	0.936
Nofal	185	8.0×10^{-3}	1.480	1.121

* We are grateful to Dr. Maynard for supplying the value.

rather good for the population of Silver (New York City) and that of Maynard (Winston-Salem, North Carolina), but less reliable for the population studied by Nofal (Ann Arbor, Michigan). There are certainly multiple points at which the populations can differ (age, sex, size of thyroid, and so on). This will be pursued in terms of thyroid size in the following section. The change in thyroid size and function occurs because of the radiation delivered; this leads to an expression for the rate constant of thyroid response in terms of the radiation dose. From equations of radiation dose delivered, we can calculate that for ^{131}I, and an effective half-time in the thyroid of 6 days, the dose in rads (D_R) is 91.2 M μCi/gm or $M = D_R/91.2$. This value for M can be combined with Eq. 4 to yield:

$$\lambda = \frac{D_R Z}{91.2}. \qquad (5)$$

The rate constant is given in this equation in terms of the radiation dose delivered to the thyroid. The units of D_R are rads, while the term 91.2 has the units of μCi/gm-rads. Since the "constant" Z is equal to 8.0×10^{-3}, Eq. 5 can be written in the simplified form

$$\lambda = D_R(8.8 \times 10^{-5}). \qquad (6)$$

This points out the direct relationship of the rate constant for cure to the radiation dose.

ANALYSIS: TOTAL DRINKS CONSUMED

To further pursue the relationship of the results of therapy with the type of thyroid gland (normal-sized thyroid, diffusely enlarged, and multinodular), we will introduce the concept of the total number of drinks consumed.

Insight into the response to radioiodide therapy of the various subclasses can be obtained by examining the total number of drinks consumed by the patient population. We will define the *total cumulative number of drinks* (C_∞) as the number consumed by the population under discussion in order to cure hyperthyroidism in each member. For example, if 100 patients required one drink each, 50 required two drinks each, and 25 required three drinks each, then: $C_\infty = (100 \times 1) + (50 \times 2) + (25 \times 3) = 275$. Hence,

$$C_\infty = \sum_{i=1}^{n} Di\ Pi. \qquad (7)$$

Here Di is the number of drinks required for the ith group, and Pi is the number of patients in the group. The value of the sum of the product (Di Pi) approaches a limiting number (C_∞) when plotted against D. For larger series of cases, there is but slight error in likening this to an exponential approach to an asymptote. At any point then

$$C = C_\infty\ (1 - e^{-KD}). \qquad (8)$$

This can be rearranged into

$$-KD = \ln\ (1 - C/C_\infty). \qquad (9)$$

A plot of the logarithm of $(1 - C/C_\infty)$ as a function of D produces a straight line with slope —K. This is shown in Fig. 2. The data of Silver (*3*) are plotted as well as the information from Nofal and coworkers (*4*) and from Maynard (*5*).

Of course, the product of (Rate constant) $\times$ (Drinks to $\frac{1}{2}_\infty$) equals the natural logarithm of 2. This approach gives a superb fit to the data of the three populations (Table 3) and introduces the concept of the number of drinks expended per patient

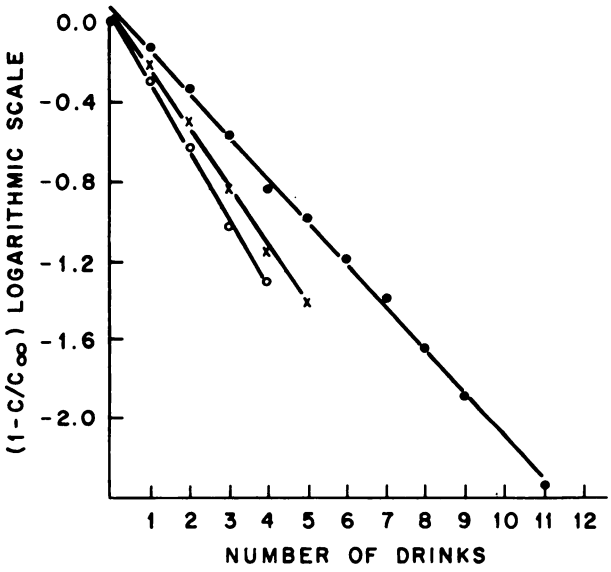

FIG. 2. Descriptions of three populations rendered into form of Eq. 9. Three lines represent (left to right) populations of hyperthyroid patients treated by Nofal and coworkers, by Maynard, and by Silver.

TABLE 3. COMPARISON OF THREE HYPERTHYROID POPULATIONS IN TERMS OF TOTAL CUMULATIVE NUMBER OF DRINKS*

Author	Rate constant	Corr. coeff.	Drinks to ½ C_∞	Mean drinks/ patient
Silver	0.217	0.99	3.2	1.97
Maynard	0.294	0.99	2.4	1.61
Nofal	0.334	0.99	2.1	1.43

* By rate constant is meant term K in Eq. 9. The difference between the slopes of the population lines of Silver and Maynard is significant, with $p = 0.001$. The difference between the slopes of the population lines of Maynard and Nofal is of borderline significance ($p = 0.05$).

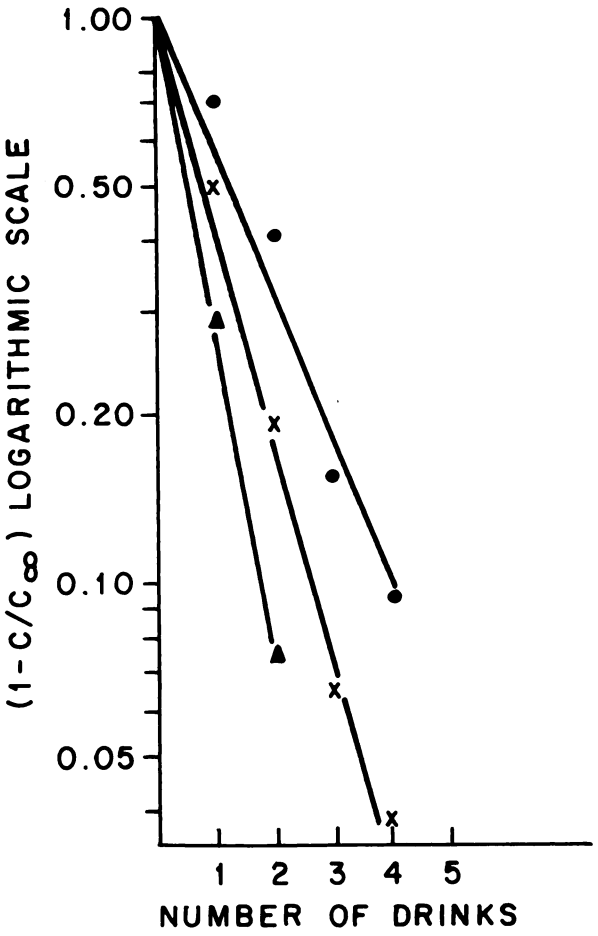

FIG. 3. Plot of data of Nofal and coworkers (*4*) on response of overactive thyroid to radioiodide therapy. From left to right lines represent normal size thyroid, diffusely enlarged gland, and multinodular thyroid.

in order to cure half the population. Again, the three populations are similar in the gross description, differing only in the rate constants.

A principal use of the concept of the cumulative number of drinks (consumed by the hyperthyroid population) is in comparing subgroupings, such as those of different ages, the two sexes, or individuals with thyroid glands of different sizes. From Table 7 of the report of Nofal and coworkers (*4*) we can obtain values for the number of drinks required to cure hyperthyroidism in patients with thyroid glands of normal size, in those with diffusely enlarged thyroids, and in patients with multinodular glands. Using the formulation of the cumulative number of drinks, we can construct Fig. 3. It can be seen that hyperthyroidism is more readily cured (fewer drinks) when the thyroid is of normal size. The diffusely enlarged thyroid requires a larger number of drinks for control. Finally, hyperthyroidism in the enlarged multinodular gland is most difficult to treat (and the data also show the most scatter). The population reported by Nofal and coworkers probably had a larger percentage of multinodular thyroid glands than the groups seen by Silver or Maynard.

ANALYSIS: THE LOG NORMAL CONCEPT

There are multiple uncertainties in estimating the exact dose of radioiodide to be used in therapy. These encompass, for example, uncertainties in the size of the thyroid, the uniformity of distribution of radioactivity, the rate of turnover of radioiodide, and the rate of repair of the radiation induced changes. When distributions with such errors are multiplied by each other, the end product is the log normal distribution. Demonstration of this type of distribution function is accomplished by plotting the cumulative percentage of patients cured (on a probability scale) as a function of the logarithm of the number of drinks. Such a plot is shown in Fig. 4 for the data of Silver (*3*). Through the 99th percentile, the plot gives a linear description of the actual clinical results. It should be recognized, however, that several other types of distribution functions can closely mimic the log normal [see the discussion by Koch (*6*)], including that of the "multitarget lethality" well known in radiobiology. The log normal approach deserves further scrutiny since it can provide data as to the spread of the population about the mean value for each parameter.

ANALYSIS: TIME COURSE

Up to this point we have not mentioned the time course of response to radioiodide therapy of hyperthyroidism. To consider all reports uniformly would

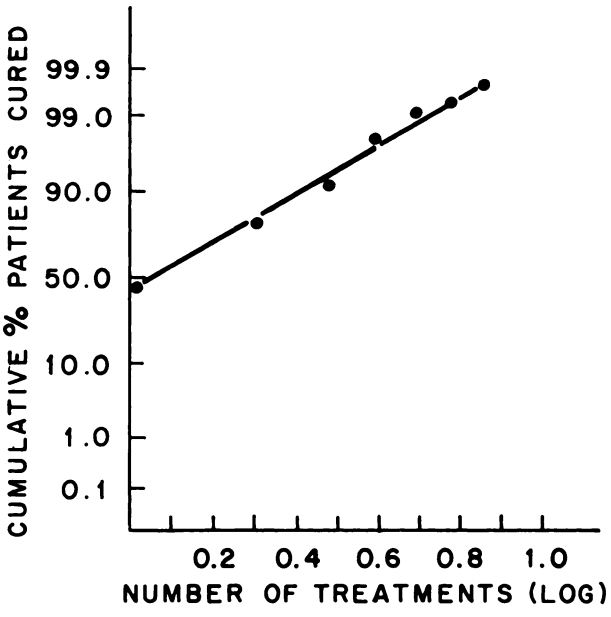

FIG. 4. Data of Silver (3) replotted to show cumulative percent of original hyperthyroid population cured (probability scale) by increasing number of drinks of radioiodide (logarithmic scale).

not be possible since various periods were allowed to elapse before retreatment was given (and various medications were administered in the interim). From the report of Smith and Wilson (7), we can follow a population given a dose of radioiodide and then followed for up to 5 years. Indeed, the initial patient population was divided into three groups: one group took a dose of radioiodide intended to deliver 7,000 R to the thyroid, while the others received half or twice this amount. Examination of the fraction of the population still hyperthyroid (H) reveals that there is a rapid initial decrease, and then an almost linear decrease with time. Knowing the form of the curve, we must also meet the boundary conditions of $H = 1$ at $T = 0$, and $H = 0$ at $T = \infty$. The simplest curves meeting these requirements are of the form

$$H = \frac{1}{1 + BT}. \qquad (10)$$

Here T is in years. There is, however, much scatter of the data of Smith and Wilson around such curves. The appeal of such a formulation is that the constant B might be directly related to the radiation dose delivered. For the case of the full treatment dose, we can attempt to equate the constant (which numerically is 1.3) with the dose of 7,000 R. Substituting into Eq. 10 gives the general formulation

$$H = \frac{1}{1 + (1.86 \times 10^{-4})\,RT}. \qquad (11)$$

Here R is the dose to be delivered to the thyroid (rads). There are insufficient data to apply this formulation to the population given the double dose of radioiodide (14,000 rads), since only 26 patients were involved (we thank R. N. Smith for the followup on these individuals). However, there were only five patients still hyperthyroid after ½ year (about 20%) and but one patient remained hyperthyroid after 1 year. This suggests that massive irradiation may produce more rapid cure, perhaps by negating reparative processes in the thyroid. When using lower doses of radioiodide, most physicians have been impressed by the small but real number of patients who appear to have an underactive thyroid when interviewed 3 months after their therapy but who return to a normal thyroid status. Repair of radiation damage is well recognized in radiobiology but is seldom discussed in the medical literature.

A quite different approach can be used to describe the time course of response to radioiodide therapy. Assume that there are two distinct cellular populations being affected by the radiation. The first group of cells are radiosensitive, readily inactivated, and contribute to the early cure of hyperthyroidism. The second group of cells are radioresistant, or perhaps more properly, they manifest radiation damage only after a prolonged period of time, perhaps when they enter into mitosis (or they may be damaged by autoimmune phenomena that develop after treatment). The resultant curve would be the sum of two contributing populations (a rapid component and a slow component). The data of Smith and Wilson (7) on the population still hyperthyroid are plotted against time in Fig. 5. Each of the curves (double dose of radioiodide, single dose, or half dose) can be closely approximated by the use of a two-component system. If we consider the first 6 months *only*, the fraction F of patients still hyperthyroid is dose dependent. This "rapid response" can be approximated by

$$F = 1 - 0.42M. \qquad (12)$$

Here M is a measure of the dose of radioiodide given by Smith and Wilson ($M = ½$ for the half dose, $M = 1$ for the full dose, and $M = 2$ for the double dose of radioiodide).

After the first 6 months, there is a slower rate of cure of hyperthyroidism. The fraction of patients still hyperthyroid in this "slow response" phase can be described by a linear expression (of the form $f = A - cY$, where Y is the time in years). For the half dose of radioiodide, the equation is:

$$f = 0.76 - 0.14Y, \qquad (13)$$

while for the full dose it is

$$f = 0.58 - 0.12Y. \qquad (14)$$

The slopes do not appear to be very different (and this is an interesting and unexplained finding).

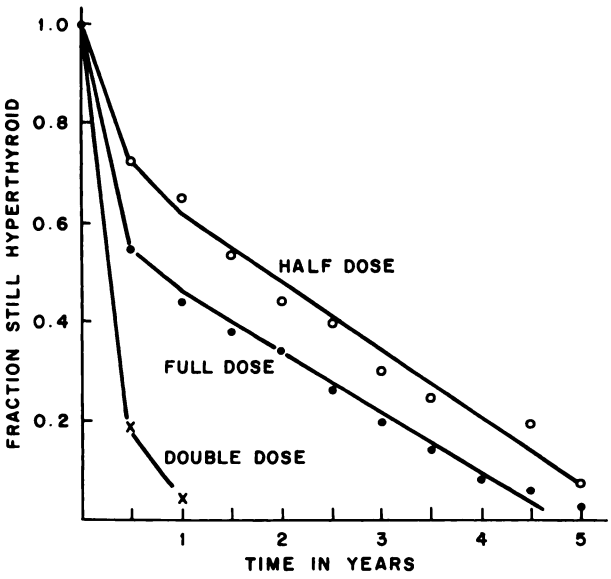

FIG. 5. Data of Smith and Wilson (7) on time course of response to radioiodide after three different schedules of treatment. X and circle marks are observed values, while lines are discussed in text.

Whether the slow response component is related to damage of the mitotic apparatus, to the development of thyroid antibodies, or to other factors is still unknown.

POSSIBLE MECHANISMS

The precise mechanism of the response of the thyroid gland to radioiodide therapy is unknown. In part, there is a loss of tissue. In a series of adults with diffusely enlarged thyroid glands and both laboratory and clinical evidence of hyperthyroidism, we have found a good correlation between the size of the thyroid before and after therapy. We studied 35 adults who responded to radioiodide therapy as judged by an evaluation 3 months after their initial therapeutic drink (*8*). In these patients, the mean length of the thyroid (the sum of the lengths of the right and left lobes divided by 2) before radioiodide therapy was 5.7 cm. Three months after treatment, the mean value was 4.7 cm (lengths were measured from scans of the gland). There was a highly significant relationship (correlation coefficient = 0.80) between thyroid length after therapy (L_A), in these cases and the length before therapy (L_B). With the lengths measured in cm,

$$L_A = 0.25 + 0.78\, L_B. \qquad (15)$$

The scan surface area of the thyroid after therapy (S_A) also correlated with that before treatment (S_B),

$$S_A = 1.18 + 0.62\, S_B. \qquad (16)$$

Here the surface area is in cm^2; the correlation coefficient is 0.87.

In addition to the gross loss of tissue, subtle changes have occurred in the biochemistry of the treated thyroid. For example, after radioiodide therapy, the thyroid becomes quite susceptible to the inducement of underactivity by exogenous stable iodide (*9*). There are many additional aspects of the problem awaiting clarification. One of the more intriguing is that while hyperthyroidism can occur in either sex, we see a 4-to-1 preponderance of females with the disease.

SUMMARY

Dividing the population receiving radioiodide therapy for hyperthyroidism into two groupings (cured and not cured) leads to quantitative expressions for the results which can be made to agree closely with actual data. A series of linear formulations are presented which may be of use in comparing populations and in testing the validity of proposed theories of the mechanism of action of radioiodide.

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