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ARGONNE CANCER RESEARCH HOSPITAL
950 EAST FIFTY-NINTH STREET • CHICAGO 37 • ILLINOIS

Proceedings of the

CONFERENCE ON RADIOIODINE

Sponsored by

THE ARGONNE CANCER RESEARCH HOSPITAL, UNITED STATES ATOMIC ENERGY COMMISSION, AND THE CLINICS OF THE UNIVERSITY OF CHICAGO

NOVEMBER 5 AND 6, 1956
CHICAGO, ILLINOIS

DWIGHT E. CLARK, M.D.
Chairman and Editor

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CARCINOMA
Chairman: Dr. Earle Chapman

RADIOIODINE CONFERENCE

DR. JACOBSON: Dr. Clark has given me the opportunity to welcome you. Actually, this is his party. All I want to say is that as Director of this hospital, which, as you know, is run by the Atomic Energy Commission here at the University, I do welcome you and hope that you have an enjoyable and profitable two days.

RADIOBIOLOGY

Part I — Dosimetry

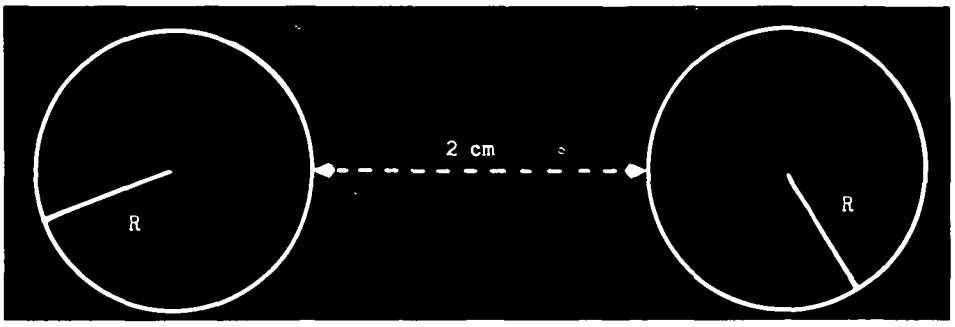
A. Basic radiation dosimetry relevant to the internal administration of I^{131}. Dose variations due to physiological factors and histological structure.

DR. MARINELLI: This session is devoted to the radiobiologic aspects of radioiodine therapy; it is divided into two parts, one concerning physics and the other, biology.

The first part of the program is devoted to dosimetry, and I take pleasure in introducing Dr. Sinclair who will discuss basic radiation dosimetry relevant to internal administration of I^{131}.

DR. SINCLAIR: The basic radiation dosimetry relevant to the internal administration of I^{131} is a subject with which most of you are familiar, so I will review it only briefly. First of all, let us consider the dose to the thyroid gland itself and particularly the average dose that we normally estimate.

To make the estimation of total dose, β and γ, to the thyroid gland, the model used is generally of the type shown in Figure 1, which indicates two spheres of radius R spaced 2 cm apart. I assume you are familiar with the derivation of the dose. We finish up with a total dose to the thyroid of $(14 + 0.73) \frac{U.A.T_e}{M}$ in rads. U is the fractional uptake, A is the amount administered in μc, T_e is the effective half-life, and M the gland weight in g. The numerical constants used here are $\overline{E}_\beta$ (average β energy) 0.187 Mev, and Γ the γ-ray dose rate from 1 mc at 1 cm which is 2.18 r/hr.[1] For those of you who are not familiar with rads, I might mention that the rad is the unit of absorbed dose that is equal to 100 ergs per g, and relative to the estimate in roentgens we have been using previously, it is about a 7% larger unit, and the numerical value of the dose in rads will be 7% or so smaller. The numerical constant 14 represents the β dose relative to the γ dose represented by 0.73 R. If there are two 15-g spheres, the radius R is 1.54 cm and the γ-ray dose is about 7.5% of the total. It may rise to about 12% for larger spheres that might be encountered in diseased glands.



TOTAL DOSE TO THYROID

$$= (14 + 0.73\ R)\ \frac{U.A.T_e}{M}\ \text{Rads}$$

U = FRACTIONAL UPTAKE

A = AMOUNT ADMINISTERED (μc)

T_e = EFFECTIVE HALF-LIFE (days)

M = GLAND WEIGHT (g)

[I^{131} - E_β = 0.187 Mev Γ = 2.18 cm^2 - r/mc/hr]

Figure 1. Model for the calculation of radiation dose to the thyroid gland. Two spherical lobes of radius R are placed with 2 cm between their surfaces.

I think it would be helpful to consider the errors to which this determination of the total dose may be liable. I am sure all of you use a formula that is similar to this one although it may not be exactly the same. One potential error may be made in neglecting the initial uptake period. If the effective half-life for elimination is 20 times or more the effective half-life for uptake, the initial uptake period can be ignored in the calculations.[1] Consequently, the error arising from this cause is negligible for I^{131} with an effective half-life for uptake at 2 to 5 hours, but it may be appreciable for I^{132}.

Let us examine the terms of the formula itself. First, the error in the amount administered, A, will generally be small, perhaps 5%, in centers where calibrations are carried out regularly. Second, the error in the mass of the gland, M, will be the largest single error, 25% or more by clinical methods of determining it, but if we use the scintigram method, the error can usually be reduced and may not be greater than 10 or 20%. Third, the error in the value of uptake, U, could be large, but is usually not so because most people are aware of the errors that may result from unsatisfactory calibration conditions, inadequate material surrounding the source, and uncertainty regarding the depth of the gland.

I should like to show our own system.

The setup for calibration is shown in Figure 2; we have a lucite jig with the iodine standard mounted 1 cm or so below the surface at a distance from the detector head.

Figure 3 shows the patient being positioned so that the gland is in approximately the same relationship to the detector assembly.

Figure 4 illustrates how the patient and equipment are finally positioned for uptake de-

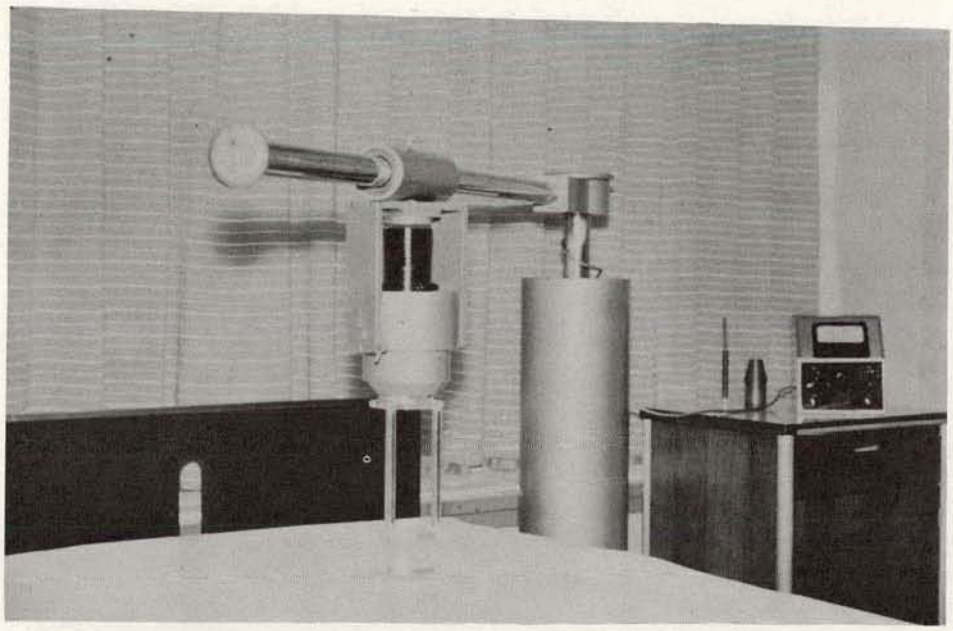


Figure 2. Iodine uptake system used at the University of Texas M. D. Anderson Hospital and Tumor Institute. The lucite jig, which mounts the standard source, is fixed at a distance from the crystal detector for purposes of calibration.

termination. The over-all error in uptake under good circumstances probably does not exceed 10%.

Fourth, the error in the effective half-life depends on whether this quantity is actually measured, and whether the decrease of I^{131} activity in the gland is actually exponential. In many instances, it can be shown that the decrease would be better represented by two or more exponentials, but in general we use a single value of T_e. In hyperthyroid cases, an average value of T_e is about 5.7 days, while in normal or euthyroid cases, an average value of T_e is about 6.9 days. Consequently, if we take an average of 6.0 days, we may have an error of the order of 20%. However, in many cases in which thyroid uptake study will be followed by therapy, the effective half-life will actually be measured, and then the value of T_e will have only a small error, probably about 10%.

I think it is evident that in the extreme case errors of the order of 50% or more are possible in this estimate of the average dose. I am sure that our results are not usually subject to errors of that extent, since in those cases that are followed by therapy we will have more information. It would be rather interesting to have the opinions of this audience as to the supposed accuracy, and to have suggestions for improvement.

If we return to the formula, we note, following a tracer dose of 10 μc, that if the average uptake is about 25% in a 25-g thyroid, using 6 days of T_e, then the average dose in the gland will be of the order of 10 rads or about 1 rad per μc. The average uptake of 25% will apply to the normal patient, but higher values may be found. Furthermore, hyperthy-

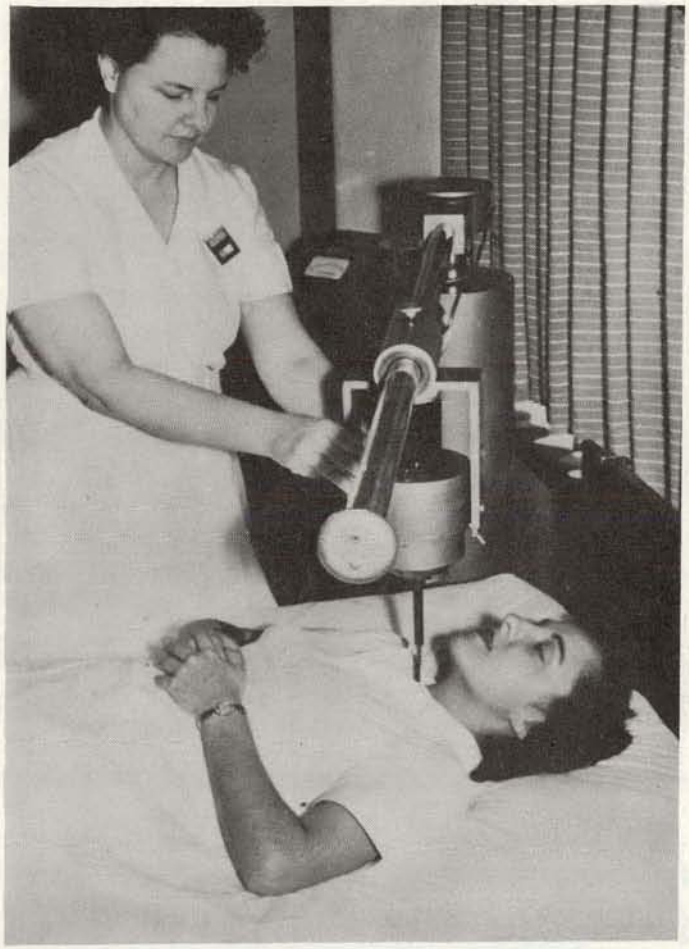


Figure 3. Iodine uptake system used at the University of Texas M. D. Anderson Hospital and Tumor Institute. The uptake device is set up so that the detector will have as nearly as possible the same relation to the I^{131} in the gland as it had to the standard source.

roid patients will have a higher uptake, and the gland dose may then rise to 2 or 3 rads per μc of the administered dose.

Now let us consider variations in the average dose. It is well known that the activity across the thyroid gland varies appreciably at any given time. Estimates made of the effect of variable activity concentrations in neighboring follicles in the thyroid gland show that the dose variation is not as great as the activity variation; it may be about 5 to 1, whereas the activity variation is about 10 to 1. Figure 5 gives the result of a calculation involving neighboring follicles of arbitrary size with an activity concentration of 10 to 1, giving a mean dose variation of approximately 5 to 1. A more comprehensive practical study of this question, however, shows that the ratio of maximum dose to the mean dose is greater than the ratio of maximum activity to mean activity, but not very significantly so.[3] I want to show you some examples from some work that was done on this problem in

London.[3]

Figure 6 shows a stained section of a gland, next a 10-μ section radioautograph indicating the activity distribution in the gland, and then a block section indicating the dose distribution, from a patient with a nodular goiter. The dose distribution is rather less variable than the activity distribution in this example.

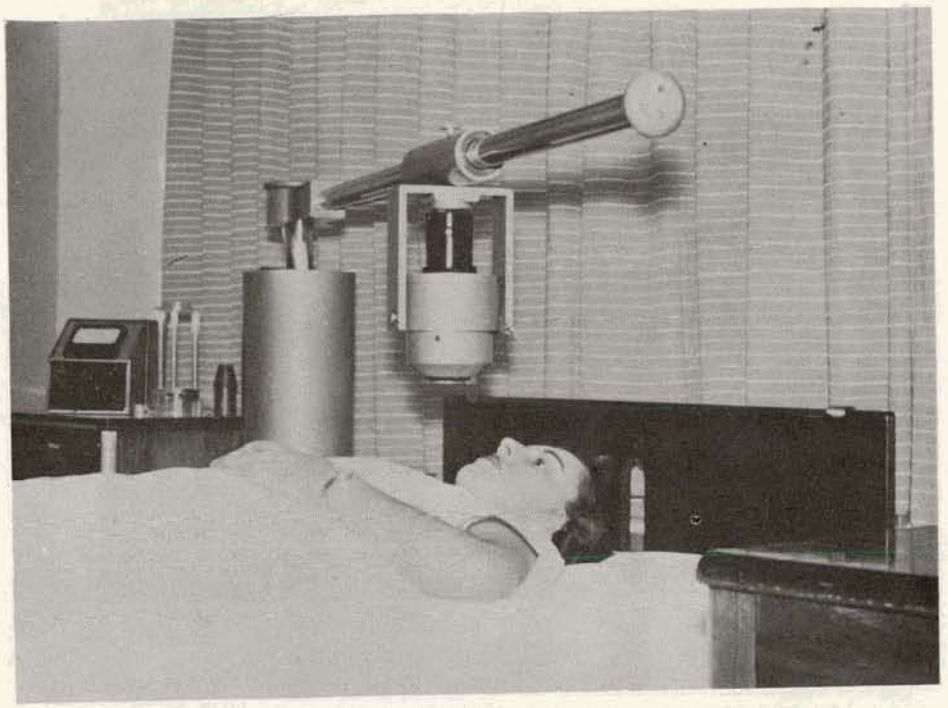


Figure 4. Iodine uptake system used at the University of Texas M. D. Anderson Hospital and Tumor Institute.

The same situation in a diffuse goiter is shown in Figure 7. As we would expect, the variation in activity and dose is less than in the previous case.

Sections from a lymphadenoid goiter show a much more acute variation in both activity and dose (Figure 8).

The information on the patients studied is summarized in Figure 9 for various histologic types. It shows the ratio between the maximum and mean dose plotted on a logarithmic scale. For non-toxic nodular goiter, the values are rather widespread but the mean value is somewhere around 10. For toxic nodular goiter, there is a wider spread with about the same mean value; while diffuse goiter has a much smaller mean value, and lymphadenoid goiter a much larger mean value. Carcinoma is more variable but the ratio is of the same general order.

The mean values for each group are shown in Table 1. There is not much difference in the first group between the dose ratio and the activity ratio; there is more difference in the second group. In lymphadenoid goiter, there is an artefact caused by the rather

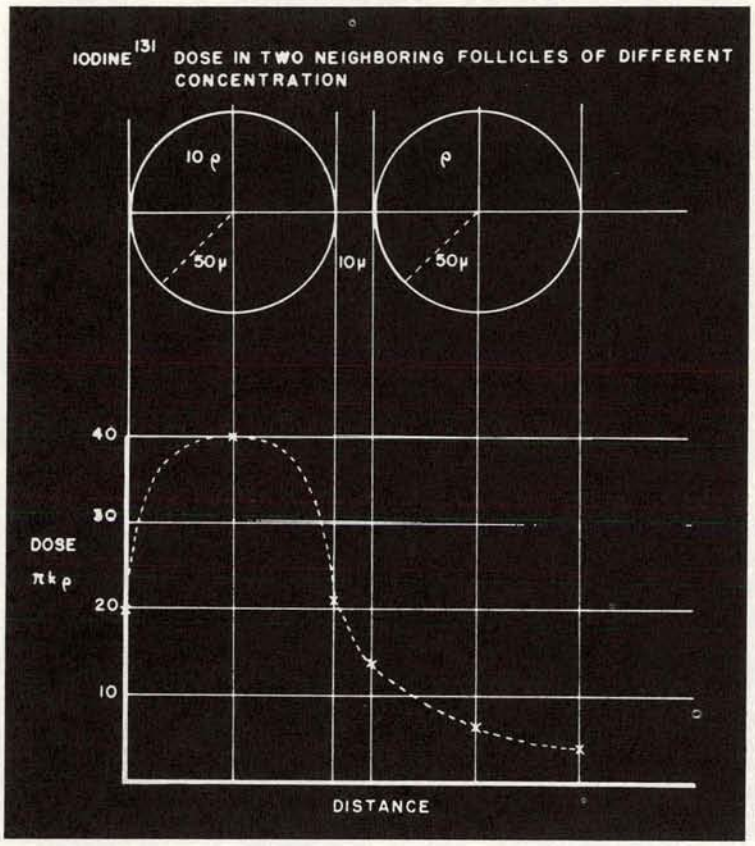
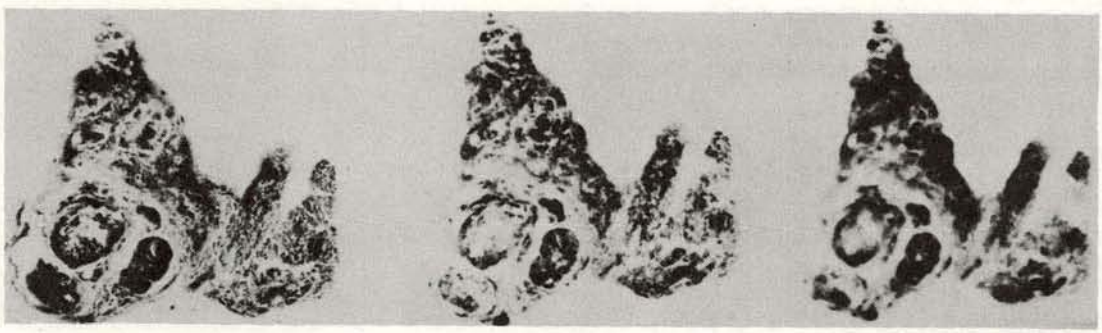


Figure 5. The variation in radiation dose across two neighboring follicles containing a concentration difference of 10:1.[2] This exact situation may never actually exist in practice, or may do so only very temporarily, but it shows that the mean dose to the follicles is only about 5:1 for a much greater concentration difference.

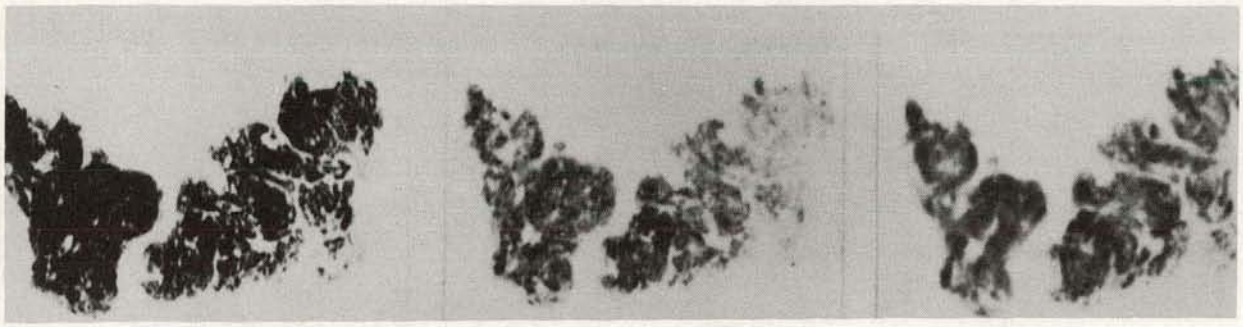


(a) Stained section

(b) 10-μ section

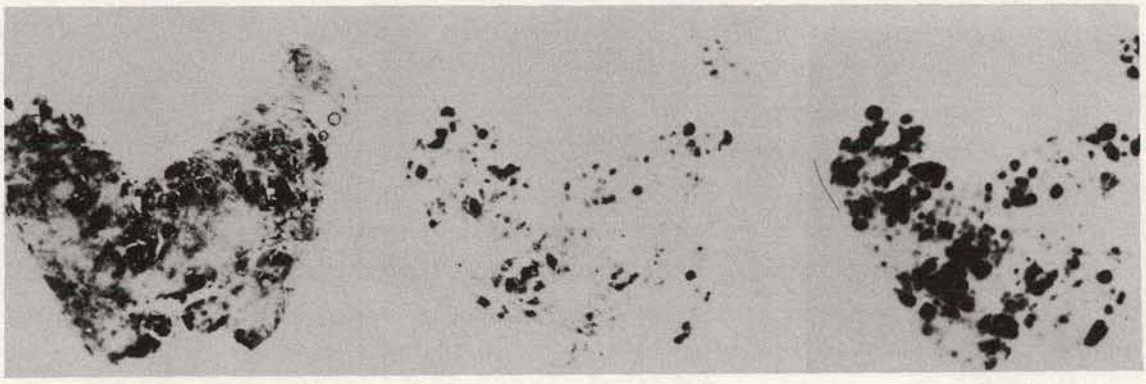
(c) Block section

Figure 6. Sections of a thyroid gland from a case of nodular goiter.
a. Stained histologic section.
b. Contact autoradiograph of 10-μ section showing activity distribution.
c. Contact autoradiograph of block section showing dose distribution.
The dose distribution is less variable than the activity distribution.



(a) Stained section | (b) 10-μ section | (c) Block section

Figure 7. Sections of thyroid gland from a case of diffuse goiter.
a. Stained histologic section.
b. Contact autoradiograph of 10-μ section.
c. Contact autoradiograph of block section.
Both the activity and dose variations are smaller in this case than in the previous example.



(a) Stained section | (b) 10-μ Section | (c) Block section

Figure 8. Sections of thyroid gland from a case of lymphadenoid goiter.
a. Stained histologic section.
b. Contact autoradiograph of 10-μ section.
c. Contact autoradiograph of block section.
Both the activity and dose variations are greater than shown in Figure 6.

small number of cases and the fact that both the activity and the dose ratio are rather difficult to measure because they are so high. The difference between the two is not of great significance in this instance.

I think it is clear that the variations in the average dose really depend on the histo-

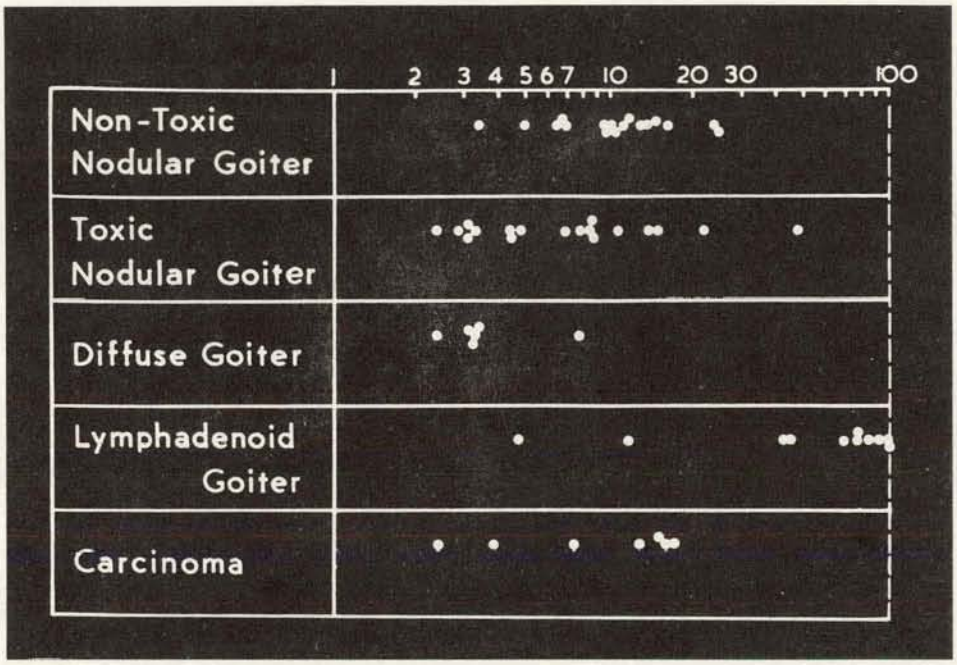


Figure 9. The ratio $\frac{\text{maximum dose}}{\text{mean dose}}$ is plotted on a logarithmic scale for each of the histologic type studied.

Table 1

RATIOS OF $\frac{\text{MAXIMUM DOSE}}{\text{MEAN DOSE}}$ COMPARED WITH RATIOS OF $\frac{\text{MAXIMUM ACTIVITY}}{\text{MEAN ACTIVITY}}$ FOR VARIOUS HISTOLOGIC TYPES OF THYROID DISEASE

Thyroid condition	Mean dose ratio	Mean activity ratio
Non-toxic nodular goiter	11.4 (3.4-25)	11.4 (3.4-25)
Toxic nodular goiter	10.0 (2.4-48)	14.9 (3.4-64)
Diffuse goiter	3.9 (2.4-7.7)	5.1 (3.4-11.4)
Lymphadenoid goiter	68 (12->100)	46 (3-150)
Carcinoma	10.7 (2.4-17)	20.4 (3.2-56)

logic type and are frequently of the order of 10 to 1, except in the case of diffuse goiter where the ratio is low, and in the case of lymphadenoid goiter where the ratio is much higher.

Loevinger, Holt, and Hine[1] show that the average dose to the whole body can be represented by the formula given in Figure 10. If the per cent uptake is about 0.5, T_e is 6 days, and we have an average body mass of 70 kg, the average dose is about 1.5 rads per mc.

WHOLE BODY DOSE

Average Body Dose (Outside Gland)

$$= \frac{(25 - 14\,U)}{V}\, A.T_e \text{ rads}$$

U = Fractional Uptake

A = Administered Amount (μc)

T_e = Effective Half-time (days)

V = Weight (grams)

for U = 0.5 T_e = 6.0 days V = 70,000

Average Dose is 1.5 rads/millicurie

for U = 0 average dose is about 2 rads per millicurie

Figure 10. Formula for estimating the average dose to the whole body, other than the thyroid gland.

If the uptake is zero, the average dose will be about 2 rads per mc; however, I should point out that in such a case, the effective half-life would probably not be anything like 6 days, and the average dose would actually be considerably less. This is just an approximate estimate. The practical studies by Marinelli and Hill,[4] estimating the concentration in the blood, give somewhat lower values, with a dose of 1.1 rads per mc on the average. Studies by Seidlin, Yalow, and Siegel[5] give an average of the order of 0.5 rad per mc administered.

The average dose to the body may therefore be said to be of the order of 0.5 to 1 rad per mc administered. I have tried to summarize the information in Table 2; most of the figures are from Marinelli and Hill.[4] Apart from the whole-body dose given here, the kidneys and the alimentary canal received average doses of the order of 7 rads per mc, and the saliva and oral cavity tissues about 20 rads per mc. Robertson and Godwin[6] have shown that the bone marrow receives a dose about 20% less than the blood because of the absorption of the particles in the bony trabeculae.

The other thing I wish to discuss is the administered activity that delivers the maximum dose in the first week. The thyroid receives a dose some 1000 times greater than the average dose to the whole body. If the dose to the thyroid is therefore regarded as the

Table 2

SUMMARY OF REPORTED ESTIMATES OF DOSE TO THE WHOLE BODY AND TO ORGANS OTHER THAN THE THYROID

Organ	No. of Studies	Range	Mean dose
Marinelli and Hill, Radiology 55 (1950) 494			
Whole body (blood)	32	0.3 - 3 r/mc	1.1 r/mc
Kidneys	12	3.5 - 13.7	7.6
Alimentary canal	7	4.1 - 14.2	7.7
Saliva	8	7.9 - 55.0	20.0
Seidlin, Yalow, and Siegel, Radiology 63 (1954) 797			
Whole body (blood)	69	0.2 - 1.8 r/mc	0.56 r/mc
Robertson and Godwin, British Journal of Radiology 27 (1954) 241			
Bone marrow	Dose is 20% less than in blood		

limiting factor from the point of view of protection, it is then of interest to estimate the amount administered that will deliver 300 millirads in the first week, the most important week, of course. Using the uptake formula and allowing for the shorter time interval, it can be shown that this amount will be of the order of 0.1 to 1 μc, depending on the per cent uptake. Consequently, tracer doses that range between 5 and 50 μc are relatively large and should not be repeated frequently unless they can be justified on clinical grounds.

I would like to summarize what I have said as follows: The average dose to the thyroid, when I^{131} is administered, is of the order of 1 rad per μc, but may rise to 2 or 3 rads per μc in hyperthyroid cases. The error in assessing the average thyroid dose is probably of the order of at least plus or minus 25%. The variation in dose within the gland may be correlated with histologic type and is frequently about 10 to 1, smaller for the diffuse goiter, larger for the lymphadenoid goiter. The dose for the whole body, as estimated from the blood activity, is estimated to be about 0.5 to 1 rad per mc, or if you prefer, 0.5 to 1 millirad per μc. Other than the thyroid itself, few tissues receive high doses from radioactivity in the blood, but the most important are those in contact with the saliva, in which the dose may average around 20 rads per mc.

DR. MARINELLI: This topic is now open for discussion.

DR. RALL: What was the dose that gave 300 millirads per week?

DR. SINCLAIR: The administered amount was in the range of 0.1 to 1 μc.

DR. FURTH: You made the important statement that the limiting factor is the thyroid. After we have heard the evidence, let me ask this question — what factor limits the use of radioiodine?

DR. SINCLAIR: I did not say the dose to the thyroid was the limiting factor, I said

"if it was . . . ."

DR. WERNER: Is there a difference in the radiation received by the body and the gland if you take the same dose and give it weekly in fractions? In other words, if you give 5 mc at once or 1 mc a week for 5 weeks, would there be any significant difference in the radiation to the body?

DR. SINCLAIR: If you gave the same total amount, but fractionated? Maybe I should think a little more about that question because I am not sure I understand you. You want to know if you give 5 mc, do we get the same dose of radiation as if you give 1 mc five times? Certainly, if all other factors, such as excretion, are the same, the total exposure to the individual will be the same.

DR. FURTH: When the thyroid of an animal is destroyed, the thyroidal iodine uptake is diminished, while the total-body iodine retention is increased. So that if you give fractionated doses, you may increase the total-body irradiation.

DR. SINCLAIR: I think that is borne out in the formula where inside the bracket there is a numerical term minus the uptake. If the uptake is very small, the dose to the whole body goes up. I think, in general, the T_e would be pretty small, if the uptake is zero because of rapid excretion.

DR. FURTH: I have two figures illustrating what I have said. These will illustrate the effect of partial or nearly complete destruction of the thyroid on whole-body retention of I^{131} and consequential change increase in whole-body irradiation.

Figure 11b (5-day study) shows that both destruction of the thyroid gland with I^{131} ($\pm$ 250 μc) and slight injury to it (25 μc) result in enhanced whole-body retention of a tracer dose of I^{131} administered a few months later. Figure 11a gives the uptake of I^{131} in the thyroid region of the same animals. Similar data with relevant information in another series of animals are listed in Table 3 (24-hr. study). In some of these groups, the mice had a minute (few mm-sized) grafted thyrotropic tumor. Similar tumors will occur in the pituitary after thyroid depression. These grafts (TtT) further enhanced total-body retention of I^{131}. (Total-body retention was measured by placing the entire animal in a 100 per cent geometry γ chamber). More detailed information about the experiments appears in the literature.[7]

These experiments serve to demonstrate that the total-body retention of I^{131} and incidental total-body irradiation is increased by thyroid destruction (or depression) and that this effect is probably magnified with time because of hyperfunction of thyrotropes following TH deficiency.

DR. TUBIANA: As was pointed out by Dr. Sinclair, the distribution of radioiodine is very heterogeneous in thyroid tissues, and this is especially so in malignant tissues. From a therapeutic point of view, in treating a cancer the important matter is not the maximum dose or the average dose but the minimum dose. For a given concentration, the minimum dose delivered by β radiation varies with the degree of heterogeneity. To facilitate the estimation of minimum dose we have tried to calculate a correction factor, assuming that all the radioactive iodine is concentrated in a few radioactive foci.

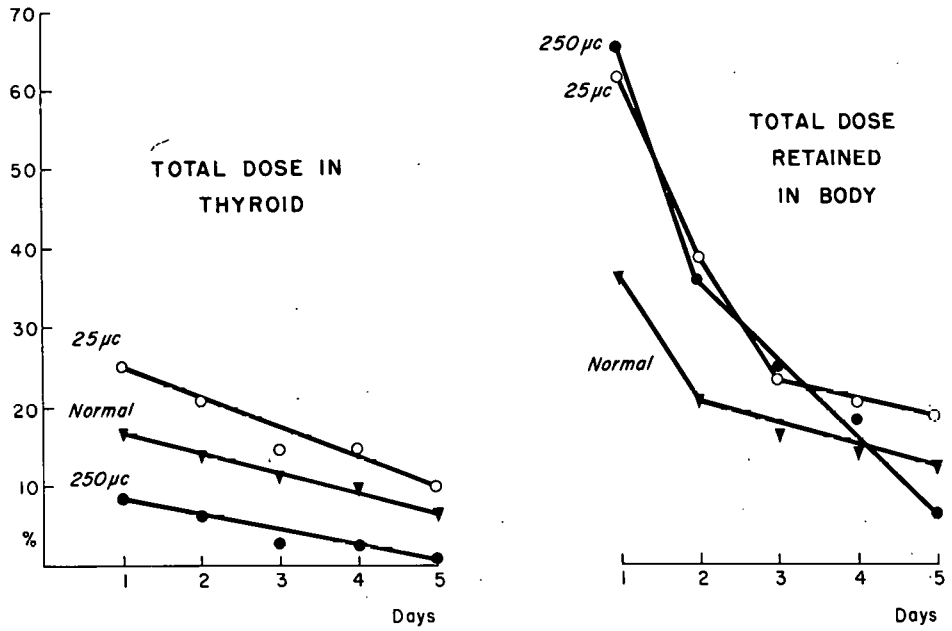


Figure 11. a. The total dose retained in the thyroid up to 5 days after injection in mice that had been given a few months earlier 25 or 250 μc, and in normal mice. b. The total dose retained in the body of the same animals during the same period of observation. The thyroid of mice receiving approximately 250 μc was completely or almost completely destroyed. The thyroid of those receiving 25 μc appeared only slightly if at all affected.

The average spacing "e" of the radioactive areas can be deduced from the average distance of the areas of blackening on the autoradiograph, when the thickness of the specimen is known.

When e varies from 100 to 1000 μ, the dose varies from $\frac{1}{2}$ to $\frac{1}{50}$ of the dose calculated assuring homogeneous distribution (Table 4).[8]

DR. POCHIN: One point on Dr. Furth's question I think; in man, if you are destroying thyroid tissue, the rads per mc go through a minimum with successive doses and then start to rise again. I think that with the first dose or two you are decreasing the amount of circulating thyroxine and therefore are reducing the dose given during the thyroxine phase. With the later doses, you are decreasing the amount of thyroid clearance and the clearance of iodide from the body and so increasing the dose from the iodide phase. I think that on calculation, in many patients, you do get a minimum and then a rise in the number of rads per mc.

DR. KEATING: In the same vein, I should like to ask Dr. Sinclair a question regarding the irradiation dose to the whole body in patients with Graves' disease. It has seemed to me that patients can be divided into two categories, in one of which the calculations

Table 3

TOTAL-BODY AND THYROID RETENTION OF TRACER DOSES OF I^{131} IN NORMAL AND I^{131}-PRETREATED MICE

Group	Mice (No.)	Original dose of I^{131} (μc)	Thyrotropic tumor size*	Thyroid size	Injected I^{131} retained in 24 hrs.	
					In body (average %)	In thyroid (average %)
I	18	0	-	Normal	19.2	14.5
IIA	10	0	Minute	Marked increase	61.9	56.2
IV	10	200-300	-	Absent or rudimentary	36.6	< 1.0
VIIA	4	75	Minute	Small	43.7	28.5
IX	8	25	-	Normal	28.6	23.1
XA	13	25	Minute	Slight to moderate increase	60.8	30.5

* Minute = measuring 1-3 mm. Similar tumors (with corresponding physiologic effects) will occur about a year after irradiation in mice whose thyroid has been destroyed by radioiodine, causing an increase in total-body iodine retention.

might not necessarily prove accurate. I refer to patients with severe, acute Graves' disease who collect a very large proportion of the administered dose of radioiodine initially and secrete in organic form a large proportion of that collected within the first few hours. This may not be reflected accurately by the calculations suggested, and as a result there may be an extraordinary and unpredictably large concentration of circulating radiothyroxine contributing to a body dose. A second point, regarding the accuracy of thyroid calculations, has to do with how one obtains an estimate of thyroid weight. Dr. Sinclair may have said how he did it, but if so I missed it, because I do not know of any method that will give a net result within 25 or 50% of accuracy.

Table 4

CORRECTION FACTOR APPLIED TO THE β-DOSE CALCULATION IN HOMOGENEOUS MEDIUM ACCORDING TO THE SPACING e OF THE RADIOACTIVE FOCI

e_μ	100	200	500	1000
Cor. Fact.	1/2	1/3	1/7	1/50

DR. FEITELBERG: I think that Dr. Sinclair was a little over-optimistic in assuming high reliability of uptake measurements. I do believe that such measurements have adequate precision in his laboratory, but a recent nationwide survey showed a wide variation, and errors by a high factor were found to be frequent. We are not yet in the position to disregard the uncertainty in uptake measurements when estimating the overall reliability of reported thyroid dose.

DR. SINCLAIR: I think Dr. Keating has a good point about the blood concentration in Graves' disease. However, if each case is studied and the blood concentration is determined with time, there is no reason why each case should not be amenable to dose estimation.

With regard to uptake, I should not have said that it was the most accurate factor. I had on my list, as a matter of fact, an estimate of about 10% for uptake under good conditions, and I think that only about 5% was assigned to the amount, A, for example. However, I meant to indicate that it should be a comparatively accurate determination as compared with thyroid weight for instance. As regards Dr. Marshal Brucer's report, my impression has always been that the results were encouraging rather than discouraging because the vast majority of results were pretty close to the correct values, but I would need more than a cursory look at the data to be sure of that, and I have never had the opportunity to study the results. We are bound to have exceptions like the 10 and 160% but we cannot really seriously consider them in the ordinary course of events.

DR. MARINELLI: I would like to point out that calculations of dose must take into account variation in concentration with time so that the single reading at a single time may not give a percentage of the dose delivered to any part of the body. You may have small follicles at a given time with a high concentration, but if you look at them afterwards you may find that they will discard iodine much faster than the larger ones. These may not have at any time as large a concentration as the smaller ones.

DR. FREEDBERG: I think I can say something about Dr. Brucer's data because I was one of the members of the Thyroid Uptake Calibration Committee. Actually, there was good separation between euthyroid, hypothyroid, and hyperthyroid uptakes. There was a bell-shaped curve in each group although I would not have drawn it quite as Dr. Feitelberg did. As compared to the known amount of simulated radioiodine in the mannequin, the average of the determined uptakes was on the whole on the high side in each group whether hyper-, eu-, or hypo-thyroid. The source did not have any contamination; it was a barium-cesium mixture with a useful life of about 10 years. The mixture fairly closely simulated I^{131} but did not exactly match the spectrum of I^{131}. There were many discrepant values obtained in good laboratories. Dr. Becker is here; it seems to me I heard it mentioned that in certain New York laboratories, rather wide discrepancies were observed in a specimen with a 65% thyroid uptake, with two values coming to mind of 45 or 49 and 80%.

DR. BECKER: I think it was 40 to 75% on a phantom that should have given an answer of 65%.

DR. QUIMBY: One of us had 85%.

DR. FEITELBERG: There were two 45, one 58, and one 85.

DR. BERMAN: I think we got 9% on one and 45% on the other.

B. Comparative dosimetry in the use of various iodine isotopes.

DR. MARINELLI: Let us go on to the next subject, comparative dosimetry in the use of various iodine isotopes.

DR. BERMAN: Much of what I shall present here has been done in collaboration with Dr. J. E. Rall, presently at the National Institutes of Health, Bethesda, Maryland.

The purpose of this study was to evaluate the relative advantage of various iodine isotopes from the point of view of minimal body irradiation for a desired amount of isotope in a specific site. I shall not go into the details of the dose calculations, but merely indicate the factors considered, the assumptions made, and the conclusions drawn.

In the case of radioiodine therapy the following variables were included in the calculations:

1. The concentration of radioiodine in blood and in the desired site as a function of time (expressed in fraction of administered quantity).
2. The half-life of the isotope.
3. The average β and γ energies of the isotope.
4. The size of the irradiated site.

The following assumptions were made:

1. Bone marrow was considered to be the most critical region in the body. The dose to the bone marrow was assumed to be the same as to blood.
2. The dose to any site from local β particles was calculated on the basis of a homogeneously distributed radioiodine source and total β energy absorption within the site.
3. The β particles in thyroid tissue are only about 40% effective as compared with γ rays for all isotopes.
4. The metabolic function of all iodine isotopes is the same.

A list of the iodine isotopes investigated and their physical properties are given in Table 5.

Certain general conclusions can be drawn on the basis of the calculations that were made.

1. The isotope with the highest β to γ energy ratio is usually more advantageous.
2. An isotope with a decay rate that best matches the biologid decay rate of radioiodine in the site to be irradiated is usually more advantageous.
3. The relative advantage of an isotope decreases with an increase in the size of site or tumor to be irradiated.
4. The relative advantage of an isotope increases for higher tumor uptakes. When the tumor uptake is low no isotope is particularly advantageous.

These factors are usually not satisfied simultaneously in any one patient. In each case a different factor may be most dominant. It is necessary, therefore, to determine individ-

Table 5

PHYSICAL CONSTANT OF IODINE ISOTOPES

Isotope	Half-life	Decay constant (hr.)	Average γ energy $(\overline{E_\gamma})$ Mev	Average β energy $(\overline{E_\beta})$ Mev	$\epsilon = \frac{\overline{E_\gamma}}{\overline{E_\beta}}$
I^{124}	4 days	.00722	2.01	0.819	2.45
I^{126}	13 days	.00222	0.395	0.353	1.12
I^{130}	12.5 hrs.	.0555	2.25	0.283	7.95
I^{131}	8.1 days	.00356	0.397	0.195	2.04
I^{133}	21 hrs.	.0330	0.581	0.484	1.20

ually the necessary variables for each patient, and then to select the "best" isotope.

The ratios, $\frac{S}{T}$, of bone marrow dose, S, to tumor dose, T, were calculated for 10 cancer patients who received 12 doses of I^{131} for each of the isotopes considered. (The metabolic function of I^{131} during therapy for each of the patients was available from collected data.) The $\frac{S}{T}$ value for each isotope relative to I^{131} is given in Table 6. The lowest relative $\frac{S}{T}$ values are underlined for each treatment. As can be seen, no single isotope was best for all patients. In most cases, I^{133} ($T_{1/2}$ = 21 hrs.) and I^{126} ($T_{1/2}$ = 13 days) were most advantageous. In one case, I^{131} was best, and in one, I^{130} ($T_{1/2}$ = 12.5 hrs.) but in

Table 6

RELATIVE $\frac{S}{T}$ VALUES FOR VARIOUS IODINE ISOTOPES COMPARED TO I^{131} VALUES

Patient	V_t (gr)	I^{124}	I^{126}	I^{130}	I^{131}	I^{133}
S.C.	275	1.47	.850	3.52	1	2.04
J.D. 1	300	1.09	.825	1.21	1	1.20
J.D. 2	500	1.23	1.04	1.37	1	1.04
O.D.	200	.93	.92	1.05	1	.49
G.F.	300	.92	1.02	.92	1	.64
S.F.	300	1.17	.84	1.58	1	1.42
P.L. 1	400	.924	1.13	.89	1	.92
P.L. 2	400	.97	1.02	1.00	1	.93
I.M. 1	500	1.09	.87	1.01	1	1.02
I.M. 2	350	1.04	1.09	.89	1	.85
M.W.	125	1.09	.95	2.63	1	1.97
J.L.	50	1.21	.79	2.31	1	1.55

neither case by much. I^{124} ($T_{1/2}$ = 4 days) was never best, although it was better than I^{131} in some cases. The value of $\frac{S}{T}$ in any one treatment varied by as much as a factor of 4 for the different isotopes.

A tracer study may be used as a guide to determine which isotope will deliver the least radiation to the bone marrow of a patient. However, for each isotope, one must realize that the therapeutic dose may have an effect that is different from the tracer.

This study, of course, is merely an attempt to evaluate the potential advantages of the various iodine isotopes. In order to confirm the previous conclusions, it is necessary actually to use the different isotopes when advisable. If the conclusions are confirmed, isotopes such as I^{133} and I^{126} may be quite useful for cancer patients in which the amount of radiation to bone marrow limits the radiation to the tumor, and for hyperthyroid patients to minimize total-body irradiation. Some factors that still have to be evaluated for isotopes other than I^{131} are the biologic effectiveness of various rates of irradiations and β-particle energies.

A study is in progress at Memorial Center in collaboration with the New York Hospital to evaluate I^{133} for therapeutic application. Several cancer and a number of hyperthyroid patients have received this isotope over the past year. Some of the results from the hyperthyroid patients will be presented later. We have been supplied with I^{133} by the Brookhaven National Laboratory.

Dr. Marinelli asked me to extend the evaluation of the various iodine isotopes to diagnostic procedures. In diagnostic application it is usually necessary to determine the radioactivity of a specimen or of a site in the body, at some time after a tracer is administered. The criterion chosen for the evaluation of the various isotopes is the amount of radiation that the blood receives from a tracer dose.

The following variables have been considered in this evaluation:

1. The time when the test is to be performed. Two independent factors are important in this respect, the metabolic function of radioiodine and the half-life of the isotope.

2. The sensitivity of the detecting device to the radiation. The disintegration scheme of the isotope (the number and pattern of the β particles and γ rays emitted per disintegration) and the sensitivity of the detector must be determined.

Calculations for a hyperthyroid patient whose metabolic function of radioiodine was known are given in Tables 7 and 8. The "best" isotope is underlined for each type of measurement. In Table 7, relative values of blood irradiation are tabulated for the various isotopes as are various times of measurement of radioactivity in the thyroid using a NaI scintillation detector, 2.5-cm thick, located at some distance away. S represents the relative radiation to the blood of the patient. The probability that a disintegration will be recorded by the detector is g_t, normalized to a 4π geometry. (A probability of greater than unity arises from the fact that for small solid angles, multiple γ rays per disintegration having random directions appear as independent events.) The physical decay of the isotope for time t is given as $e^{-\alpha t}$. The relative amount of radioiodine in the thyroid at time $\underline{t}$ is m_t.

Relative blood radiation is tabulated in Table 8 for the various isotopes, and indicated

Table 7

RELATIVE BLOOD DOSE FOR VARIOUS IODINE ISOTOPES FOR A DESIRED THYROID UPTAKE DETERMINATION

Isotope	g_t	S	$S/g_t e^{-\alpha t} m_t$				
			2 hrs.	6 hrs.	24 hrs.	48 hrs.	7 days
I^{124}	1.26	10.2	10.71	9.27	13.16	17.34	46.92
I^{126}	0.471	9.05	25.25	21.36	27.78	32.40	48.15
I^{130}	1.71	.888	0.764	0.797	2.69	11.24	large
I^{131}	0.67	4.39	8.69	7.33	9.79	11.81	20.55
I^{132}	1.31	.188	0.342	0.938	247.	large	large
I^{133}	0.56	1.30	3.26	3.09	6.90	16.52	89.04

g_t = efficiency of external counter - 2.5-cm thick NaI scintillator.

times when blood samples were collected are included. A well-type NaI scintillation detector, having a thickness equivalent to a 1.6-cm spherical shell, was used for calculating the detector sensitivity. S and $e^{-\alpha t}$ are as defined earlier. g_w is the probability that a disintegration will be recorded by the detector. (Here, g_w cannot exceed unity because the solid angle is assumed to equal 4 π.) The relative amount of radioiodine in the blood at time t is m_i.

Table 8

RELATIVE BLOOD DOSE FOR VARIOUS IODINE ISOTOPES FOR A DESIRED BLOOD SAMPLE DETERMINATION

Isotope	g_w	S	$S/g_w e^{-\alpha t} m_i$				
			2 hrs.	6 hrs.	24 hrs.	48 hrs.	7 days
I^{124}	.832	10.2	1010	1826	587	579	1530
I^{126}	.352	9.05	2091	3729	1086	950	1385
I^{130}	.756	.88	107	234	179	562	large
I^{131}	.510	4.39	70.7	126	37.5	34.0	57.9
I^{132}	.680	.188	40.6	235	313,340	large	large
I^{133}	.400	1.30	282	563	282	508	2653

g_w = efficiency of well counter - 1.6-cm shell of NaI scintillator.

Tables 7 and 8 represent but one type of patient and give only a limited number of measurements. It is obvious, however, that because of the nature of the variables, considerable variation may be expected among isotopes. In general, radiation to the blood may be reduced considerably by a properly chosen isotope.[9]

This study did not include factors that could reduce blood irradiation equally for all isotopes, such as accuracy, detector efficiency, and others.

DR. POCHIN: There is a point that I would like to add—the importance of a high β energy. This is important in view of the nonuniform distribution of radioiodine within the tissue of tumor.

C. Management of radiation exposure to patients and hospital personnel.

DR. MARINELLI: We will now consider the problem of management of radiation exposure to patients and hospital personnel.

DR. CORRIGAN: A discussion of the management of exposure to patients and laboratory personnel really involves two general subjects. One is the handling of radioisotopes so that people are not exposed knowingly, and the training of people so that they do not accidentally expose themselves or those around them. The other is the controlled limitation of exposure to patients.

The management of the exposure to patients is the more complicated, and we feel that the most important single feature in keeping down exposure to the patient, specifically in diagnostic studies, is to get the most possible information out of tracer studies; otherwise, obviously, something else will have to be done. We will have to have repeat tracer studies or continued X-radiation studies or possibly even a radiation therapeutic test dose that will make the total exposure much higher.

The radiation laboratory at Harper Hospital (Figure 12) stands on the roof of one of the main buildings and is thus relatively inaccessible to nonauthorized individuals. It is arranged so that there is no possibility of air contamination to the rest of the hospital. The laboratory was built just 10 years ago and has proved to be very satisfactory. It has served as the prototype for a number of others. Prior to this time our laboratory was in an old building on the first floor.

One of the dispensing units we use is shown in Figure 13. It is quite satisfactory for handling 200 mc or more of radioiodine. The shipping container can be positioned without removing any of its lead, and an automatic siphon picks up the radioactive material and returns it to a leaded reservoir. Then the dose can be drawn up into the burette and measured accurately.

In actual use, Figure 14, these instruments are separated from the operator by lead glass. Mirrors have been used, but the lead glass has proved more satisfactory. The equipment is vacuum-operated so that in case of a break, everything falls back into the reservoir; so far, there has never been an accidental break. If this did happen, there would be no pressure to blow the radioactive material around the room.

The doses are measured out into lead carriers (Figure 15), which are shielded by a minimum of 1/4 inch of lead and a steel shell with an extra lead slug to protect the hand. These are safe for quantities up to 100 mc but are not used for more than 25 mc.

The administration is done by laboratory personnel, resident physicians in training

Figure 12. High level isotope laboratory in converted penthouse.

and especially trained nurses, who handle the carrier without exposure. The patient takes the dose out of the carrier (Figure 16). With a tracer dose, the γ exposure is probably not serious. However, radiation badges are worn, and if a therapeutic dose is being handled there would be a greater distance between the individuals than is shown in Figure 16.

In all procedures, the resident physician learns to make his own safety measurements, to do standardizations, to measure out doses, and to do all of the laboratory work. They learn to use the various instruments, and we show them that these do not all respond in the same way to radiation. They are provided with standard sources on which they can evaluate the usefulness of these instruments. In setting up a new procedure, measurements of this sort are made not only for training personnel but also to be sure that the procedure is safe. If excessive exposures are found, the procedure is modified.

We do not consider the uptake measurement (Figure 17) to be particularly significant in a diagnostic tracer study. If the diagnosis is known, and all we are doing is evaluating the possibility of therapy, it may be useful. An ordinary counter with a 20-cm spacer is used, and the measurement serves primarily as a check on the rest of the method. As a part of the complete tracer study, we measure uptake, excretion, and total-body retention and try to come as close to 100% as possible. We do very well except with patients who have liver congestion or edema.

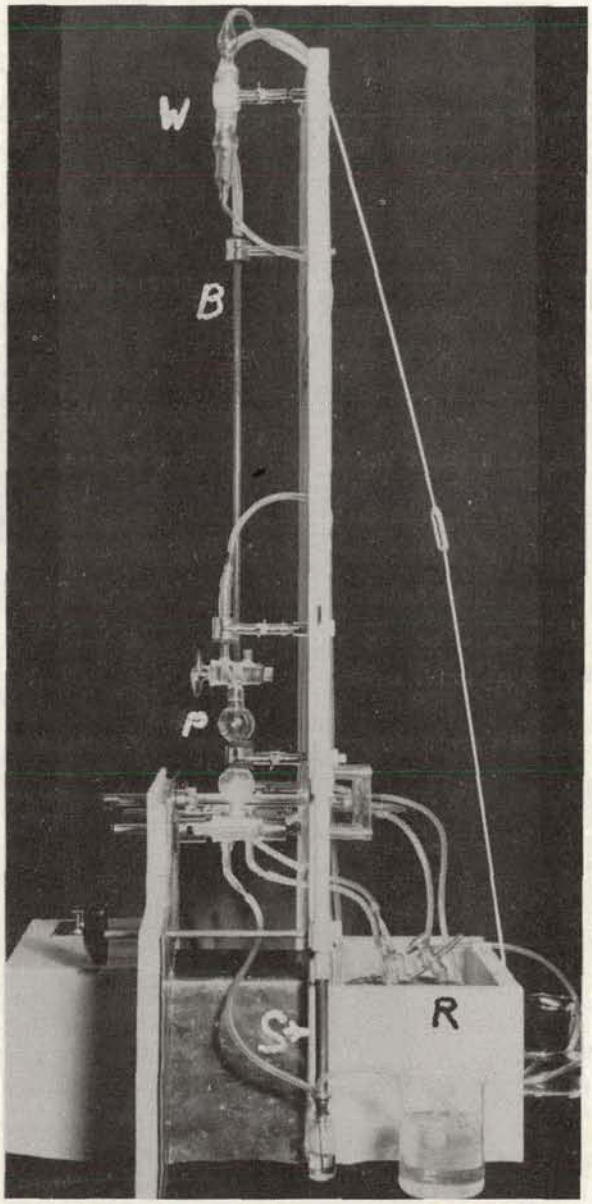


Figure 13. Automatic dispensing unit with shielding removed. The shipping container is placed in the position of the bottle in lower center of the picture. The siphon, S, controlled by the knob to the left, picks up the shipment and the diluent and delivers it to the dilution pipette, P. From here the entire shipment is transferred to the reservoir, R, which has a minimum lead thickness of 1 inch. (The visible portion of R is a wooden box. The upper edge of the lead cylinder is just visible.) The diluent contains 1% potassium salicylate. From the reservoir the solution is lifted into the burette, B, from which doses are measured out. W is a self-filling water pipette which delivers 30 cc of water into the carrier with each dose measured. The water flow is arranged to take the last drop off the tip of the burette.

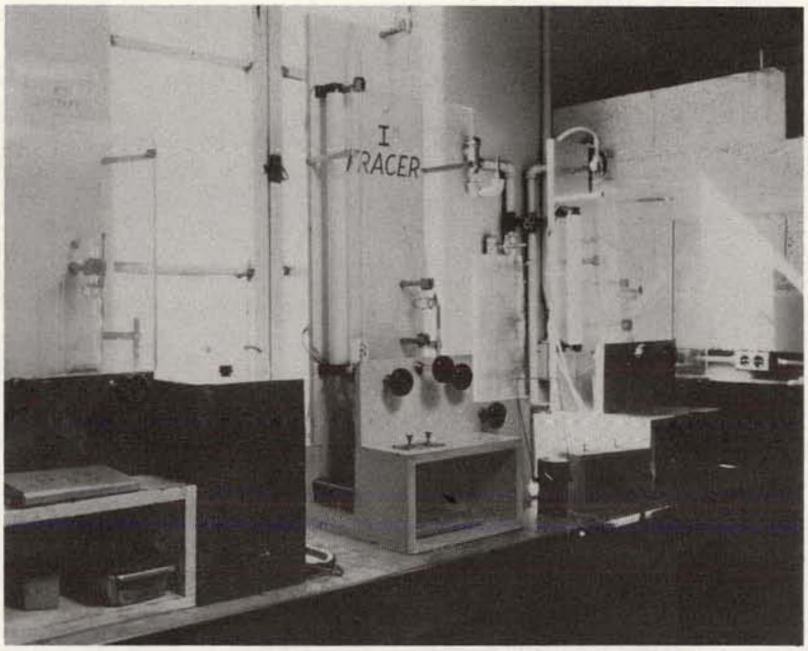


Figure 14. Three automatic dispensers in actual use. Large knob to the left controls the burette. Cornet valves apply vacuum or air at atmospheric pressure to the dilution pipette or the delivery burette respectively. All of the equipment is vacuum-operated. Concrete facing of bench for chemical syntheses is visible to the right.

Figure 15. Dosage carrier. Paper cups have not proven satisfactory for sick or nervous patients. No adsorption will occur on glass if the glass is properly washed with soap and water before use and if the solution is alkaline.

Figure 16. Simulated administration of therapy dose. Nurse and resident physician are closer to patient than when a dose is actually given.

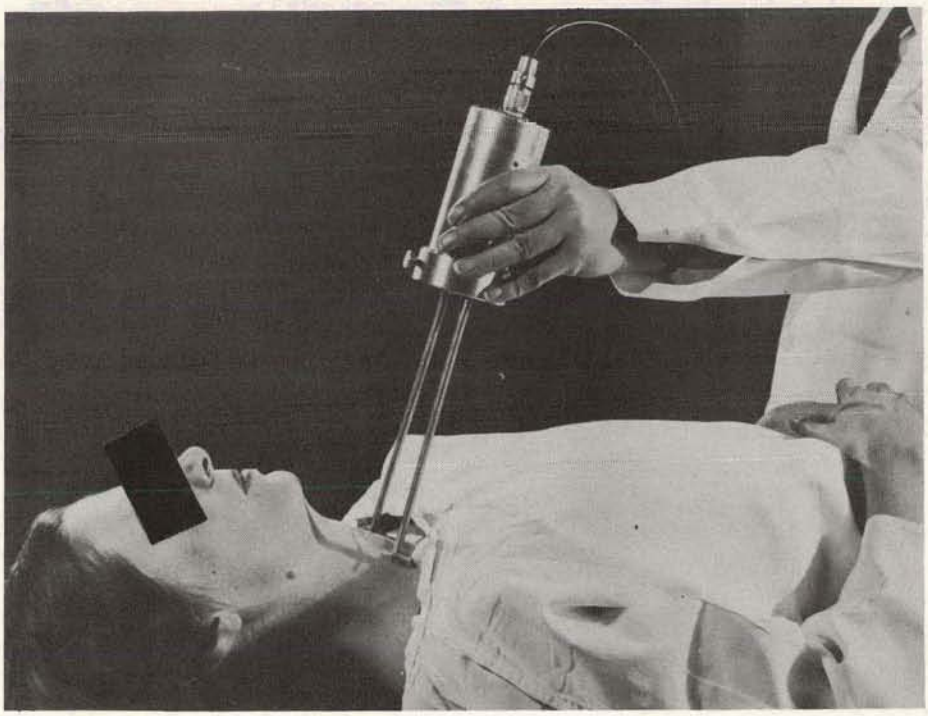


Figure 17. Accessory for measuring total thyroid content at 20-cm distance.

For therapy doses, the arrangement shown in Figure 18 is used. A scintillation counter or TGC 8 is used with a conical collimator, and at least 2 mm of lead filter below the cone. With this setup, accurate measurements of the total thyroid content can be made, and radiation dosage is determined by measuring retention of the dose at intervals after administration.

Much of the resident physicians' time goes into learning how to handle the patients. We do not use technicians for any radiation measurement on patients, but we do have graduate students who are attending Wayne State University and working in the laboratory. Work on patients, however, is done either by physicists for teaching purposes or by resident physicians.

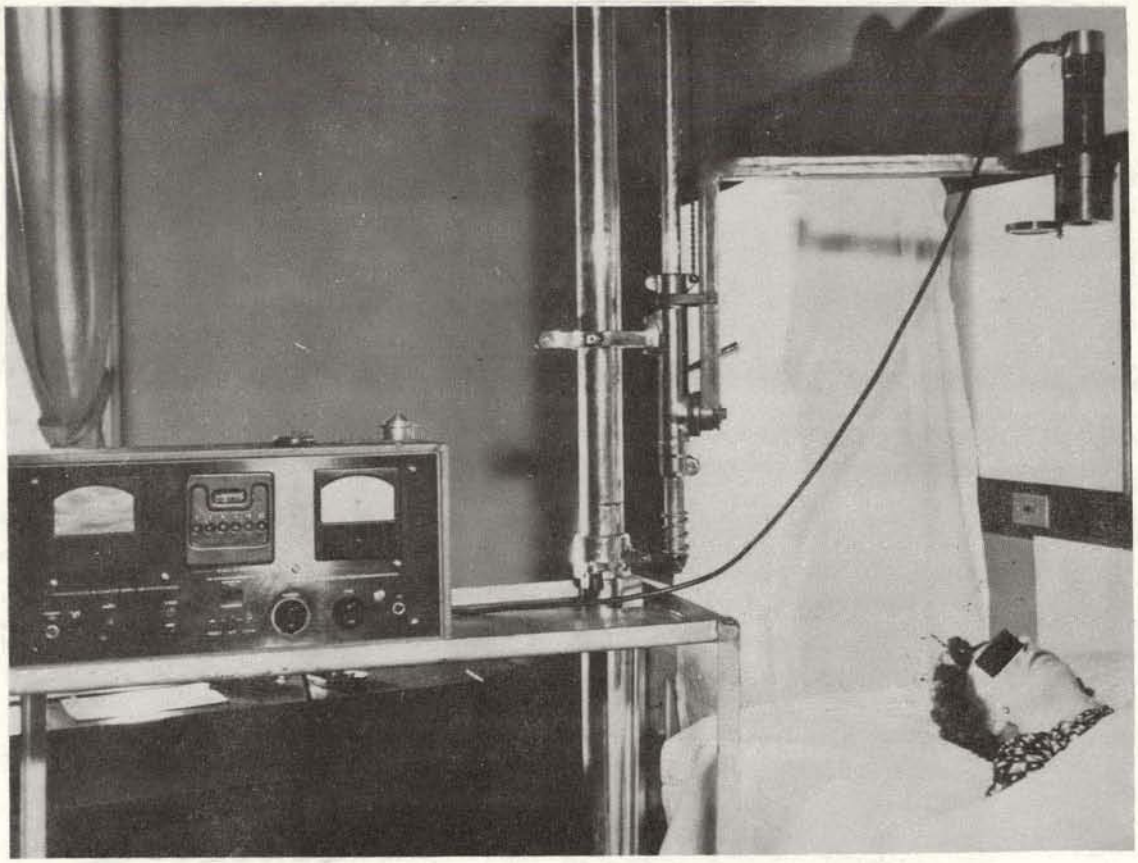


Figure 18. Fixed distance counter for measuring retention of therapeutic doses. 80-cm distance, lead filters shown are swung out to left of axis of collimators. Filters are 2, 3, and 5 mm in thickness.

In our opinion, the vitally important thing in a tracer study is to find out what is wrong with the patient. The following is a typical example: A patient was supposed to have an inoperable malignancy (Figure 19). Tracer study showed this to be a rather ordinary sort of thyroid tumor, probably not malignant. It was removed surgically (Figure 20). The patient has been entirely well since 1949.

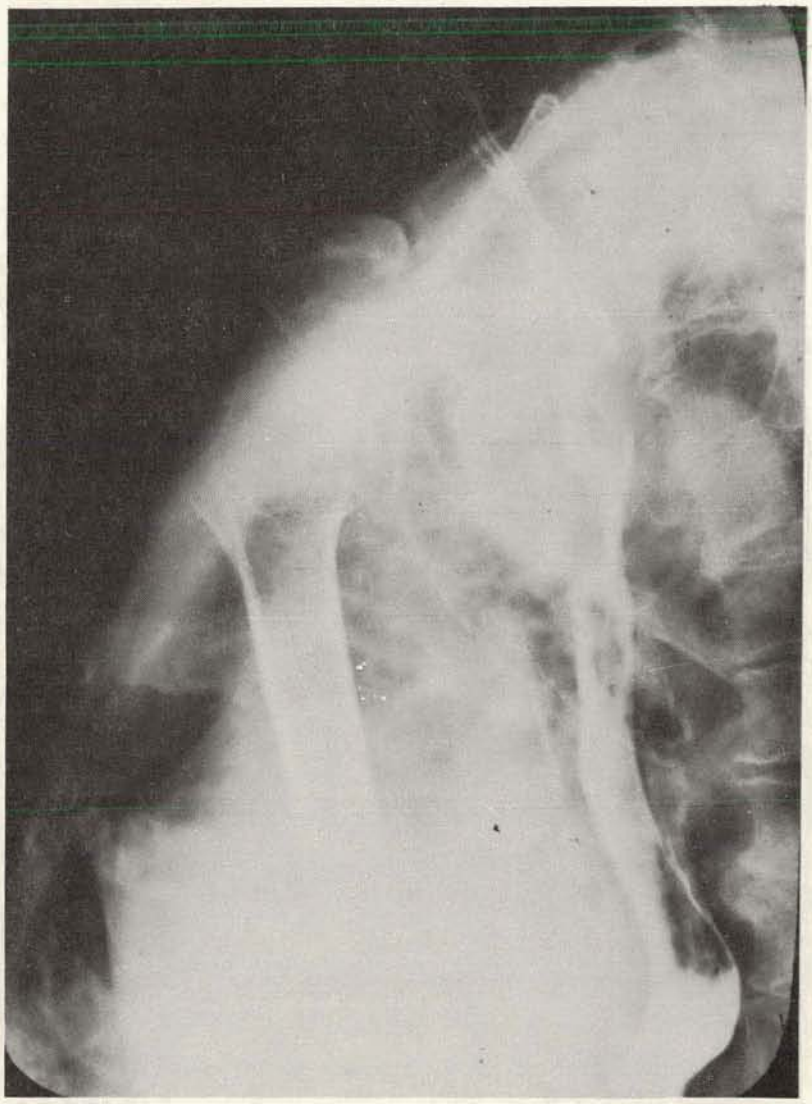


Figure 19. Mediastinal tumor.

As to mechanical scanning equipment, it has its virtues but also its limitations. Its greatest limitations are lack of flexibility and lack of discrimination for the small differences upon which identification of a lesion usually depends. Its greatest virtue, in our opinion, is to save argument. There are occasions when quantitative measurements are simply not appreciated. Even if you give a bad picture you are away ahead. Figure 21 illustrates such a case; and I am sure you all have interpretations. This is the story of a patient who had a thyroidectomy 20 years previously and who now has thyrotoxicosis and cardiac disturbance with essentially no thyroid in the normal thyroid region, but a considerable amount in the mediastinum (Figure 22). Thyroids are great simulators; they can assume the appearance of many other things. In this case, the mass was uniformly hyperactive and easy to delineate. In the previous case, Figures 19 and 20, only little islands of functioning

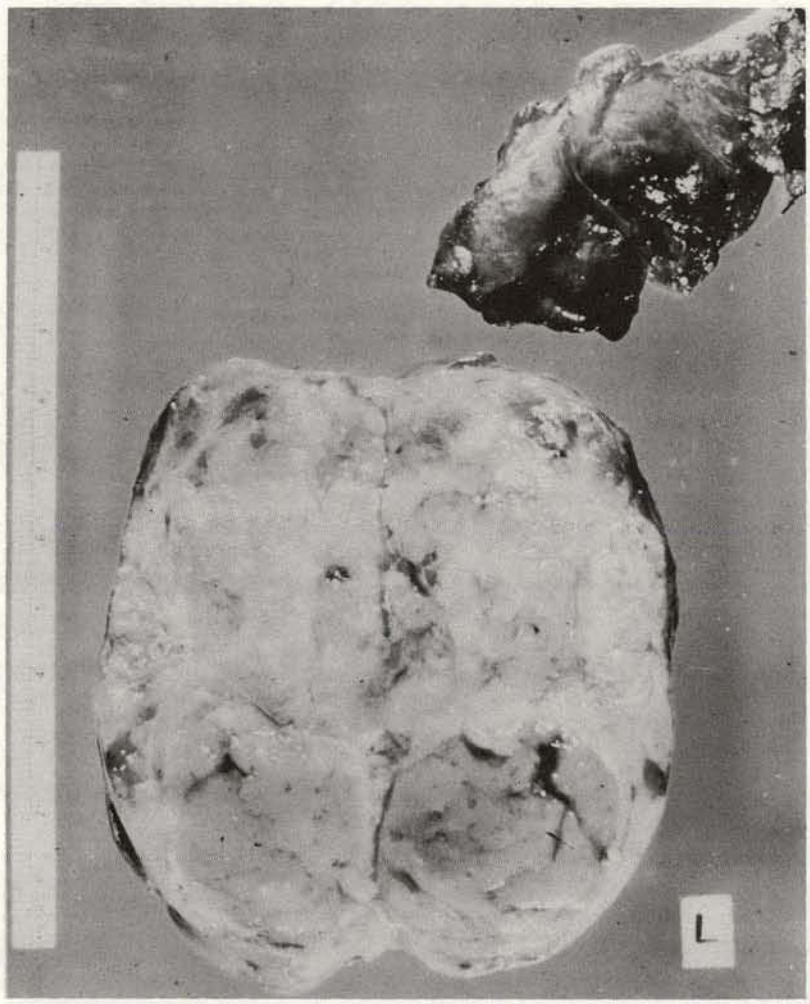


Figure 20. Benign mediastinal thyroid tumor removed from patient wnose roentgenogram is shown in Figure 19.

tissue were present in, and on the surface of, a large degenerated mass. Only a counter that can make a very close approach to these small and weakly functioning spots can detect them. The value of using a close-contact counter has been demonstrated in 238 cases of substernal thyroid and intrathoracic tumor of thyroid origin;* and 219 cases of carcinoma of the thyroid. During the course of this evaluation, 92 students, largely radiological residents or fully accredited radiologists who came to our laboratory for study, have received a complete course of training. Properly trained individuals have never encountered any difficulty in repeating these procedures and have returned many case records to our

*The distinction is made on the basis of the intrathoracic mass being 1) an extension or 2) a separate entity.

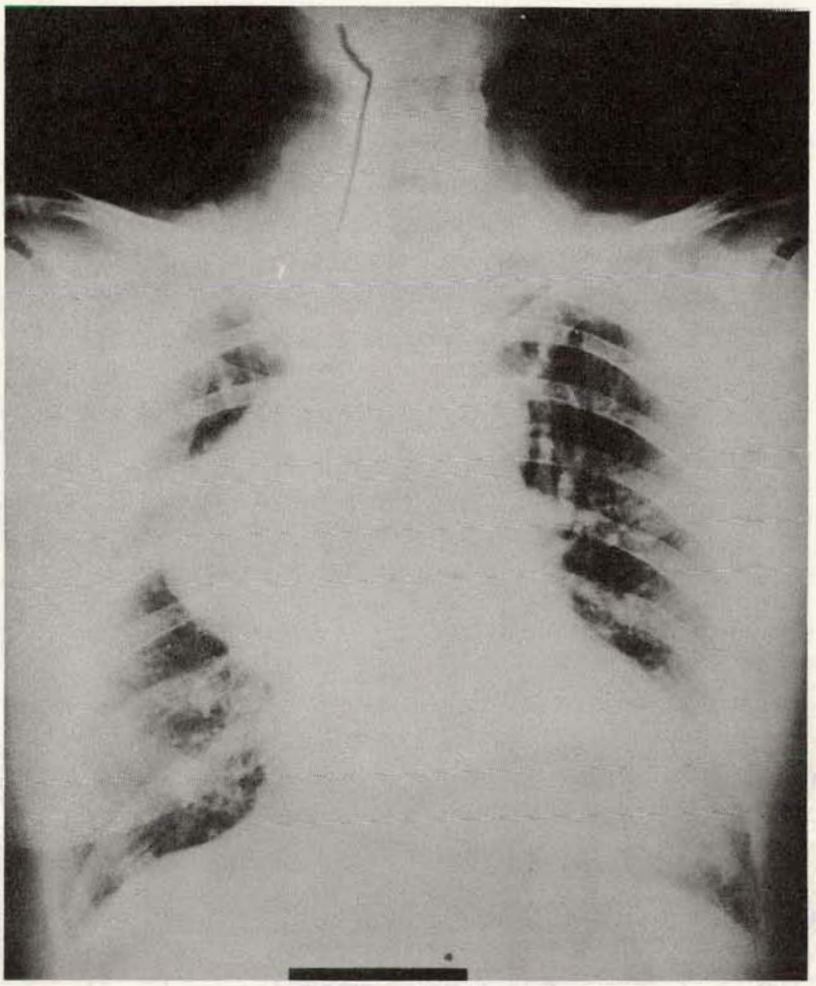


Figure 21. Roentgenogram of the chest of a 65-year-old woman. Clinical symptoms suggest thyrotoxicosis. Patient has no palpable thyroid. Her cardiac status was poor. Mediastinal shadow was tentatively interpreted as an aneurysm.

laboratory from institutions to which they have migrated. This, after all, is the greatest protection to the patient.

As to the sensitivity of scintillation scanning versus hand scanning with a properly shielded counter, a comparison is shown in Figure 23. This is an anatomical model and shows the thyroid in rather nonuniform areas. There is also a good-sized substernal area. The small focus might be a metastatic localization in the intercostal space. With about two weeks of training, a student scanned this "patient," and his diagram (Figure 23) is compared with that made by about the best scanning device in existence at the time. The dosage he elected to give the patient was about 85 μc. The relative sensitivity is shown here, and for a given count over the most active area, the scanner recorded about

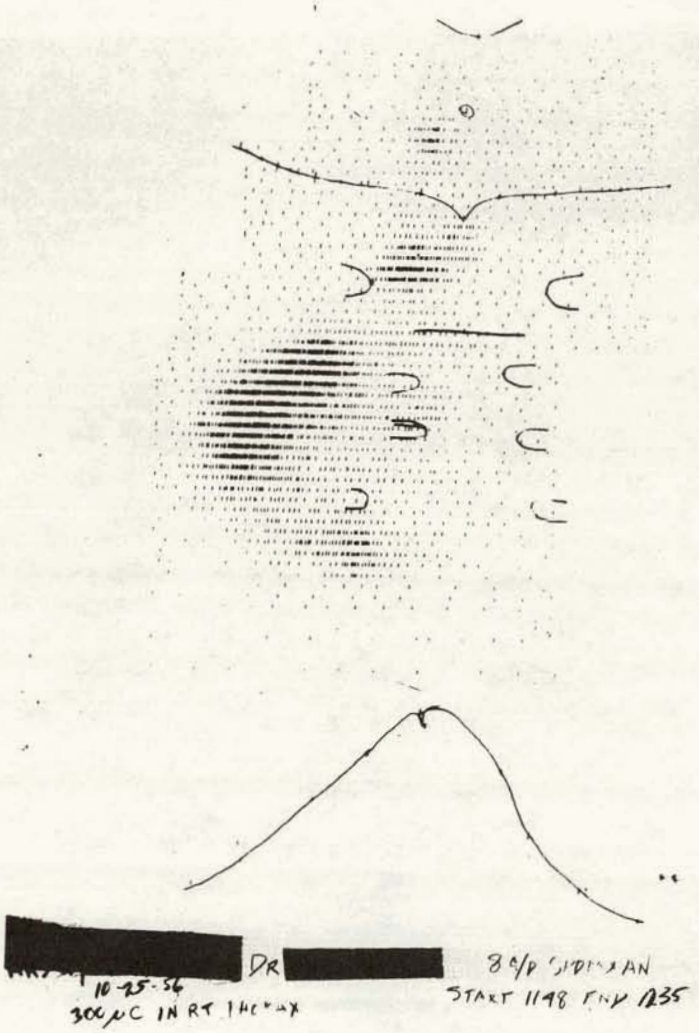


Figure 22. Same patient as in Figure 21. Pattern made with the scintillation scanner shows a fairly large localization of I^{131} in the mediastinum and a small area in retromanubrial area and in the region of the right lobe of the thyroid. Patient responded to isotope therapy; was well 7 months later.

250 cpm, and the hand counter 4000 cpm. There is nothing very difficult about performing the technic if you learn how to do it and use the proper equipment. The results are far superior to those obtainable by mechanical means.

DR. FEITELBERG: What was the exposure to the personnel in mr/week?

DR. CORRIGAN: The isotope people never exceeded 60 mr in two weeks, as recorded by the film badge.

DR. GLASS: One of the few people here who is not a physician has stipulated a tolerance level for exposed personnel. I would like to point out that the tolerance level of 300 mr per week is based entirely on the possible physiologic effects and disregards the ge-

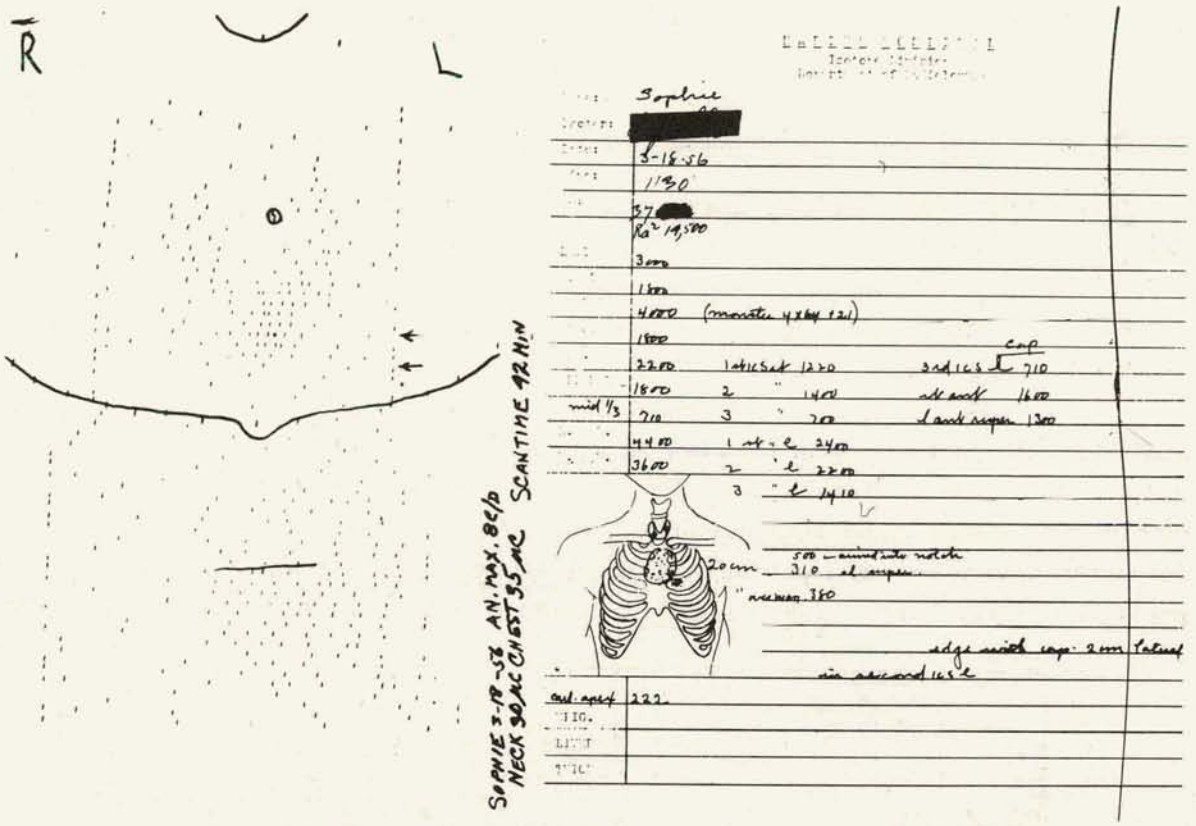


Figure 23. Comparison of results obtained by means of a scintillation scanner and by a resident physician in training using a close-contact scanning counter.

netic ones. Most of our people are relatively young and still within the most active period of reproductive life, or have that ahead, and I think we therefore should take into cognizance the recommendation that, because of possible genetic damage, no individual ought to receive more occupational exposure than a cumulative dose of 50 r over a 10-year period. This works out to an <u>average</u> of about 100 mr per week, but of course this would have to be calculated on a cumulative basis. We ought to make sure that no person gets more than 300 mr a week.

DR. QUIMBY: I would like to know how many people in this audience have technicians that ever get anything like as much as 300 mr a week. We seldom see more than 30 in our laboratory, and I would like to know how many people habitually get even 100 mr a week. I will bet very few.

Part II — Some Quantitative Aspects of Radiation Damage in Mammals Relevant to the Clinical Use of Radioiodine

A. Hematological, myeloid, lymphoid, and leukomogenic response.

DR. MARINELLI: We will now consider some quantitative aspects of radiation damage in mammals relevant to the clinical use of radioiodine. Dr. Jacobson will open this part with a discussion of hematological, myeloid, lymphoid, and leukomogenic response.

DR. JACOBSON: Actually the amount of quantitative information we have on hematologic response is quite limited.

Figure 24 is probably the best illustration I have on the problems on which we have worked for the past 14 years. It shows the effect of a single total-body X irradiation on the lymphocytes of the peripheral blood. The dosages range from 25 to 800 r. You will note that the first dose one can consider significant is 50 r. Actually, we have other data which definitely indicate that 25 r produces a significant reduction in lymphocytes. It is interesting in this connection that doses of 500 r or more produce approximately the same effect,

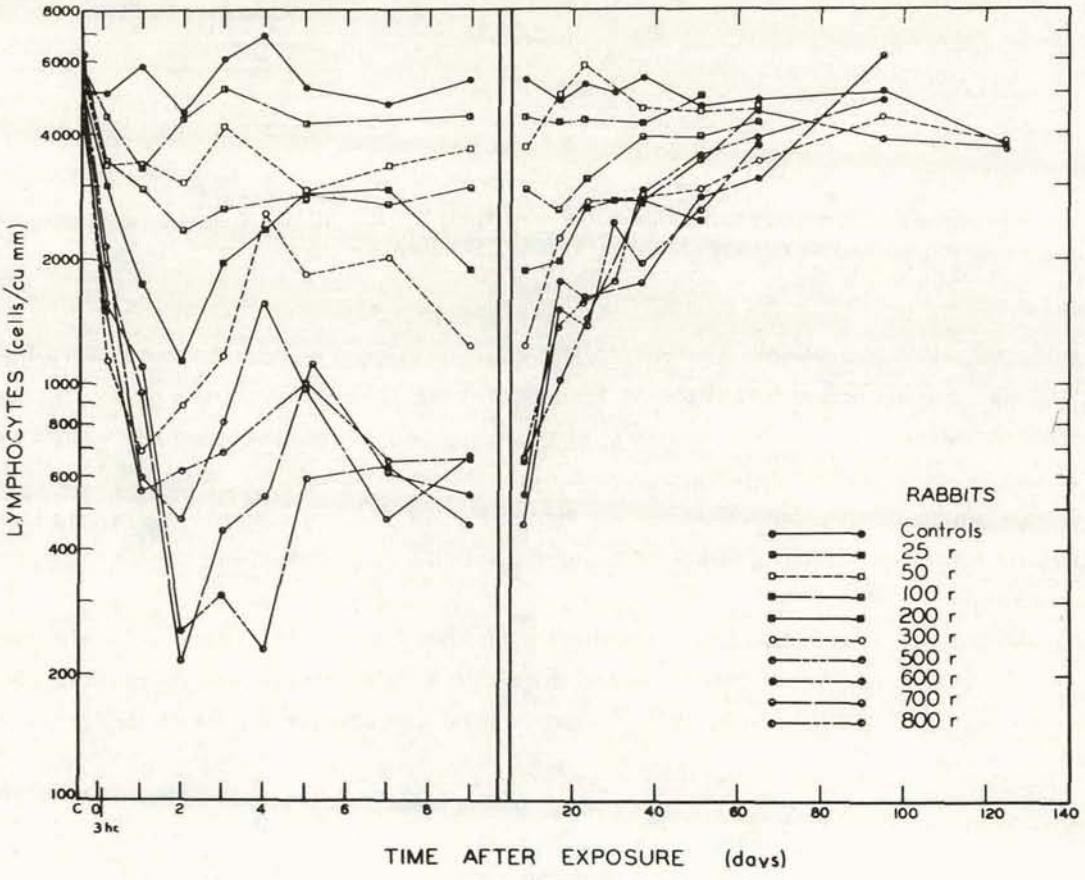


Figure 24. The effect of a single total-body exposure to X radiation on the number of lymphocytes in the peripheral blood of rabbits. The dosages range from 25 to 800 r.

largely indistinguishable from one another. This is as one might expect since 500 r or more produces a uniform depletion of the lymphatic tissue and profound injury to the bone marrow.

The quantitative radiation effect on the heterophils of the rabbit caused by doses below 500 r is shown in Figure 25. We feel that we are able generally to delineate the effect of 100 r on the heterophils but not that of lower dosages. On the other hand, of course, you are all familiar with the fact that a number of workers have been able to show that there is a depression in the number of reticulocytes measured in terms of iron incorporated into the blood cell at doses below 25 r. There are claims that exposure to as little as 5 r can be detected by this effect. I do not remember offhand how significant the 5 r level is. At any rate, with 10 r and above the effects are significant. In other words, we are talking about the effect of a dose of 25 r on the lymphocytes and something between 5 and 10 r on iron incorporation into the red cells as the lower limit for single X irradiations. As a matter of fact, I could have used illustrations for neutron effects that are practically identical with these.

The experience that they had out at the Argonne National Laboratory and work we have done here on single doses would indicate that in the human being an appreciably significant

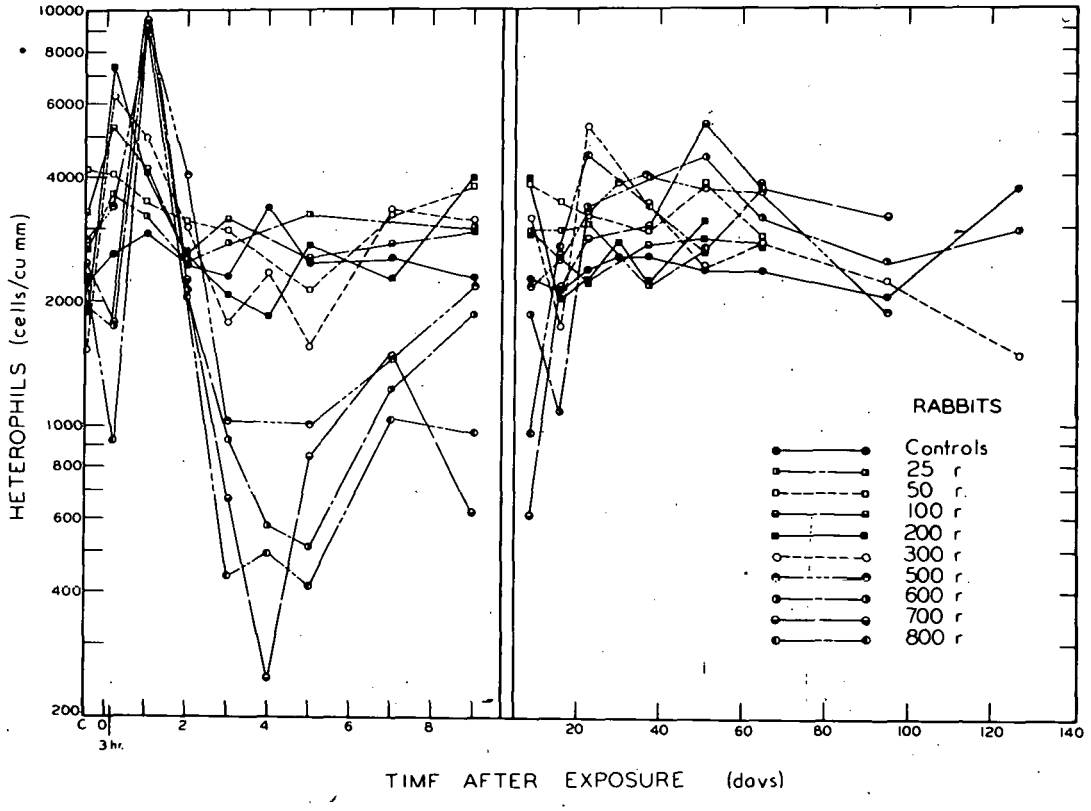


Figure 25. The effect of a single total-body exposure on the number of heterophils in the peripheral blood of rabbits. The dosages range from 25 to 800 r.

effect can be obtained with as little as 50 r and probably down to 25 r. We would have to have data from many individuals exposed to this level in order to get what we would consider to be statistically significant effects. If we talk about the platelets, we generally assume that the effects upon the megakaryocyte and platelet levels are about equivalent in terms of sensitivity of the granulocytes.

So far as divided dosage is concerned, I have very little to say about this. As you know, there is a tremendous amount of literature, principally from the laboratory of Dr. Lorenz. He exposed mice and guinea pigs to doses ranging from 0.1 r on up to 8 r or more per day. The data, which were collected over a period of 3 years, are very confusing and do not appear to be significant from the point of view of effect. I think, however, that Dr. Furth will bear me out when I say that 0.1 r given continuously produces no discernible effect on the blood-forming tissue. That beginning with a dose of 0.2 r per day, there are changes shown especially by a depression in the number of lymphocytes. On the basis of a single animal, these data are not significant, but on the basis of large groups of animals, this effect has significance. I shall leave the leukomogenic aspects of this problem to Dr. Furth, and will discuss briefly the problem of the effect of therapeutic doses of radioiodine on the blood-forming tissue.

I should like to say that we learned many years ago, just as we did with X radiation, that isotopes such as iodine, when given parenternally in doses that Dr. Brues tells me were about 1/10 of the LD 50, affect the circulating lymphocytes. This effect is due presumably to the circulation of the radioemitters through the lymphatic tissue. One is always concerned with the effect, if any, radiophosphorus or radioiodine will have on blood-formation in the long run. As you may remember, the workers at Mayo Clinic were the first to report that radiophosphorus given to patients with chronic leukemia produced an acute leukemia in many recipients. I was not too struck by this report because I felt that practically all of our patients with chronic leukemia died in acute exacerbations. However, the work that they have reported recently on the incidence of leukemia in patients with polycythemia rubra vera treated with radiophosphorus makes it difficult to say, at the moment at least, that the incidence of leukemia is not increased. In our own series of polycythemics, which is about 150 cases, we have had two cases of leukemia in the past 10 years of observation. If we follow them another 20 years, we may have a much larger incidence. I think it is a little too early to say very much about radiophosphorus in terms of production of leukemia. I only know of two reports on the incidence of leukemia in radioiodine-treated patients. I hope that one day we will get to the point where we can determine the minimal dose that may conceivably produce leukemia. At this time, on the basis of Hiroshima data, it looks like a rather large dose is necessary to induce the disease, but it would not surprise me if we would find cases eventually resulting from total-body doses in the neighborhood of 100 r or even less. Some evidence for this is coming from the British studies on localized irradiation for the treatment of arthritis and so forth.

DR. SONENBERG: Dr. Tubiana and I were just going over the cases we have; we

have found in the literature reports of 7 cases of leukemia in patients treated with I^{131} for thyroid cancer.

DR. JACOBSON: Do you know the total iodine dose?

DR. TUBIANA: My patient received 340 mc in 4 doses. She was found to be leukemic 3 years after the treatment.[10]

DR. FURTH: There are about 5 published cases of leukemia among I^{131}-treated people. The common denominator is the large dose, evidence of acute radiation damage, a few years of latency, and type (myeloid).

DR. WERNER: I have had one patient die of leukemia following therapy for hyperthyroidism. He was a 63-year-old man with a small goiter who received only 6 mc of I^{131} and died about 2-1/2 years later of a very acute condition of what seemed to be monocytic leukemia.

DR. POCHIN: I have had one case of leukemia following radioiodine for hyperthyroidism, having 6.7 mc.[11] There has been one other case reported in London.[12]

DR. CHILDS: We have had one case, a man of 46. He was given a single dose of 5.3 mc with a radiation dose to the thyroid of 7000 reps. He developed acute leukemia 18 months later. We have no calculations on the radiation dose to the blood.

DR. FEITELBERG: We had no cases of leukemia in patients with Graves' disease following therapy. In patients with thyroid cancer we have been watching mostly the bone marrow, which shows changes earlier than the peripheral blood. We have seen damage to the bone marrow with about 800 mc.

DR. JACOBSON: I think that the important aspect of the problem is related to the size and frequency of the dose. In cases in which the dose was sufficiently high to damage seriously the bone marrow, leukemia might be expected to occur, whereas with smaller doses and relatively little bone marrow damage, we might not see it.

DR. RAWSON: I would like to ask a question about the Graves' disease cases; one was monocytic and then we heard of three others but the type was not mentioned.

DR. CHILDS: Our patient had acute myelocytic leukemia.

DR. RAWSON: The group at Ann Arbor has talked about the occasional appearance of leukocytic leukemia in patients with Graves' disease. Krumbar talked about it but never published it. There may be a natural relationship between those two.

DR. FEITELBERG: I feel very strongly with Dr. Jacobson that the peripheral blood picture should not be used as a guide for cancer therapy, because the peripheral blood shows changes months after changes have occurred in the bone marrow. If you are guided by the bone marrow response, you have a much more rational indication of when and how long to wait. That we have had no permanent leukemias is due to the fact that we were guided by the bone marrow response.

DR. RALL: It is also true that if you do bone marrow studies at weekly intervals after a very large dose of radioiodine for cancer therapy, you will see minimal changes in the bone marrow in, say, the first month; when you see rather definite and marked changes in the blood. But I think what you are speaking of is at a later time, 3 to 60 months.

DR. CLARK: We have some 800 cases of thyrotoxicosis which we have treated with radioiodine and we do not have any cases, that we know of, who developed leukemia. Some of the individuals in this group had quite large doses of radioiodine. In the early days of our program, we gave as much as 200 mc to individuals with very large glands. Today we believe that such people are better treated with surgery. In our carcinoma group we found something similar to what Dr. Feitelberg described, that the peripheral blood does not always reflect what is going on in the bone marrow. We have done bone marrow biopsies on some of these patients in which the peripheral blood was essentially normal, and found considerable change in the bone marrow. We have a large group of patients to whom we have given between 400 and 500 mc of radioiodine, and have found that is about the dose at which they start to show changes. One patient who received 1500 mc of I^{131} in divided doses over a period of 1-1/2 years, upon whom a number of bone marrow studies were made, started to show bone marrow changes after receiving 700 mc, and at about 1000 mc there was a very marked depression in the cellular elements of the bone marrow. We stopped the therapy for a while and the marrow regenerated. Therapy was continued, but after another 500 mc, the marrow again showed a marked depression, and therapy was stopped. The marrow subsequently returned to normal.

On the other hand, a girl to whom we had given 2200 mc has shown very little bone marrow change, illustrating the individual differences in the susceptibility of the bone marrow. On the whole, we have found that if we stay under 500 mc, we do not see any ill effects on the marrow. We use divided doses, 35 mc every 2 weeks over a period of time, which may be a little different than giving a huge dose at one time.

DR. BERMAN: We seem to be using the millicurie as a criterion of radiation dose. Is it possible to give some figures in terms of rads or reps?

DR. TRUNNELL: We have a 14-year-old boy who showed very definite bone marrow changes after a single dose of 60 mc. These changes were documented by bone marrow studies made serially over a period of several months following that single dose.

DR. JACOBSON: That is not at all surprising. Occasionally you find patients who are so sensitive to phosphorus that 2 to 4 mc will completely knock out the marrow, whereas to many you can give 8, 9, or 10 mc without much concern. I would imagine the same thing would obtain with iodine.

DR. CORRIGAN: I do not want to get into a clinical argument, but I do have some statistics that are pertinent. In our laboratory, hematologic studies are done under the direction of Dr. E. C. Vonder Heide, who I am sure you all know, and are controlled very carefully. I have a list of patients who have received the largest doses. These are not all of our carcinoma cases, but we gave 1326, 1124, 1128, 744 mc, and so on. The earliest patient on this list was treated in 1949, and she is alive and well. Like Dr. Clark's patients, these were all given relatively small doses; the largest single ones being 100 mc, and these were exceptional. Commonly, about 25 mc per week was used. Of the cases in this list, the latest treatment is 1953, the others were treated in 1951 or before. In many of them there has been enough suppression of the circulating components to stop therapy un-

til recovery occurred, when therapy was started again. But in no case—I do not have the number of hyperthyroids that have been treated in our laboratory, but it is a matter of hundreds—have we seen any evidence of leukemia. I wonder then if we are not dealing here with a purely statistical phenomenon.

DR. KEATING: Relevant to the discussion of the peripheral blood and bone marrow of patients receiving large doses of radioactive iodine for the treatment of cancer is the fact that both peripheral blood and bone marrow are affected profoundly by lack of thyroid hormone. This effect may become evident in some patients in whom myxedema is allowed to develop as a result of irradiation, a myxedema which may be associated with pancytopenia or anemia. I do not know whether leukemoid reactions have been seen in this situation or not. The anemias and cytopenias observed have responded to treatment with desiccated thyroid substance. To what extent does this consideration impair the validity of the serial observations on bone marrow which Dr. Feitelberg proposes?

DR. MILLER: We have observed this as well. First of all, studies on marrow are difficult to do and small variations are difficult to determine. In addition, there apparently is, as Dr. Jacobson has pointed out, tremendous variation in response to a given amount of radiation. With respect to Dr. Keating's comment, our patients who were treated over a period of several years were given 100 mc per month and were treated in profound myxedema so that the number of mc given and the total-body radiation can be determined pretty well. A number of patients were given thyroid at various times with respect to the end of therapy, having achieved their maximum hematologic depression. We found the blood effects to be independent of the time thyroid was given, but very dependent upon the time therapy ended. It is a small number of patients, of course, but the effect seemed to be fairly independent of the thyroid, although we expected to find that it would depend upon it.

DR. WERNER: Is there any evidence that if the bone marrow is more radiosensitive, it is more apt to make a transition to leukemia?

DR. JACOBSON: Dr. Furth can probably answer that question.

DR. FURTH: Hyperplasia of the bone marrow probably enhances the likelihood of radiation-induced leukemia. This is an interesting problem that has not been studied adequately. Leukemia induction is a statistical event. About 40 to 90 r are believed to double the likelihood of the development of leukemia in man. The dose is probably smaller for children and still smaller for fetuses. Analysis of the human material is much needed, with consideration of the dose as well as the time after radiation, also the sequence of doses and many other factors, as Dr. Jacobson pointed out.

In order to minimize the induction of leukemia, I should like to suggest that patients be kept on a low iodine diet; this tremendously enhances the iodine uptake and thereby reduces the total-body iodine and irradiation doses while destroying functional thyroid with equal efficiency.

DR. MARINELLI: What is the time sequence of events? It has been my understanding that the incidence of leukemia would be practically confined to a period of, say, 10 years after exposure to radiation and that then it would disappear as a syndrome.

DR. FURTH: The best data are those on the Japanese exposed to the atomic bomb. Leukemia began to appear after 2 years. After about 5 or 6 years, a peak was reached, but I am informed cases are still occurring in fair numbers. Not until all of those exposed are dead shall be know the exact leukomogenic dose. Different types of leukemia occur at different times and may have different peaks.

DR. MARINELLI: Is it the same in the experimental animals? Should they be followed throughout that time?

DR. FURTH: Most work with animals relates to the so-called thymic leukemias. The latency period of myeloid leukemias in mice is longer. Induction rates and types vary with different strains of animals and methods of treatment.

DR. GORDON: We are in the process of struggling with data on about 1000 cases of thyrotoxicosis, and we have not to date seen any unusual response of the bone marrow in any of these cases. The maximum dose that any one has received has been up to, I think, 60 mc over a period of 2 or 3 years. I will say more about that case in a later session. However, I wanted to bring up again the point that Dr. Keating has mentioned, which I think is pertinent to this discussion; namely, the rate of turnover of iodine by the gland as related to its level of function. In the most toxic patients, by and large, the rate of turnover will be the fastest and there will be a high circulating level of radioactive thyroxine following therapy with radioiodine. This would then increase the amount of exposure of the bone marrow and all the other organs to ionizing radiation much more than if the patient is very mildly toxic. Of course, the euthyroid patient has a much lower rate of turnover. Therefore, it seems to me that it is very difficult to calculate the total-body radiation in these patients unless this factor is taken into consideration. I would wonder, then, in answer to Dr. Berman's comment, how one can fall back on any common denominator other than the mc dose.

DR. BERMAN: I agree that it is necessary to do kinetic studies on the patient, and from the results calculate the dose.

DR. FREEDBERG: I would like to make a comment on the bone marrow changes that occur in patients with myxedema. Since 1946, we have induced myxedema in over 150 cardiac patients with total intake doses of I^{131} averaging somewhat less than 74 mc. We did not measure the blood radiation dose. We do have 24-hr. thyroid I^{131} uptake and the effective half-life as well as urinary excretion for the vast majority of the patients. These patients are given 6 to 25 mg of desiccated thyroid daily; their BMR's are -25% and they have other minor manifestations of hypothyroidism such as facial puffiness. Other than a very minor decrease in red blood cell and hemoglobin values, no changes in the peripheral blood have been seen. We have seen a fair number of patients with spontaneous myxedema, and while there may be a disturbance in cellular proliferation in the bone marrow in myxedema, I am not impressed that the bone marrow is atrophic. We have seen in our I^{131} series two patients who developed, under observation, pernicious anemia. One might ascribe that to the radioactive iodine but since I don't know the spontaneous incidence of pernicious anemia, no conclusion can be drawn. We have seen other changes that I think

might be of interest to this group. We have seen several patients who have shown a bleeding tendency 3 months to 7 years after the induction of hypothyroidism by I^{131}. A study of the blood coagulation mechanism before and after the induction of hypothyroidism by I^{131} has been carried out in 28 euthyroid cardiac patients by Drs. Benjamin Alexander and Robert Goldstein of the Beth Israel Hospital, Boston. They have studied many components; for example, prothrombin concentration, prothrombic activity, Ac globulin, serum convertin, thromboplastin generation, bleeding and clotting time, platelets, etc. Several patients exhibited prolonged clotting times, impaired prothrombin consumption, and delayed thromboplastin generation. In 2 of the 28 patients, a hemorrhagic diathesis in the skin was characterized by dark red, irregularly-shaped ecchymoses. The clotting data were within normal limits for these 2 patients, and their pathogenesis remains obscure. The blood clotting mechanism has been found to be normal in 6 patients with spontaneous myxedema that have been studied.

DR. SINCLAIR: I should like to make just one more reminder on this question of dose so that we do not go away with the idea that all dosimetry with radioiodine is vague. Although it may not be possible to have a precise estimate of the dose in rads, I think we do know fairly exactly between what limits the dose can lie and to what general errors our estimate may be liable. That is what I tried to indicate earlier in the session. In the hyperthyroid cases it is very unlikely that they received as much as 2 rads per mc because of more rapid turnover in the thyroid.

DR. RALL: I think that in both hyperthyroid and in carcinoma cases, the variation in doses that will be almost but not quite a direct function of blood concentration of I^{131} can easily vary by a factor of 30. So I think there is a great difference in the amount of general body radiation that will be delivered to patients with different states. For example, a myxedematous patient that we treated some years ago who had almost no function in a thyroid carcinoma, perhaps a 24-hr. uptake of a few per cent, got 600 mc in a single dose without a serious complication. On the other hand, in some patients with very high blood levels, about 3% of the dose per liter of blood in a few days, 150 mc may produce a very profound response. So I think that factor may be as much as 30.

DR. SINCLAIR: But you would agree there is a limit.

DR. RALL: Yes.

DR. DOBYNS: I am very much impressed with this variability in the therapeutic response of patients as well as the highly variable and unpredictable levels of circulating radioactivity immediately following I^{131} therapy.

The uptake of I^{131} by the thyroid is a primary factor in the appraisal of radiation to the thyroid but, as has been mentioned, the turnover of the I^{131} is another highly important factor. It can be assumed that the retrapping mechanism should bring the I^{131} of the metabolized thyroxine back to the thyroid in approximately the same per cent as the original uptake. Since the thyroid does not retrap organically bound I^{131}, the rate of deiodination in the tissues of the body is also important in appreciating the total radiation delivered to the thyroid. Thyroxine, being bound to protein in the circulation, is not excreted by the kidney,

but the iodide is excreted in inverse proportion to its return to the thyroid. We have observed that in many instances there comes a time when the I^{131} disappearance curve from the thyroid gland becomes steeper as time passes following the administration of I^{131}. Simultaneously, the I^{131} iodide excretion in the urine rises. Presumably it is about this time that the trapping mechanism by the thyroid becomes damaged by radiation. Our studies have shown that the butanol extractability of the total radioactivity often declines then or shortly afterward, suggesting further damage to the gland. Iodinated compounds not commonly found in the blood then begin to appear in some instances.

We have also found that triiodothyronine is much more likely to appear in the blood in extremely toxic patients. In a highly toxic patient studied recently, the loss of I^{131} from the thyroid was found to be extremely rapid. The I^{131} iodide in the blood was negligible after only 6 hours and remained so for many days. Triiodothyronine appeared in surprisingly large quantities in the blood, and also in the urine. The thyroxine in the blood was almost equal in amount to the triiodothyronine, but the thyroxine did not appear in the urine. Presumably the thyroxine was not excreted because of its protein-binding, but the triiodothyronine, being relatively free, passed through the kidney, yet, being organically bound, was not free to return to the thyroid. This may be another way that radioactivity is lost and not given an opportunity to return to the thyroid as it might in the average patient with moderate hyperthyroidism. Thus there are many variable pools of I^{131} that have a bearing on the total amount of radiation delivered to the thyroid.

B. Embryonal response, growth interference, shortening of life, and genetic effects.

DR. MARINELLI: The next presentation by Dr. Brues will be on embryonal response, growth interference, shortening of life, and genetic effects.

DR. BRUES: The fact that the widely ranging discussion of the last few minutes did not touch on the subject I have been given by the Chairman, bears out my belief that very little is understood about this clinically, and, in fact, this represents a group of situations where we lack as much definitive experimental information as we have in most of the others. So I will speak more or less with reference to dosage levels of external radiation, in terms of rads or roentgens, in relation to each of these.

Concerning effects on the embryo, this of course is something that the clinician may have to consider in delivering radiation to the whole body and to the embryo by radioiodine. This appears to be a situation in which there is some sort of threshold for radiation effect; in other words, there is probably a level below which little or no effect occurs and above which there is an extreme probability that developmental changes will be produced in embryos. This is indicated experimentally in the work of L. B. Russell, which suggests that developmental changes, occurring at the time when the skeleton is being formed, appear at times that are very specific for particular developmental changes, and that the dosages involved for frequent effects are of the order of 200 or 100 r, or perhaps 50 in the case of changes to which the animals are most susceptible. Caution would probably dictate that one

should assume that changes might rarely occur at lower levels but there is no evidence that anything would occur at much lower levels. Most anomalies require somewhat larger doses.

Concerning the factor of growth (if we exclude the effects on the thyroid itself), I think we can say that retardation of growth to any important degree requires considerably higher doses than we are likely to receive from I^{131}. A study of the exposed population at Hiroshima, in which roentgenographic changes were observed in bones of children that had been growing at the time of the blast, indicated that these changes were minimal and were qualitatively similar to those that are seen under conditions of depressed nutrition.

As to shortening of life, it is accepted that external whole-body radiation has an effect on the life span. This is a statistical fact that has been observed in large groups of animals as well as human beings. It has not up to the present been subjected to any sort of analysis that would serve to indicate whether all pathologic phenomena are influenced equally by body radiation, or whether certain ones may be more than others. The relationship of life shortening to dosage is understood only at the higher dosage levels. There is certainly evidence that some of the deleterious effects on the life span (or, expressed loosely, acceleration of the aging process) are irreversible or that they are cumulative with successive dosages of radiation. Whether the effect is completely cumulative or not it is impossible to say on the basis of available evidence.

We may say that in the case of life-shortening in small animals, which have been studied in large groups, there is a threshold for this effect. The most definitive evidence lies in the experiments of Lorenz, which were discussed by Dr. Jacobson, in which animals given daily dosages at the lowest level actually showed an increase in the life span, rather than a diminution. In some experiments of similar nature being carried out at present by Sacher and associates, the same thing is found to be true; namely, that the mean survival of the animals receiving the lowest daily dosage is somewhat better than the mean survival of control animals. I think in these latter experiments we have gone a step farther and shown that this apparently beneficial effect is due to a reduction in the incidence of diseases of the young and middle-aged animals and not to a prolongation of the ultimate life span. In any case, although it is being stated rather freely that life shortening may be calculated linearly in terms of days per roentgen or what not, I think this has yet to be demonstrated.

The best human observations we have had is in a report by Warren, based upon a study of life spans and causes of death in American physicians, broken down by specialties. Here we see that there is approximately a 5-year difference between the mean life spans of radiologists and of nonradiologists, while in certain of the specialties where radiography is more commonly used, there are also statistically valid differences from the normal. If one were to try to guess what the average dose is received by a radiologist up to age 60 or 65, although this is a question to which there is no well-justified answer, it is presumed that it is in the range of 500 to 1000 accumulated r.

Concerning genetics, I see that Dr. Glass is going to tell you about this, as a geneticist, so permit me only to say a few words which I hope may set the thing in somewhat of

a perspective. The National Academy of Sciences has looked rather carefully into this question within the last few months and has come up with certain suggestions as to what may be safe. It has been well pointed out that a distinction must be made between the effects of radiation on the individual and effects on the genetic composition of the human race as a whole or of large groups of individuals which interbreed. In the genetic case, the individual dose is disregarded and importance is given only to the average dose to a large poplation, which determines the total genetic load. In the case of individuals, it is considered safe to accumulate up to a total of 50 r at the end of the reproductive period (which is placed at 30 years). When one looks at the average radiation that might be allowed to be received by all individuals, considerably lower figures are suggested. In the final analysis we have to refer to doses that are more or less determined by the natural radiation background (not an inconsiderable factor) and so we assume a factor of 10 less than the dosage that is considered proper for an individual to get. If I might present a rough figure for the average radiation background to which individuals in the more civilized parts of the world are exposed, it appears that one between 0.1 and 0.2 r per year comes from natural radioactivity; perhaps an equal amount through diagnostic radiography, and negligibly small amounts from other sources.

I should like to make one other brief comment. In considering the permissible or tolerance doses, we must remember that these dosages are based on the industrial or occupational exposure of individuals. Lower average doses are desired on the basis of genetic damage to the population as a whole, but it is suspected that these are not likely to be achieved by radioiodine in relation to, say, routine chest radiography. But we must also not forget that the industrially permissible dose may justifiably be exceeded somewhat where radiation is used for well-indicated diagnostic purposes, somewhat more in the case of therapy, and very much more in the case of therapy of serious diseases.

DR. FEITELBERG: I should like to ask Dr. Brues a question on work he has done which is not generally known. It is the question of the different biologic effect between a radiation exposure that is uniform over an area as compared with localized exposure. He has done some work on this, and we are just speculating about it.

DR. BRUES: As I have to leave shortly I will undertake to reply now. We have been interested also, of course, in the question of the relation of localized radiation to the skeleton, and localized radiation in the lung, to the production of malignant tumors. We set up experiments utilizing the carcinogenic effect of β rays on the skin, a somewhat more accessible tissue for this type of work. A flat source of strontium-90 was used, and then the same amount of radiation was administered in the form of point sources in various numbers placed over the same area of skin. To make a long story short, carcinoma production was actually less when the radiation was in the form of point sources; the production of sarcoma was about the same, and we assumed that this was because the radiation field below the surface of the skin was more uniform than it was on the surface of the skin. So we would feel on this basis that in dealing with sources of high intensity they are somewhat less efficient in carcinogenesis if they are concentrated than if they are spread out.

DR. GLASS: I would like to make one comment and to ask Dr. Brues a question. I think it should be made quite clear that from the point of view of the geneticists, and specifically from the point of view of the National Academy of Science Committee, it does not matter from the genetical point of view how much radiation is given to individuals over 40 years of age, and very little how much is given to individuals between 30 and 40. What matters is essentially how much is given to individuals from the time of conception to the statistical midpoint of the reproductive lifetime. In estimating the medical exposure of individuals to ionizing radiation from X rays, isotopes, and so on, the Committee had to rely on published data, chiefly from studies made by physicians. You can help us very much here to refine our estimates or guesses, if you wish, by giving us a better breakdown on the age distribution of the individuals who receive treatments. In particular relation to our present topic I should like to ask Dr. Brues the question: How many individuals are treated with I^{131} during pregnancy and is there any information that would tell us whether the iodine concentration in the blood of the embryo or fetus is the same as it is in the blood of the mother?

DR. BRUES: I would be happy to throw that question on to those who might be able to answer it. I would certainly suspect, in regard to the second part of the question, that the iodine in the embryo and in the mother would be of the same order of magnitude. I avoided speaking of radiation exposure to the gonads because I do not know any figures. Perhaps Dr. Rawson has some figures.

DR. RAWSON: We have recently been going through the data on the gonads of our patients who have been treated for carcinoma of the thyroid with radioactive iodine. This was started by a telephone call from a physician who advised me of the fact that a patient whom he had studied and who had been treated with radioactive iodine, had fathered a child. As a matter of fact, his wife delivered while he was in the hospital. Presumably he was the father. Now the patient is infertile. Extensive studies have been done on him, and we have testicular biopsies which reveal that he has no sperm whatsoever. So we have gone through all our data. Unfortunately, most of the records of testes had been made at a herniorrhaphy, or at necropsy, or at the time of any alteration; so the testicular picture did not reveal an awful lot.

This young man did receive, we calculated, about 450 rep to the testicles, based on Dr. Trunnell's observations on the amount of radiation that can be demonstrated in the testes and in the blood. There is another young man about the same age or a few years younger when he was first treated, who received a little less radioactivity. I probably can give you the figures on the blood radiation tomorrow. He received about 200 or 250 mc, in contrast with 450 mc over a period of 3 years in the first case. His wife is now pregnant. Three of the women we have treated, who are approaching the age of 40, have developed a transient amenorrhea. Two of them have had a return of menses after a few months. We have also recently had the opportunity to examine the ovaries of two young women in their 30's who came to necropsy. Both had had rather extensive radiation with radioactive iodine. Their ovaries did not show any histologic changes.

DR. BRUES: I think that perhaps Dr. Rawson's statement may be useful in this regard. A dose to the testes of 450 rep had been observed in cases given 200 or 300 mc; that is correct. Perhaps we could say that 5 mc would give not much more than 5 rep, the annual amount permitted for a few individuals.

DR. HASTERLIK: There are a few data from the human exposures that might be of interest so far as just talking about the sperm counts are concerned and not considering the genetic factor. In the Los Alamos accident, one physicist had about 350 rads to his gonads, and after 2 years his sperm count returned to normal. Three years after the exposure he had a child and since has had another child. I would like to stress that I am not speaking about the genetic effects. In the Argonne accident, 3 men were exposed, they were all 29 or 30 years of age; one had an exposure of about 190 rads, one had an exposure of 160 rads, and one had an exposure of about 15 rads. This was instantaneous exposure to total-body X radiation; the neutron component was less than 1% of the total energy delivered. We followed their sperm counts rather carefully. Figure 26 shows the total sperm versus time, months. The sperm count of the man who had an exposure of 190 rads (patient 1), fell to 0 at 10 months; at 20 months, the count was back to the pre-irradiation level. We got the first sperm count 10 days after the accident, and since the radiation effect would not affect the total number at the time of irradiation we have used this as our baseline. For the man who had 160 rads (patient 2), we had a baseline count which was 5×10^7 total sperms. Unfortunately, he went to another laboratory and the count was not followed after he left us. We did have occasion to get 3 further counts at 14, 18, and 20 months. His values were returning to normal at the same rate as those of the first individual. The sperm count of the man who had about 15 rads (patient 4), fell off at the same rate as patient 1, and reached a low point of 7×10^5 sperm at 2 months and then recovered at the same rate as those of the other individuals. The value was back to normal at about 14 months.

DR. JACOBSON: What were those doses again?

DR. HASTERLIK: 190, 160, and one between 10 and 20 rads. It had been assumed generally that 10 to 20 rads did not give this effect. We had these counts done frequently, and the values for this man did fall and then rose. Recovery was on the same slope as that of the man who had had the highest dosage.

DR. MARINELLI: It was called to my attention that psychologic effects can have the same effect on the sperm count.

DR. RALL: You mentioned that the individual might receive as much as 60 r by this 30-year reproductive life span. I wonder if you would give us the order of magnitude on this.

DR. BRUES: Might I suggest that there will be discussion on this tomorrow. With relation to Dr. Rall's question I would like to mention another thing about the Hiroshima accident, that is that the menses were affected much more seriously than the birth rate in the months following.

DR. VANDER LAAN: I should like Dr. Brues to comment on the recent English study

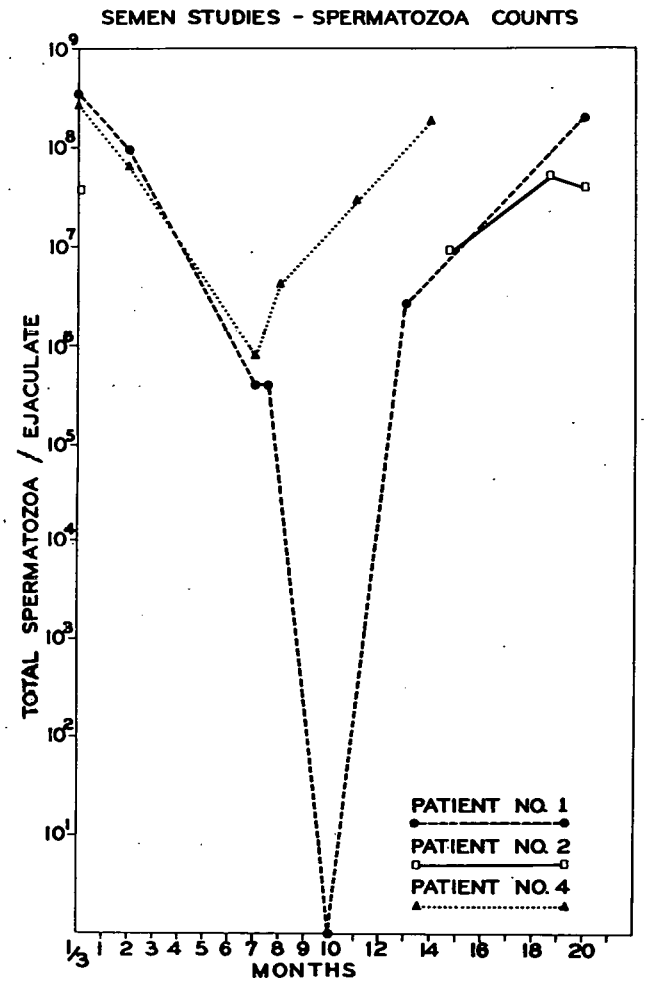


Figure 26. The effect of an accidental total-body exposure to γ radiation on the number of sperm from three individuals. Patient 1 was subjected to about 190 rads, patient 2 to about 160 rads, and patient 4 to 15 rads.

on the incidence of leukemia in infants following X irradiation.

DR. BRUES: These are rather striking figures that I have just had an opportunity to see and have not had the opportunity to evaluate. If these data are significant, they indicate that the leukogenic dose may be somewhat lower than I think we had been assuming.

DR. FURTH: The lowest doses are those given in utero to fetuses incidental to diagnostic pelvic irradiation of mothers. This work has been described by Stewart et al.[13]

DR. MARINELLI: Was it proven that all the children had been irradiated in utero?

DR. FURTH: The great (2- to 3-fold) increase in the incidence of leukemia in children between 2 to 6 years of age, noted in recent years, is correlated by Stewart and coworkers with diagnostic pelvic irradiation of pregnant mothers. The presumed exposure may have been about 5 to 40 r.

DR. MARINELLI: I would like to mention also that in the series that Dr. Warren reports, the incidence of carcinoma in neuro-surgeons was also high.

DR. WERNER: An important point about the question whether I^{131} passes across the placenta: I^{131} is freely permeable but thyroxine also passes across the placental barrier. Thyroxine-labeled I^{131} will progressively increase in the fetal circulation, the longest time we had the opportunity to measure being 11 days. A concentration was obtained in the fetal serum of about 13% of the concentration in the mother's serum.

DR. FEITELBERG: We have refrained from using I^{131} for hyperthyroidism during pregnancy. It will be helpful if the data of Dr. Brues and Dr. Sinclair were put together. They are encouraging.

DR. BRUES: I was thinking rather in terms of the developmental anomalies produced in the growing embryo at a particular stage because of the destruction of certain growing areas. This requires a fairly high dose in relation to some of these other things. I am open to conviction on this matter because what I say is based on the small animal experiments.

DR. CLARK: We had one patient in her 20's, with a carcinoma of the thyroid, who had been receiving 35 mc every 2 weeks for 2 months. At this time she stated she was approximately 2 months pregnant. She had received a total of 140 mc. Apparently she had become pregnant at the beginning of her radioiodine therapy. We were tremendously upset about this, and thought about performing a therapeutic abortion. She refused, and delivered a perfectly normal child. This happened about 5 years ago, and the child is being checked at periodic intervals and has remained perfectly well. Treatment was discontinued. She has subsequently had 3 normal children. The fetal thyroid obviously had not started to function, but the fetus must have received a fair amount of radiation.

DR. MILLER: We had a young couple who had several things in common, one being carcinoma of the thyroid and the other, radioiodine treatment. They were the mutual parents of the 2 children. All of this after having received radiation; the wife having received a 50-mc dose for thyroid ablation, the husband having received 500 mc.

DR. GORDON: We have one case that will match Dr. Clark's; a woman of 34 who got pregnant every time she received a dose of 80 mc of radioactive iodine. That happened on three occasions, and all three children are perfectly normal, the last one having been delivered after she had received a total of 240 mc of iodine for thyroid carcinoma.

DR. WERNER: I assume a fourth dose was not given.

DR. GORDON: No, it was not given, for obvious reasons.

C. Carcinogenesis in experimental animals treated with radioiodine; and hyperplasia and neoplasia of thyrotropes in relation to depression of thyroid function.

DR. MARINELLI: Next, Dr. Furth will discuss: 1) carcinogenesis in experimental animals treated with radioiodine; and 2) hyperplasia and neoplasia of thyrotropes in relation to depression of thyroid function.

DR. FURTH: This is to supplement and amplify what Dr. Clark has said on thyroid tumors.

When the thyroid gland is exposed to sub-ablating doses of I^{131}, different cells in this organ receive different quantities of ionizing radiation, ranging from those fatal to cells to those barely injurious, depending on the position of the cell and its functional state. Lack of homogeneity of irradiation has been amply documented by radioautography. Consequently, one would presume that, as a late effect, development of tumors in the thyroid gland would be common events, resulting either from a direct mutagenic effect of radiation or, indirectly, from a TH-TSH imbalance.

Goldberg and Chaikoff[14] described the development of malignant tumors in Long-Evans rats 2 years after a single injection of 400 μc of I^{131}. Doniach[15] found benign and malignant thyroid neoplasms in rats treated with I^{131} alone, or in combination with methylthiouracil but, in more recent studies,[16] he failed to observe neoplasms following injection of I^{131} alone. Numerous investigators have studied the possibility of inducing malignant neoplasms by I^{131} but their results were almost uniformly negative. We are grateful, therefore, to Dr. Chaikoff for allowing us to cite a manuscript describing the more recent work of his team.[17]

This is a thorough study of about 200 Long-Evans rats surviving 2 to 2.5 years following a single injection of 10 to 400 μc of I^{131}. Ten per cent of the animals developed single or multiple benign thyroid adenomas, and 2.5%, follicular and papillary carcinomas, the highest incidence of both being in the 25-μc group.

Histologic studies indicate that both benign and malignant thyroid neoplasms originated in foci of nodular regeneration and that the carcinomas originated in previously benign neoplasms. Regional or distant metastases were not observed, and the diagnosis of malignancy was based on parenchymal, capsular, and vascular invasion.

The most important findings in this recent work of Dr. Chaikoff's team are: 1) the high incidence (30-35%) of alveolar carcinomas in the control (untreated) Long-Evans rats used in this study; 2) the tumor incidence was the same in rats injected with low doses of I^{131} as in controls; and 3) the incidence was actually lowered in rats injected with the higher dosages (100 to 400 μc). They emphasized that spontaneous carcinomas were alveolar, those in irradiated rats were follicular and papillary. Regenerative changes in the thyroid, similar to those described by Chaikoff and his associates in rats, have been observed by us and by others in mice receiving smaller doses of I^{131}.

Similar tumor nodules in an I^{131}-treated mouse are illustrated in our paper.[7] Metastasizing thyroid tumors were not seen in mice. These adenomatoid lesions are similar to those induced by goiterogens and by low iodine diet alone. In our experiments, large quantities of thyroid-stimulating hormone delivered to mice endogenously by grafts of autonomous functional thyrotropic pituitary tumors will cause such adenomatoid changes in abundance, sometimes with invasion of blood vessels[18] similar to those reported by Dr. Chaikoff. However, none of these thyroid tumors proved to be autonomous neoplasms.

It seems to us that the basic mechanism is the same in all of these situations; name-

ly, diminution of available thyroid hormone (either because of damage to the thyroid gland by I^{131}, or unavailability of iodine, or interference with thyroid hormonal synthesis) causing excessive production of thyroid-stimulating hormone which is the proliferating stimulus of the thyroid gland. There is no work on record proving that radiation has caused autonomous thyroid cancers, but the thyroid neoplasms occurring in irradiated animals have not been assayed adequately for autonomy and perhaps not enough time has elapsed to finally assess the results of I^{131} treatment of man. The morphologic difference between radiation-induced and spontaneous tumors, described by Lindsay et al.,[17] can well be explained by difference in the character of the thyroid cells in I^{131}-treated and normal animals. In I^{131}-treated animals, vascular sclerosis and diffuse fibrosis interfere with normal regenerative and proliferative processes. Thyroids heavily treated with I^{131}, as irradiated organs in general, contain many cells with chromatin abnormalities similar to those considered characteristic of cancer cells, but these bizarre cells, for reasons unknown, stay put and do not go on to produce cancers. Injury caused by lower doses is latent, demonstrable physiologically by aberrations in I^{131} uptake, or abnormal responsiveness to TSH.

Many problems of thyroidal carcinogenesis remain to be solved. Is the high sensitivity of the Long-Evans rats to thyroid carcinomas a genetic trait or is this due to dietary conditions? Co-carcinogenic factors proved important in thyroidal tumorigenesis by non-radioactive substances. The age of the host, the quantity of dietary iodine, and the presence of goiterogen in the diet may be co-factors determining tumor development.

To summarize, 1) Subtotal destruction of the thyroid gland by I^{131} is often followed by nodular regeneration. Some of these nodules are functionally active, others inactive. Some are locally invasive, others are not. It is debatable whether these are adenomas or carcinomas. There are no reports to indicate that they are autonomous cancers.

2) Such nodules grow but slightly in spite of the presence of excessive quantities of circulating TSH. Thus, on the one hand, they do not respond well to TSH; while on the other, they do not possess sufficient autonomy.

3) Contrary to expectations, the observations thus far made do not indicate that I^{131} is a thyroid carcinogen.

4) Further experiments with meticulous consideration of the following co-carcinogenic factors are desirable: a) host genetics (species and strain); b) sex; c) age of host (from fetal life to senescence); d) I^{131} dose and dose rate; e) importance and quantitation of stable iodine in diet; f) antithyroidal agents in diet; and g) gastro-intestinal-hepatic disorders interfering with the thyroxin-recirculatory cycle and other host factors. The animals should be kept until natural death, and the incidence of all neoplastic changes recorded and studied from morphologic and functional standpoints.

Such research would be rewarding; it may clarify existing problems and yield information on thyroid-thyrotropic interrelationship.

DR. FRANTZ: In answer to a question by someone as to the induction of thyroid tumors in rats with I^{131}, Dr. Marinelli, I cannot give this paper because it is not yet written and I have not studied the slides with sufficient care. I do intend to present it at the

American Goiter Association meeting in May.[19] We attempted to set up an experiment in which we might confirm Chaikoff's[20] original work. There is some suspicion as to the interpretation of the histology of his original tumors, and I took the precaution last year, therefore, to go over all of our tumors with Dr. Lindsay, who had reviewed the pathologic findings in Dr. Chaikoff's series after the publication of the paper. We had a somewhat similar experience, but I cannot give you the exact figures. We also induced similar tumors with what was supposed to be an equivalent dose to the thyroid by external irradiation. We had three groups of animals: 1) controls, 2) externally-irradiated thyroids, and 3) internally-irradiated thyroids, i.e., with I^{131}. This was the same intraperitoneal dose that Chaikoff gave his original 25 rats. We attempted also, and I think we came fairly close to it, to reproduce the low iodine diet. This is a factor we did not realize was possibly tumor-inducing. But the high incidence of tumors in the control group is somewhat disturbing and needs further study. We had only one thyroid tumor that metastasized in the series. That was in an X-irradiated rat in which the damage to the thyroid, in spite of the fact that the dose was supposed to be comparable, was apparently less than in those treated with I^{131}.

DR. FURTH: May I now take a few minutes to speak on thyrotropic pituitary tumors?

The production of pituitary tumors in mice by I^{131} has been amply confirmed and adequately reviewed elsewhere,[21] and I shall merely enumerate and illustrate some basic findings.

Destruction of the thyroid gland by I^{131} leads to stimulation of the thyrotropes of the pituitary which, if thyroid deficiency remains uncompensated, will result in pituitary tumor formation. Multicentric microscopic tumors occur after about 8 months; gross tumors after about a year. These pituitary tumors are often locally invasive; nevertheless, they can be grafted only on animals whose thyroid function is depressed. Such grafted tumors metastasize to regional lymph nodes. The metastases are also composed of dependcent tumor cells; they cannot be grown on normal hosts. The tumors and the blood of tumor-bearing animals contain tremendous quantities of thyroid-stimulating hormone. Similar tumors can be induced by surgical ablation of the thyroid gland, or by blocking thyroid hormonal synthesis with goiterogen. The three procedures have a common denominator: sustained deficiency of thyroid hormone.

Pituitary tumors could be induced by I^{131} in all strains of mice thus far tested, but not in rats. All of more than 10 primary tumors assayed by us proved to be conditioned in the first generation, but in subsequent animal passages, sooner or later, almost all of them gave rise to autonomous variants.

With the acquisition of autonomy, hormone production diminishes. Dependent tumor cells resemble a population of normal cells. Autonomous tumor cells have features of highly autonomous cancers.

It is an intriguing problem why rats fail to develop pituitary tumors following adequate destruction of the thyroid by I^{131}. Possibly, the rat possesses an extra-thyroidal synthetic mechanism of TH or of a substance structurally similar enough to TH to inhibit the pitui-

tary, or the food commonly used contains adequate quantities of such substances, or there is a species difference between thyrotropes of mice and rats, the thyrotropes of rats being unable to respond with compensatory hyperplasia to a sustained deficiency of thyroid hormone.

The possibility of thyrotropic pituitary tumor induction in the rat is indicated by the work of Axelrad and Leblond[22] who induced pituitary tumors in rats by merely keeping them on iodine-free diet, and by the observations of Bielschowsky[23] who noted the spontaneous occurrence of similar tumors in a population of rats kept on inadequate diet. In the presence of dietary (iodine) deficiency or goiterogen, radiothyroidectomy might cause pituitary tumors in the rat and other species, and perhaps even in man.

To summarize, experiments on mice indicate the potential hazard of pituitary tumor induction by I^{131} but they also indicate that TH will prevent development of thyroid and pituitary tumors following destruction of the thyroid gland. It is uncertain whether or not similar tumors will occur in man following thyroid destruction.

DR. KEATING: I wish to ask a question about semantics. If the speaker's definition of "cancer" is universally accepted, then many patients whom we have seen with low-grade papillary adenocarcinoma, which killed them, did not die of "cancer" because their tumors were not autonomous by the definition he has given.

DR. FURTH: Yes, dependent tumors, if uncontrolled, are also fatal. The terminology of growth needs reconsideration. The basic question is: is this tumor reversible or hormone-dependent or responsive, or is it not?

DR. GORDON: If we are allowed to accept the idea that these tumors are chiefly produced by thyrotropic hormone, and I think that is a very satisfactory hypothetical explanation, it makes one wonder if the recurrences of thyrotoxicosis that we see clinically and the nodules that grow in the gland following thyroid resection are manifestations of this same process. I would rather assume that they are. However, in our rather long series of thyrotoxic patients treated with radioiodine we have not seen a recurrence and have not seen the appearance of nodules, and in this series there are at least 100 cases that have had recurrent disease before our therapy. It makes me wonder, therefore, since both procedures will release thyrotropic hormone, why it is that we do not see them following radioiodine as we have seen them following surgery. I have speculative answers but I do not care to take time to discuss them now.

DR. FURTH: The regenerative capacity of surgically-resected thyroid is excellent while that of thyroid treated with I^{131} is much impaired. There is sclerosis of vessels and fibrosis, and the irradiated cells are altered. As to the relation of hyperthyroidism and TSH excess, I should like to call on Dr. Rawson. Hyperthyroidism (Graves') is not a simple disease. I do not understand it.

If by the administration of thyroid hormone we can bring about reduction of the size of the thyroid tumor and check its progression, we would have a means that would be as important in the management of thyroid tumors as is the use of I^{131} in preventing goiters. If the tumor is very large, it is technically difficult to give enough TH to bring about tu-

mor regression, even if it is responsive. Hence, TH therapy should be attempted early.

DR. VANDER LAAN: I should like to present one experience with regard to a woman who had an adenoma removed in 1939. I saw her first in 1952. She had two bone lesions at that time which ultimately proved to be identical with the tumor removed from the thyroid gland 13 years before. She had pain in the area of the metastases, and we treated her with thyroid hormone. About 2 weeks later she reported that she had complete relief from pain. She did very well for 2 years and then was in an automobile accident and fractured her arm through one of the metastases. With this accident there was rapid progress of the tumor radiologically. We were inclined to think that perhaps radioiodine should be reconsidered for treatment and we gave her a dose of thyrotropin to see if we could induce the tumor to take up radioiodine. This was in the morning and late that afternoon she telephoned to ask what we had done. For the first time in 2 years she had recurrence of the original pain. I am inclined to believe it is quite possible that thyroid tumors in man, especially those of the slow-growing variety, are thyrotropin-dependent. This is the basis for thyroidectomy prior to radiation therapy, of course. The administration of thyroid hormone to suppress thyrotropin may be more effective in treating thyroid cancer than destructive measures; it is an important experiment.

DR. DOBYNS: We must keep in mind that one cannot draw a sharp line between malignant and benign lesions. Among thyroid lesions there is also probably a big realm of gray between the black and white so far as autonomy is concerned.

We placed rats on a low iodine diet for about 10 days, and they developed thyroidal hypertrophy amounting to about 12 to 14 mg. They were then given varying doses of I^{131} (Figure 27). After a period on normal diet, the thyroids all returned to normal size. Two to 4 months later, only the thyroids of rats that had received 50 μc or more showed histologic evidence of damage. In the thyroids of the irradiated animals, with no evidence of histologic change, a real hypertrophy could be induced with thiouracil administration, but the capacity to hypertrophy was impaired to varying degrees. It was then under the stimulus of thiouracil that bizarre nuclear forms appeared. I wonder if we must have the dose of radiation in this realm where we produce subtle or latent changes in order to produce a tumor. In other words, the dose that causes some subtle effect in the cells but is not sufficiently damaging to inhibit proliferation, may be the dose that may be followed by tumor formation. Dr. Furth has pointed out that one usually sees tumors following a low dosage of radiation.

DR. FURTH: I should like to say a word about the silent change caused by irradiation. It seems that even resting and so-called radioresistant cells are altered by ionizing irradiation, and this can be demonstrated in mice as late as half a year after irradiation by subjecting the cells to a proliferating stimulus; e.g., liver cells to hepatic resection. The proliferating irradiated liver cells then exhibit profound mitotic abnormalities—a true anamnestic reaction.

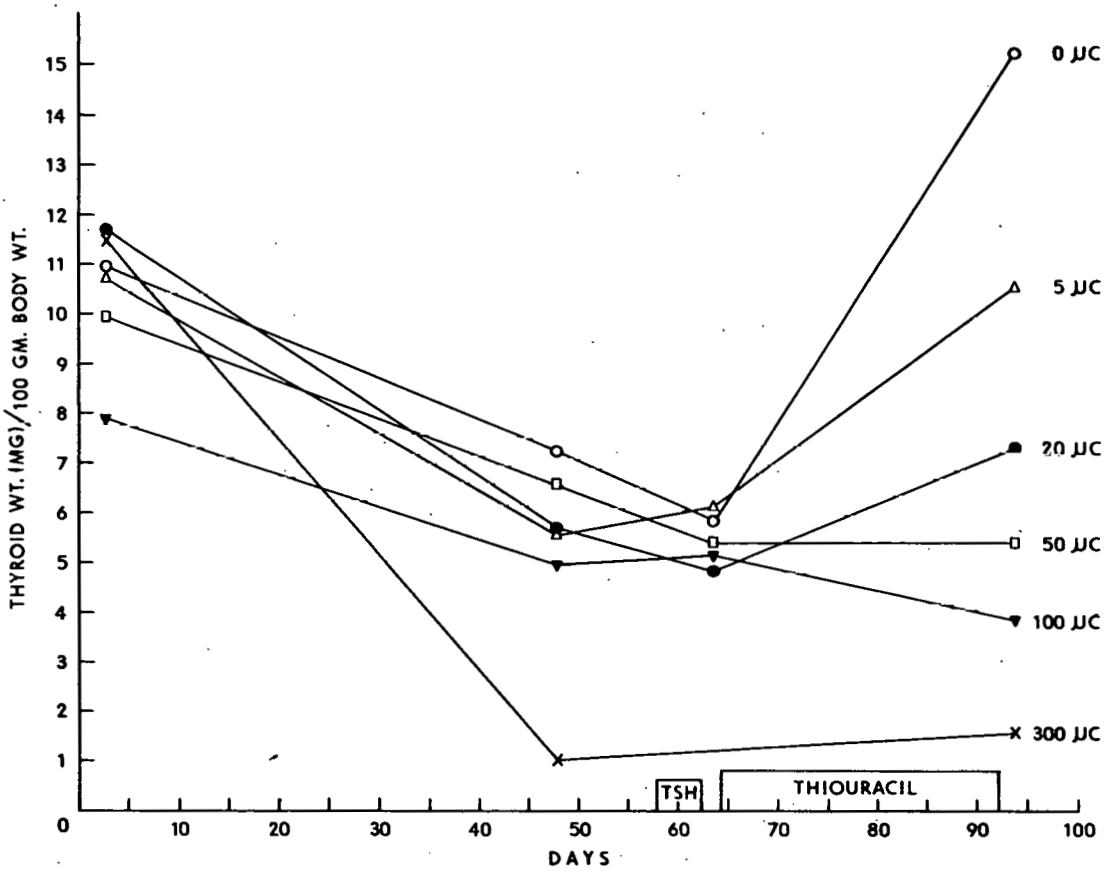


Figure 27. The effects of various doses of radioactive iodine on the function and structure of the thyroid of the rat.[24]

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HYPERTHYROIDISM

DR. WERNER: It seems to me that it would be best if, in this session, we had each subject introduced by a 5-minute talk followed by ample time for discussion; I think it might also be nice to list the various therapeutic results this group has obtained with I^{131}

Part I — Dosage Methods

A. Review of methods for determining I^{131} dosage.

DR. WERNER: Dr. Stanbury will open with a review of the methods in current use for determining I^{131} dosage.

DR. STANBURY: I think it is fair to say, and manifestly true, that there has not yet been devised a method that enables us to predict precisely the quantity of radiation that should be delivered or that will be delivered to the thyroid gland with a given dose of I^{131} And even when that dose has been reasonably well calculated, at the present time I think it is fair to say that nobody has as yet devised a method of predicting what the response of the thyroid gland will be. Dr. Werner has seen perfectly good temporary responses to radioactive iodine in patients receiving as little as 100 to 600 r to the thyroid, and in other people has seen failure of response when it appeared that the gland received 15,000 to 20,000 r. There must be factors that we simply do not know how to assess.

Many dose schedules have been employed. Our own, in Boston, was begun by Dr. Chapman in 1946 and 1947. It comes under the heading of the "arbitrary or empiric" dose schedule. In those days, patients were being treated with radioiodide, and there were 36 who made a good response to a single dose. Their uptakes were averaged, the gland sizes as estimated were averaged, and then Dr. Chapman calculated that the administered dose in these patients was 0.16 mc per g of estimated thyroid weight. This factor has been used in our clinic ever since, and as will become evident later, has been a perfectly good way of getting a reasonably satisfactory response rate. Many other people have used equally empiric and arbitrary methods to determine dosage. Larson in Stockholm divides his patients into groups, depending upon whether the glands are large, middle-sized, or small, and gives a dose accordingly. Other people give the same dose to all patients regardless of gland size and repeat the dose if the patient fails to give a response, or in accordance with the response rate. Most investigators have tried to consider the size of the dose. The factors that probably play a role in the response that may be expected from a given dose are size of dose, uptake, effective half-life, size of the gland, distribution in gland, geometry of gland, and radiosensitivity.

In estimating a proper dose most people base their calculations upon the size of the

gland. With increasing elegance, other groups have tried to employ the factors of uptake and effective half-life. Dr. Freedberg, particularly, and Dr. Vander Laan have brought into the equation the factor of effective half-life as measured with a tracer dose. This introduces another complication, i.e., whether one can extrapolate from a tracer half-life to the half-life after a therapeutic dose, and this is certainly not true in many cases because of the effect of therapeutic quantities of radiation on the gland. The results of these various methods of prediction, have not given an entirely adequate measure of the results obtained. Perhaps the reason for this is that there are two remaining factors that are undoubtedly of importance in estimating response. One of these is the geometry of the gland. This is probably not a very important factor although there may be differences because the shape of the gland may permit varying amounts of β radiation to escape from the surface. Perhaps the most difficult of all these factors to assess is the one that really escapes any assessment at all. This is radiosensitivity. I do not know of any way to judge this, but I should like to suggest for discussion, at least, a possible way of bringing radiosensitivity into the equation. I think there is evidence to suggest that radiosensitivity of the thyroid is proportional to physiologic activity. Perhaps if this could be brought into the evaluation in some way, it might be possible to measure the radiosensitivity of the gland. It seems to me that the simplest way to do this would be to measure, by means of a tracer dose, the clearance by the thyroid per g of thyroid tissue as a measure of the physiologic activity of the gland. I would suspect that the more physiologically active glands, measured in these terms, would have a higher radiosensitivity and accordingly would require a lower dose for an adequate response. In the larger glands in which the uptake may be quite high, the clearance per g may be quite low. Thus one would account for the fact that the patients with the large glands are those who require the largest number of repeated doses in order to attain a satisfactory response. By taking into account the clearance per g, one would give a dose accordingly to balance in the factor of radiosensitivity.

The upshot of it all is that no matter what schedule has been employed by a variety of groups, the results seem fairly comparable across the board. Why this should be so I do not know, but I suppose that no matter what the dose, most schedules that have been employed kill off the active elements of the gland, and its homeostatic relationship to the pituitary brings the gland back to what we call the normal state.

B. Results from various methods (toxic, diffuse, and recurrent goiter; toxic nodular goiter), and analysis of variations in radiosensitivity.

DR. WERNER: I should like to present the incidence in our clinic of remission and failure after I^{131} therapy in hyperthyroidism. The discussion of hypothyroidism and other complications will be deferred until later. This effort is one to establish the remission rate from 1 dose, 2 doses, or more and to try to establish whether any one clinic has better results than others and whether there is a possibility of bettering the outcome from a single dose.

We have a total of 525 cases that I have personally treated and then followed up to 10 years (Table 9). Dr. Quimby supervised the physical aspects, and Dr. Day most of the eye measurements. When we started, we spent the first 2 years determining the effect of a fixed dose, 3 to 4 mc. Subsequently, we began to take liberties. Since our calculations of

Table 9

DOSES OF I^{131} IN PATIENTS ENTERING REMISSION
447 OF 525 PATIENTS

No. of doses	Type of goiter			Total patients
	Diffuse	Toxic recurrent	Nodular	
	(No. patients)			
1	124	78	44	246 (55%)
2	74	32	24	130 (30%)
3	33	9	13	55 (12%)
4	8	1	1	10 (2%)
5	2	2	1	5 (1%)
6	1	0	0	1
Total	242	122	83	447 (100%)

dose per estimated g of tissue, of roentgens equivalent physical received by the patients' glands, and of effective half-life failed to reveal any correlation with the outcome of the treatment, we abandoned these indices and gave a range of doses of I^{131} from 1 to 8 mc. Small glands with low toxicity received the smaller doses, and big glands with greater toxicity received the higher doses. By the time a third dose is needed, however, we have given 25 mc if necessary.

With all the different types of toxic goiter treated according to this plan, we find that 55% of our patients had remission with 1 dose, and another 35% with 2 doses. We had some patients who are extremely resistant and required more than 3 doses. We consider these a failure of therapy but nevertheless have followed them through in order to see how much they would need. As Dr. McCullagh pointed out some years ago, the total may be considerable.

We also have investigated total dosage rather than number of doses. As you can see in Table 10, about 63% of our patients required no more than 6 mc; yet about 22% of patients required more than 10 mc. Again, the same wide range in sensitivity to radiation effect is evident.

In Tables 11 and 12 we simply tried to correlate the data with gland size. It is interesting that although more patients with enlarged glands, meaning over 30 g in weight, required over 3 doses, nevertheless there is a sizable number of patients with smaller glands in this category, with both toxic nodular and toxic diffuse goiter. It seems then that

Table 10

DOSAGE OF I^{131} IN PATIENTS ENTERING REMISSION
447 OF 525 PATIENTS

Dosage (mc)	Type of goiter			Total patients
	Diffuse	Toxic recurrent	Nodular	
	(No. patients)			
0 - 3	53	29	7	89 (20%)
4 - 6	94	60	36	190 (43%)
7 - 9	38	21	9	68 (15%)
10 - 14	42	6	11	59 (13%)
15 - 25	6	6	15	27 (6%)
Over 25	9	0	5	14 (3%)
Total	242	122	83	447 (100%)
Summary				
0 - 6	147 (61%)	89 (73%)	43 (52%)	
7 - 14	80 (33%)	27 (22%)	20 (24%)	
15 -	15 (6%)	6 (5%)	20 (24%)	
Total	242 (100%)	122 (100%)	83 (100%)	

Table 11

GLAND SIZE* BEFORE I^{131} THERAPY AND NUMBER OF DOSES REQUIRED TO INDUCE EUTHYROIDISM
447 OF 525 PATIENTS

Type of goiter	Estimated gland size	No. doses		
		1	2-3	Over 3
		(No. patients)		
Toxic diffuse	Small	59	35	1
	Moderate	48	48	4
	Large	17	23	6
	Total	124	106	11
Toxic recurrent	Small	53	21	1
	Moderate	23	16	2
	Large	2	4	0
	Total	78	41	3
Toxic nodular	Small	15	6	0
	Moderate	18	15	0
	Large	11	16	2
	Total	44	37	2

*Small - under 35 g estimated weight; moderate - 35-60 g; large - over 60 g.

Table 12

GLAND SIZE* BEFORE I^{131} THERAPY AND DOSAGE REQUIRED TO INDUCE EUTHYROIDISM. 447 OF 525 PATIENTS

Type of goiter	Estimated gland size	Total dosage			
		0-3	4-9	10-25	Over 25
		(No. patients)			
Toxic diffuse	Small	34	40	12	0
	Moderate	17	59	23	1
	Large	2	23	13	0
	Total	53	122	48	1
Toxic recurrent	Small	27	45	3	0
	Moderate	2	31	8	0
	Large	0	5	1	0
	Total	29	81	12	0
Toxic nodular	Small	6	13	1	1
	Moderate	1	22	10	0
	Large	0	10	15	4
	Total	7	45	26	5

*Small - under 35 g estimated weight; moderate - 35-60 g; large - over 60 g.

it is in the estimation of radiosensitivity of the thyroid where progress has to be made to better the results of I^{131} therapy.

I should like to turn this subject over for discussion and have others present their remission rates with single doses, as well as the incidence of patients needing the larger number of doses.

DR. CLARK: Table 13 shows the number of doses of I^{131} required to effect a remission in 628 cases of thyrotoxicosis. A total of 352 or 56.1% received one dose; 25.5% required 2 doses, and 116 cases or 18.4% were given 3 or more doses. These results are

Table 13

NUMBER OF DOSES OF I^{131} REQUIRED FOR REMISSION

Number doses	Gland type			Total patients	%
	Diffuse	Nodular	Recurrent		
1	164	102	86	352	56.1
2	52	75	33	160	25.5
3 or more	46	52	18	116	18.4
Total	262	229	137	628	100.0

remarkably similar to those presented by Dr. Werner. The type of gland or whether it was a recurrent thyrotoxicosis did not seem to make a significant difference. Also in this series, the age of the patient did not seem to make any difference as to the number of doses required to effect a euthyroid state.

Table 14 gives the breakdown of the 116 cases that required 3 or more doses. Sixty-one required 3; 29, 4; 15, 5; 6, 6; and we had 5 cases that required 7 doses. Analyzing these 116 cases and comparing them with the group of 512 that got good results with 1 or 2 doses, it was interesting that 213 cases or 42% in the latter group had no previous medication. On the other hand, only 21 or 13% of the 116 did not have any previous medication. Although we usually wait a month after stopping Lugol's solution, and varying periods of time after stopping antithyroid drugs, it seems that if the patients have had previous medication, they frequently require more doses than if they have not had previous treatment.

Table 14

NUMBER OF CASES RECEIVING 3 OR MORE DOSES

Doses	3	4	5	6	7	
No. Cases	61	29	15	6	5	Total-116

Another factor which seems to play an important role, as far as the number of doses of I^{131} required, is the size of the gland (Table 15). The average estimated weight of the gland in 510 cases that required 1 or 2 doses was 49 g, while the average estimated weight of the thyroid gland in 113 of the cases which required 3 or more doses to effect a remission was 66 g. Some of the glands that required over 3 doses were estimated to weigh from 200 to 300 g.

Table 15

WEIGHT OF GLAND IN RELATION TO NUMBER OF DOSES

No. doses	No. cases	Avg. wt.
1 - 2	510	49 g
3 or more	113	66 g

We have based our original dose determination on the weight of the gland, the type of gland, and the age of the patient.

In patients under the age of 40, with diffuse glands, we give 150 μc per estimated g of thyroid tissue as an initial dose at the present time. It seems that the group over 40 years of age, with diffuse glands, requires more radioiodine, and we give them between 200 and 250 μc per estimated g of thyroid tissue. In the toxic nodular goiters, we found, as many

others have, that it requires much larger doses to effect a good remission, and we give such individuals 300 to 350 μc per estimated g of thyroid tissue as our initial dose. These doses were arrived at by studying the amount of I^{131} per estimated g of thyroid tissue to effect a remission in our first 300 cases treated.

Table 16 shows the results in 628 cases; 520 or 82.8% were restored to euthyroid states. We have a 17.2% incidence of hypothyroidism. This is quite high because many of these we purposely made hypothyroid because of complicating cardiac problems. If we eliminate the cardiac group, our incidence of hypothyroidism is 11%, and that is just about what we have from surgery in thyrotoxicosis. We had 3 cases of recurrence of thyrotoxicosis; 1 was 2 years and 2 were 3 years after the initial treatment. Both were given more radioiodine and both responded nicely, and they are included in our euthyroid group.

Table 16

GLAND TYPE AND THERAPEUTIC RESULT

Gland type	Therapeutic result			Total %
	Euthyroid	Hypothyroid	Post I^{131}* recurrent	
Diffuse	214	48	(2)	262 (41.7%)
Nodular	201	28	(1)	229 (36.5%)
Post surgical recurrent	105	32	0	137 (21.8%)
Total (%)	520 (82.8%)	108 (17.2%)	(3)	628 (100.0%)

*These cases have all been treated again with I^{131} and are included in the euthyroid groups.

DR. STANBURY: Do you always precede your calculated dose with a tracer dose?

DR. CLARK: No, we do not. I suppose we would have fewer cases that require 3 or more doses if we did uptakes on all of our cases. We do it in many but not routinely.

DR. WERNER: In the Medical Clinics of North America 4 or 5 years ago, we analyzed the effect of iodine and antithyroid drugs upon the results obtained with I^{131}. Although the statistician said the figures showed borderline significance, the fact was that we had only 42% of patients entering remission from a single dose of I^{131} in the group receiving antithyroid drugs or iodides, whereas we had 67% with no preceding therapy responding. I think that probably the drugs do influence the outcome adversely.

DR. DOBYNS: I would like to ask Dr. Clark to tell us a little more about the 3 patients in which the disease recurred after radioiodine therapy.

DR. WERNER: We shall cover that tomorrow. What I hope we can obtain from the

present discussion is an analysis of results from the various therapeutic methods, and some explanation of the cause for these variations in radiosensitivity.

DR. BERMAN: I would like to ask Dr. Clark what the size of the second and third dose was compared with the first dose, and whether he re-estimated the size of the gland before each dose.

DR. CLARK: Yes we did. Each time when we decided to give a second dose we tried to re-estimate the gland size to see if it had decreased or remained the same. We did in part base our second dose on the size of the gland, as well as on the severity of the residual thyrotoxicosis. We usually waited 8 to 10 weeks before considering a second dose of I^{131}. If we thought an individual had improved approximately 50% from his original dose of I^{131} and the gland had decreased in size to the same extent, we would give as a second dose about 50% of the first.

DR. FRANTZ: I have a question for Dr. Werner. Were those not cases that were rather stubborn to therapy of any kind?

DR. WERNER: I think that is a fair assumption.

DR. FEITELBERG: I have wondered about the validity of the statement that I^{131} therapy for Graves' disease has failed if more than a certain number of therapeutic doses are given. I believe that it is not the number of doses, but the total dose administered that should be considered the limiting factor.

The maximum dose that we are willing to give for hyperthyroidism is between 50 and 100 mc. Actually, we are very hesitant to exceed 50 mc, which corresponds to a whole-body dose of about 50 r. The rationale for this number is not very substantial, and the figure is really an arbitrarily selected one within the range of 25 and 200 mc. But it is better than to select a number of doses (unless each dose is equal to a fixed number of mc) because there is no reason to expect that biologic damage is correlated with this amount. Damage does depend on the total dose.

In our series of a little over 3000 treated cases with a follow-up on 1600 of them, we have had only 2 that we consider as failures and in which we have discontinued I^{131} therapy. I shall discuss one as an example. This patient had a large 400-g gland, with an initial uptake of 75%; the uptake went down to 20% 3 months after we began I^{131} treatment. After the patient had received 65 mc, we discontinued treatment. The patient still had Graves' disease and was referred to surgery. The limiting dose that we have selected may be too high or too low, but the number of administrations to attain this total dose I believe to be immaterial. The criterion for failure of I^{131} therapy should be set on the basis of the total dose administered, i.e., the radiation only which we are prepared to deliver to the gland and particularly to the entire body.

DR. WERNER: I think, though, that by "failure" a clinician means that the patient has been kept ill for so long that he believes that another method would have been more efficacious and more expeditious for the patient. Dr. Keating, what do you think about it?

DR. KEATING: We have seen, I think, only two patients whose condition we entirely failed to control with large doses of radioiodine. I cannot provide the detailed clinical data

on either of them, nor can I provide the total number of patients we may have seen who required 3 or more doses. There is a point that you just raised that I would like to enlarge upon; namely, the proper criteria for evaluating treatment with radioiodine and for comparing it with other therapeutic modalities available to the patient, including, among other considerations, the duration of illness that any proposed form of treatment entails. When we first began to use radioiodine in 1946, we, like many others, deliberately chose to treat patients who, by reason of complicating diseases or their general physical debility, were considered unsuitable for other forms of treatment—in particular, thyroidectomy. For the most part, these were people who were rather ill, often with cardiac decompensation, and in whom there was often reason for considerable urgency about bringing thyrotoxicosis under control. We deliberately chose, therefore, to investigate the dose that would do this at a maximal rate, and intentionally gave those whom we treated in the early years what we hoped was (and what subsequently proved to be) a very large dose of radioiodine, with the object of achieving, if possible, a one-dose control within the shortest possible time. As some of you may know, in the same period and more or less in collaboration with this plan, the late Mayo Soley elected to evaluate the other end of the dosage spectrum. He studied, in a different kind of patient—the one who had an average, uncomplicated condition —the effect of very small, repeated doses of radioiodine without regard to the possible duration of thyrotoxicosis.

We soon learned that the range of doses that we had chosen for these patients did not seem to make much difference; because all the doses we used fell within the upper end of the range of biologic response. With all the doses then used, we had a rather high incidence of hypothyroidism, and we are in the process of analyzing that earlier experience thoroughly. Our more recent experience has been with smaller doses than we initially employed. The average early doses, if I remember correctly, were around 200 μc per g of thyroid weight, based not upon the total dose given by mouth, but upon radioiodine that reached the thyroid gland.

DR. WERNER: How many patients did you have? I would like to see your bookkeeping.

DR. KEATING: We cannot help you too much with the bookkeeping, I fear, because we have thus far analyzed only one small series. Dr. Childs may have these data.

DR. CHILDS: I have the data on a small series of 170 patients in whom serial uptake studies after administration of the therapeutic dose permitted calculation of radiation dose to the thyroid. The oral dose was calculated from tracer information and estimation of gland weight to give a retained dose in the thyroid of from 175 to 250 μc per g.

DR. WERNER: Was there a preliminary test uptake?

DR. KEATING: Our estimate of doses was based, first, upon the uptake observed with a preliminary tracer dose, and second, upon an estimation by the clinician of the weight of the thyroid gland.

DR. FEITELBERG: Our average dose was about 115 μc per g retained.

DR. WERNER: Do you have any idea how many patients got well with one dose?

DR. CHILDS: A single dose controlled 84.9%. There was only one patient in whom the

disease was not controlled with additional doses. The myxedema rate, however, was 31.2%.

DR. WERNER: What was the maximum number of doses given?

DR. CHILDS: In answer to Dr. Werner, the maximum number of doses given was three. This particular study was carried out in a small group of 170 patients in whom we had measurements following therapy sufficient to permit calculation of the radiation dose to the thyroid, effective half-life of I^{131} in the thyroid, and uptake of I^{131} in the gland at 24 hours. Dr. Peterson has reviewed these data for us as a thesis subject. Table 17 shows some of these data.

Table 17

THE RADIATION DOSE DELIVERED TO THE THYROID AND THE PERCENTAGE OF PATIENTS CONTROLLED BY A SINGLE DOSE (175 TO 250 μc PER g) OF I^{131}

24-hour uptake (%)	Effective half-life (days)	Radiation dose to thyroid (rads)	Patients controlled with 1 dose (%)
Under 40	5.7	16,300	90
40 - 50	5.3	12,900	92
50 - 60	5.0	14,200	88
60 - 70	4.5	14,200	81
Over 70	4.6	15,300	77

The patients were divided into groups according to their 24-hour uptake. The second column shows the mean value for the effective half-life of I^{131} in the thyroid for each group. The third column gives the mean radiation dose to the thyroid. The fourth column gives the per cent of patients in each group in whom the disease was controlled with 1 dose. The half-life varies inversely with the 24-hour uptake in this series. There is no apparent correlation between radiation dose and the control of the disease, uptake, or half-life. There is some indication that patients with lower uptakes are controlled more easily than those with higher uptakes. Incidentally, Dr. Werner, you mention this latter observation in your book. I do not know whether others have had a similar experience.

DR. QUIMBY: I have an illustration that I intended to use later, but I believe it fits right in here. Figure 28 shows 100 cases of toxic diffuse goiter that were studied very thoroughly by members of our group. In each case the effective half-life was determined by repeated measurements over the gland. Dr. Werner estimated the gland size for each case. Also shown are the successes and failures according to the calculated radiation dose to the gland. Beyond a dose of 2500 rads to the gland, the ratio of success to failure is

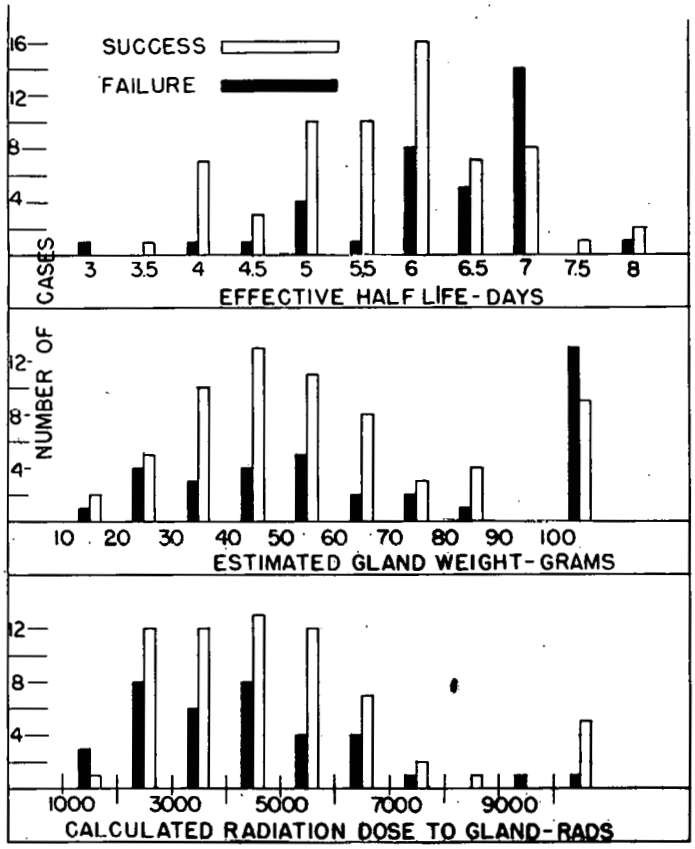


Figure 28. Response to treatment with I^{131} in 100 cases of toxic diffuse goiter.

about constant. So far as estimated gland size is concerned, this does not seem important. For all gland sizes there are about twice as many successes as failures.

But the thing that was interesting to us, that we cannot explain at all, is that as the effective half-life goes up the percentage of successes goes down. All radiologists know that there is a time factor; that the longer time you take to give your dose the less effective it is. If you consider the effective half-life as 4.5 days, the effective time to deliver the dose is about 9 days, an effective half-life of 7 days would be an effective dosage period of 14 days. There should be approximately 10 or 15% correction for the time factor. Such a correction would not change the distribution in Figure 28. This partly bears out something Dr. Childs said, and is something we have not been able to understand at all.

DR. KEATING: Pardon me, Dr. Quimby, but I should like to ask what is your definition of success or failure?

DR. QUIMBY: This is the result of a single dose. Many of these patients were retreated so that those listed here as failures were ultimate successes.

DR. STANBURY: What is the sensitivity of these cells? Here you have a long half-

life, and the cells are probably not very active. Here is evidence that radioactivity may be related to physiologic activity.

DR. CHILDS: We are assuming that they all have the same disease, the same disease of the same severity, which may not be true.

DR. QUIMBY: These were all toxic diffuse goiters—there is a limit to what you can get in one illustration.

DR. WERNER: I think Dr. Childs' point is well taken, that there may be different diseases. On the other hand, there seems to be a great weight of opinion favoring the view that there is but one disease and that toxic nodular goiter is no more than toxic diffuse goiter with incidental nodularity.

DR. TRUNNELL: I have no wish to jump down your throat but I would like to try to explain something that has bothered me. Many of you will recall the report[1] written several years ago that shows a rebound to abnormally high uptake in a patient after thyroiditis. Since then we have seen 7 similar cases. The uptake is low initially, and as the patient begins to recover, it rises to what might be regarded (if seen as an isolated value) to be indicative of hyperthyroidism. However, if one follows these patients with serial measurements for several months, the uptake is seen to decrease spontaneously. It occurs to me that perhaps those few patients you reported getting well after receiving only tracer doses were tested at such a peak point. Perhaps they did not really have diffuse goiters or Graves' disease. If so, the reason they seemed to get better was that they were going to get better anyway and that the tracer had nothing to do with it. In this connection, it seems to me that your good clinical sense tended to ferret this out in these cases because you chose evidently not to treat them despite their high uptakes. You must have had some sixth sense telling you they were going to get better without real therapy.

DR. WERNER: So far as I know, they were just average hyperthyroid patients referred to the clinic. All we did for a while was to give small doses to this series because we felt it was perilous in the face of heart failure, arrhythmias, and so on, to put them on larger doses. Since then, we have engaged in a study with 1.5 μc in order to test the uptake in a group of patients with very mild thyrotoxicosis. We are up to, I think, about 30 patients now, and it is true we have had some spontaneous remissions, but the incidence is under 10%, whereas we reported something like 25% in children and something like 17 or 18% in adults. I want to expand my series.

DR. KEATING: Since it has been brought up, and since it appears to have some relation to the group of patients Dr. Childs has spoken about, I should like to go on record as saying that we are impressed, from our own experience, by the fact that the condition of patients with hyperthyroidism may be regarded as falling naturally into more than one clinically significant category. The series you have seen, as well as the other series that we are currently evaluating, involves only patients who had what you all would classify as toxic diffuse goiter or (to use other synonyms) hyperthyroidism with parenchymatous hypertrophy, Graves' disease, and so forth, but without endemic nodular goiter as a component. It is our belief that, clinically, hyperthyroidism occurring in the course of endemic

nodular goiter (i.e., "adenomatous goiter with hyperthyroidism") is a different disease, in most practical respects, from ordinary Graves' disease, and particularly with regard to the patient's response to radioiodine. The reason we have excluded adenomatous goiter with hyperthyroidism from consideration here is that, in our hands, this type of nodular goiter simply does not act at all as exophthalmic goiter acts, particularly in response to therapy. We have treated, I think, about 50 patients who had adenomatous goiter with hyperthyroidism. The doses required are, for the most part, in the carcinocidal range, especially those administered to patients with large adenomatous goiters. The experience gained from treating diffuse toxic goiter has not helped us at all in the management of these patients with hyperfunctioning nodular goiter.

DR. WERNER: Because we were aware of this difference—there was mention of a patient who received 100 mc for toxic nodular goiter and failed to respond at your clinic, and also the report of McCullagh some years back—we analyzed the experience in our clinic and found virtually no difference between the average dose that causes remission in toxic nodular and in toxic diffuse conditions. We are in a non-endemic area.

DR. FEITELBERG: Our experience with nodular goiter is exactly like yours. There does not seem to be any difference. On the other point, I hope you will not think me presumptuous, but I would like to ask you and myself: what is an adequate dose? This can be answered only after we decide what the criteria of success and failure are. It should be obvious, but I don't think it really is.

DR. CHAPMAN: What are the criteria? What do we establish as the point at which we say the patient is well or has responded to a single dose or not? I think we have been the ones who have exercised the greatest restraint. I think the point Dr. Feitelberg mentioned is important. I know at the Mayo Clinic the patients are transient and have to be cured in a hurry. We have patients who are near us and who can come back at regular intervals for a long time. We give 160 μc per g, and the patients usually retain about 120 μc. On 1 dose, approximately 75% do well, and on 2 doses or more about 15%. Our myxedema rate is running about 8%, and you can add another 3% where things happen to them, e.g., they disappear or undergo surgery. With the very large glands that do not seem to shrink, we go ahead and operate, thereby getting rid of the disease. That number is very small. But coming back to the main point, we have tried to hold off a second dose for at least 6 months. We give a single dose and then try to wait at least 6 months even though the patient is in a toxic condition during the period, watching him in the clinic at intervals of about 6 weeks to 2 months. A toxic patient who has been given a single dose is asked to return 2 months thereafter. His BMR may have dropped significantly, he may have gained a little weight, and yet he may be still toxic though improved. Then we see him at the 4th month and again around the 6th month. We have seen patients who finally go gradually down to normal at 8, 10, or 12 months; once this biologic reaction is initiated in the tissues, it continues slowly. The corollary is that we are now beginning to see myxedema, at 5, 8, and 10 years after the first single dose. Meanwhile, they come down to normal by the end of 6 months to a year; they remain normal over a period of years, then finally the thyroid be-

gins to wear out. This is especially so in women who go through menopause, which seems to be a factor. Then they may slip into true myxedema. Among the 15% who required more than 1 dose, there are only 3 patients who were given 4 doses, to my knowledge. An interesting thing, something was said about the second dose. Our tendency is to give the same quantity or more for the second dose. If the patient does not respond to the first dose, e.g., 8 mc, we assume we have underestimated the size of the gland. So the second time we give 10 mc. If he does not respond to the second dose, he is apt to receive 12 mc for the third, and by that upward scale of dosage we finally render the patient euthyroid. We think our error has been in underestimating the size of the gland. We usually give a low initial dose of 5 or 6, or even up to 8 or 10 mc with the average being about 8. Occasionally, in untreated youthful people with succulent tissues we have seen myxedema produced by as little as 4 or 5 mc. The curious thing about this biologic response is that if a person becomes myxedematous, he never seems to become so any faster than in about 3 or 4 months. If he is going to develop myxedema, he will do so very near the 4th month. I do not think that giving a person 75 mc will cause him to develop myxedema any faster than if he is given 6 mc. My point is that I do not see any virtue in higher doses when you are trying to get results in short order. If you want to get the job done in a hurry, I do not think that a bigger dose will work.

DR. KEATING: I agree that between 6 and 75 mc you would not obtain more rapid control by use of the larger dose. What I referred to was the obtaining of maximal recovery rates in terms of the year 1946, not the year 1956. It is significant that we do not now do what we did 10 years ago. We feel that we have proved our point and are quite satisfied nowadays that we no longer need to give such large doses.

DR. WERNER: Yet on the other hand, what percentage of your cases who are toxic at 2 months will become euthyroid by waiting 6 to 8 months?

DR. CHAPMAN: About 30 or 40% I would say.

DR. WERNER: So you keep 70 or 60% of them ill.

DR. CHAPMAN: But we do not think they are ill. They are feeling better, their pulse rates are slower, and they are satisfied with the state of their health. Only rarely do we have one complain, and he may be borderline. A great deal depends, of course, on the individual view of a metabolic disease. If you get excited about it and worry about your patients—other patients do not worry and get along all right. . . .

DR. GORDON: Our experience might be appropriate here because it is an interesting modification of some of the plans that have been proposed already. We have taken things every bit as cautiously as Earle Chapman. We are inclined to go very slowly on therapy so long as we have the patient in an acceptable state of health. The method of choosing the dose is much the same as Keating and Chapman have used. It is a simple formula of how much you wish to obtain in the gland times the estimated weight of the gland divided by the per cent uptake. Contrary to anyone's remarks here, we have tried to get a concentration of 75 μc per g. This is the therapeutic dose we give to our patients, and it obviously leads to an increase in the number of patients who will need 2 or more doses, but it has

decreased our post-treatment myxedema rates to under 4%. We also have been inclined to wait. We usually do not even check the patient until 3 months after the initial dose. If he is improved but still not euthyroid we are much inclined to wait another month or so before giving any further treatment. After that original month or so two things may happen. Either the patient is still further improved or he has shown what we call a rebound which means he has become more toxic than when we saw him at 3 months. We think this is due to some sublethal injury to a large number of thyroid cells which have now recovered and have continued to produce thyroid hormone. We have not seen any patients that we considered failures; in other words, in all of our series we have been able to render the patient euthyroid except when some surgeon took the patient away from us before we were through. We do have several that were exceedingly resistant, and I have an illustration of one of these in the discussion of failures.

DR. RAWSON: I want to ask Dr. Chapman a question and then apply this to a generalization. You remember, Earle, a number of years ago a very lush looking girl came in with a near thyroid storm. She had obviously had hyperthyroidism or Graves' disease off and on since the age of 16; she was about 36 when we saw her. She looked familiar to all of us because she had appeared as a model on the cover of many magazines. She was prepared for thyroidectomy with thiouracil only because some of us were sure she would turn down surgery when she became euthyroid and got religion—since she was a Christian Scientist. The morning of surgery she refused thyroidectomy so we offered her treatment with radioactive iodine, and Earle offered her the glass of I^{131}. Just as she got it almost to her mouth, she threw it so that it almost landed in his lap. She came back a few months later euthyroid, because she wanted to go abroad. Where would you put her on this curve?

I think it is very interesting to think about what several people have commented on and stated about this disease before. Maybe they just go on digitalis and get better. Dr. Rall took a few patients at Brookhaven and exposed them to no obnoxious stimuli except TV, and they got better. I just wonder how we would classify those people. As a matter of fact, one patient we saw at the M.G.H., who refused treatment because she had been a nurse there in 1912, refused all types of treatment. She came back 2 or 3 years later with a full-blown Gull's disease; we asked what had happened to her and she said she had taken up Christian Science but had been over-treated.

DR. CHAPMAN: No one knows the natural history of the disease, as you are pointing out. I had this same experience very recently. A patient had another disease, and as I walked into his room, his wife stepped up and said, "You know, I was reported by Larry Gross, in Toledo, Ohio, as a very unusual case of Graves' disease with such bad eyes and all, they wanted to operate on me back in 1917." Now I happened to know Larry Gross II, his son. I examined and talked with this woman. She seems perfectly well today. She had been put to bed, studied, and had been given some sedatives. What you are pointing out is that we really do not know the natural history of the disease.

DR. KEATING: I would like to ask Dr. Rall whether he plans to publish these cases of successful Christian Science cures under the category of cosmic rays.

DR. FEITELBERG: I should think then we are all quite familiar with the phenomenon of the burnt-out Graves', the spontaneous remission of Graves' disease after a number of years, with or without therapy.

DR. WERNER: Dr. McCullagh, I think, is the man who can speak about that.

DR. McCULLAGH: I do not think I can add a great deal to what has already been said except to show that I too can be inaccurate when it comes to dosage of I^{131} in treatment of Graves' disease. The disagreements I may have with you with regard to nodular goiter can be taken up at some other time. We have treated about 1600 patients with radioactive iodine. The method we have used through most of this time has been, I think, inconsistent because we do one thing at the first treatment and believe that we are working on a system, and when the patient comes back we decide to do something different.

At the first treatment we try to calculate a dose that will give 100 μc per g of gland, and we do not know how long it stays in the gland; we do not make that type of estimate. I can't give you the statistics on all of these, but when we got to about 800 patients, we found that our figures for Graves' disease were about as follows: 75% were euthyroid with 1 dose, 15% required 2, and about 10% required 3 or more. We have gone as high as 6 doses. We have some failures of treatment that we will consider later. In the early group we had much more hypothyroidism than we have had of late.

Recently, we reviewed the results in 100 consecutive cases of the earliest cases treated, and in 100 cases treated more recently (Table 18). About 23% of the earliest cases had

Table 18

INCIDENCE OF THYROID FAILURE IN 200 CASES OF GRAVES' DISEASE AFTER RADIOIODINE THERAPY, ACCORDING TO NUMBER OF DOSES GIVEN

	1947-49	1955-56
No. of cases	100	100
Thyroid failure	23%*	16%*
Thyroid failure following 1 dose	31.4%	18%
Thyroid failure following 2 doses	18.2%	12%
Thyroid failure following 2 or more doses	12.2%	12.1%

*Approximate permanent unintentional hypothyroidism—10% (excluding intentional hypothyroidism and temporary thyroid failure).

hypothyroidism, and among these, 16% had thyroid failure—I will explain that in a moment. In patients who received 1 dose, we got a higher incidence of thyroid failures than in those that required 2 or more doses. If we deduct from this percentage, the percentage of cases intentionally made hypothyroid, and an estimated 2% having temporary hypothyroidism, we have approximately 10% with permanent hypothyroidism. We have seen myxedema occur

that lasted for as long as a year, after which it was followed by recurrent hyperthyroidism.

Table 19 gives another sampling. There were 332 patients in this group. Approximately 2% had presumably temporary thyroid failure.

Table 19

INCIDENCE OF THYROID FAILURE AFTER RADIOIODINE THERAPY FOR GRAVES' DISEASE

Number of patients treated	332
Number of patients with permanent thyroid failure	32 (9.6%)
Number of patients with temporary thyroid failure	7 (2.1%)

We too have tried to find some practical way of estimating the proper dose earlier. We do not wait 6 months between doses. Most of our patients were seen every 2 months. Instead of estimating the uptake and the size of the gland as we did the first time, we look at the patient and decide how sick he is. If the BMR has come down, for example, from 60 to 30, we consider that the patient is approximately half well; but if we think the patient needs some more radioactive iodine, we give approximately half the previous dose. If he is no better at all, we give a larger dose. We have thought that we have had more myxedema in patients with smaller glands, and sometimes the condition is very impressive. We have seen myxedema in one instance, resulting from 3 mc, another from 4, and one from 2.5. Apparently these are going to be permanent. A calculation does not seem to bear out the impression that the size of the gland is a factor of much importance so far as frequency of hypothyroidism is concerned (Table 20).

Table 20

INCIDENCE OF THYROID FAILURE IN 200 CASES OF GRAVES' DISEASE AFTER RADIOIODINE THERAPY ACCORDING TO AVERAGE ESTIMATED WEIGHT OF THYROID GLAND

	Number of cases	1 dose	2 or more doses
Thyroid failure	39	52 g	61 g
No thyroid failure	161	49 g	63 g

We looked then at the dose in relationship to hypothyroidism, the 100 patients mentioned who were treated successfully with 1 dose. If we exclude the patients who were intentionally made hypothyroid, we find that the average estimated dose in μc per g was 101

in the hypothyroid patients and 119 in the remainder (Table 21). This does not tell us much except that we need to learn more about the problem.

Table 21

INCIDENCE OF THYROID FAILURE IN 63 CASES OF GRAVES' DISEASE SUCCESSFULLY TREATED WITH ONE DOSE OF RADIOIODINE, ACCORDING TO μc I^{131} PER g OF THYROID TISSUE

	Number of cases	μc I^{131} per g thyroid
Thyroid failure	11	101
No thyroid failure	51	119

DR. JAFFE: Before radioiodine was employed in our department we used to estimate the weight of the thyroid gland at the time of surgery. We found that our estimations of thyroid weight were sometimes in error as much as 100%. It is obvious, therefore, that there is no formula that will give us a correction factor of 100%. When we started to use radioactive iodine therapeutically, we decided to employ clinical factors to determine our dosage range rather than the "calibrated finger technique" of estimating the gland size. As Dr. McCullagh has just pointed out, we must examine the patient and try to treat him according to the degree of thyrotoxicosis. We administer an initial dose of 3 to 6 mc, depending on the severity of the disease. For the more toxic patients we usually give a smaller initial dose. When we review our cases, we find that the dose usually averages about 150 μc per estimated g of thyroid tissue.

We have used I^{131} therapeutically in more than 3000 patients to date. In 1948 we attempted to treat the patient with one therapeutic dose of I^{131}. We checked our patients at 2-month intervals following treatment. Of these patients, 72.3% became euthyroid following a single therapeutic dose of I^{131} averaging between 4 and 6 mc. Some of the patients who became euthyroid had a recurrence of toxic symptoms and required a second therapeutic dose. A second oral dose of radioiodine varying from 3 to 6 mc was required by 16.9% of this group before they finally became euthyroid. Of the total group, 6.7% required 3 therapeutic doses, and 4% of the total group required more than 3 therapeutic doses before they finally became euthyroid. At the time that we analyzed these results in 1948 we considered the latter two small groups to be therapeutic failures because our criteria for a good result was the response of the patient to 1 or 2 doses of radioiodine in a 4-month period. We now know that certain patients who improve partially require additional radioiodine before they become euthyroid. We agree with Dr. Werner that it is unwise to keep these patients in a toxic state for too long. Nevertheless, even though the patients require additional treatment after the 4-month period, they are certainly not as toxic as they were when treatment was first started. It is only by fractionating the doses of radioiodine and waiting at least 2

or 3 months after each additional dose that we are able to prevent a high incidence of hypothyroidism and myxedema.

DR. CHAPMAN: What subsequently happened to that group? Have you ever segregated that 6.7%, to see what happened to them?

DR. JAFFE: A few of these patients were treated surgically because the referring doctor was impatient. A few received other antithyroid drug therapy, while the majority came back for additional radioiodine therapy and had good results.

DR. CLARK: None got well spontaneously?

DR. JAFFE: As far as I can remember none of these patients got well spontaneously. Something had to be done for them. The impatience of the referring doctor made it necessary to refer some of these patients for surgical treatment. A breakdown was made of the cases according to the type of thyroid gland as determined on palpation. Of the 148 patients in this group, 93 showed diffuse enlargement of both lobes of the thyroid gland. Of these, 67.7% showed an excellent response following 1 therapeutic dose of I^{131}, 17% required 2 doses, 9.7% required 3 doses, and about 4% required more than 3 doses. There were 19 patients with toxic nodular goiter. Of this group, 73% had a good response following 1 therapeutic dose of I^{131}, 10% required 2 doses, 5% required 3, and 10.5% more than 3. I agree with Dr. Keating that there are certain types of toxic nodular goiter that are more resistant to radioiodine treatment and therefore may require very large therapeutic doses of I^{131} in order to obtain a good result. It has been our policy to refer to surgery, those patients who do not show a satisfactory response 4 months after radioiodine treatment. Twenty-six patients of the total group were thyrotoxic but did not show an enlarged gland on palpation. Of this group, 84.6% responded to 1 therapeutic dose ranging from 3 to 6 mc, and 15% required a second small therapeutic dose. This group showed the highest satisfactory initial response to treatment, probably because of the relatively smaller size of the thyroid gland.

A breakdown was also made of the patients according to previous antithyroid treatment. Eighty-nine patients were treated with I^{131} alone, and 81% of these had a good response to the initial dose; a few more required a second dose, making a total good response of 88%. Forty patients had been treated previously with propylthiouracil. Only 50% of this group showed a good response to the initial radioiodine treatment, while 85% showed a good response following the first and second treatment. The patients who had postoperative recurrent thyrotoxicosis showed a good response to the initial treatment (86.6%), while about 14% required a second therapeutic dose. The incidence of post-treatment myxedema was much higher in this group as might be expected since the volume of thyroid tissue was considerably less in each of these patients.

DR. POCHIN: In my country a test dose is used regularly in about 2/3 of all clinics. That means that in these institutions there is an effective calculation in reps or rads, and the dose varies between about 9000 and 11,000 reps. A dose of the order of 100 μc per g or higher is given in one or two clinics. The frequency of resulting myxedema runs at about 10% for the whole group, with 5% additional for temporary hypothyroidism.

There are two points I would like to raise: firstly, the problem of what drugs should be used in treating the patient who is too toxic at the time of radioiodine to leave without drug therapy; and secondly, although I think again this comes later, there is one important thing we might like to do. It seems from a private discussion this morning that there were 4 cases of leukemia in the experience of those attending this meeting following radioiodine treatment of hyperthyroidism. This could still be random. It would be useful to have a figure as to the number of patients treated, multiplied by the number of years of follow-up because 4 cases of leukemia would be expected to occur by chance amongst females of the age of 45, on the basis of about 100,000 patient years. I think these cases of leukemia have corresponded to a total experience of about 64,000 patient years.

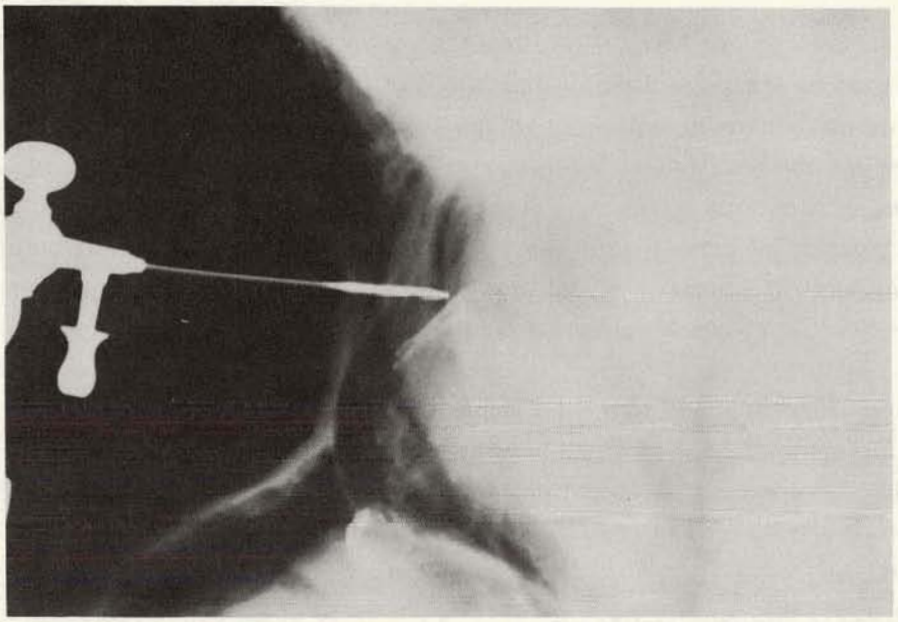
DR. TUBIANA: Since 1950, we have treated about 600 cases of hyperthyroidism with I^{131}. The thyroid uptake of each patient was measured at 6 and 24 hrs. after the oral administration of a tracer dose of I^{131}. Our aim was to put 100 u c per g of radioactivity into the thyroid.

After 1 dose, the results were good in about 60 to 65% of the cases. In a few instances we have had to give 4 or 5 doses. The overall results are good in more than 80% of the cases. Hypothyroidism occurred in about 5%. Difficulties arose on two points:

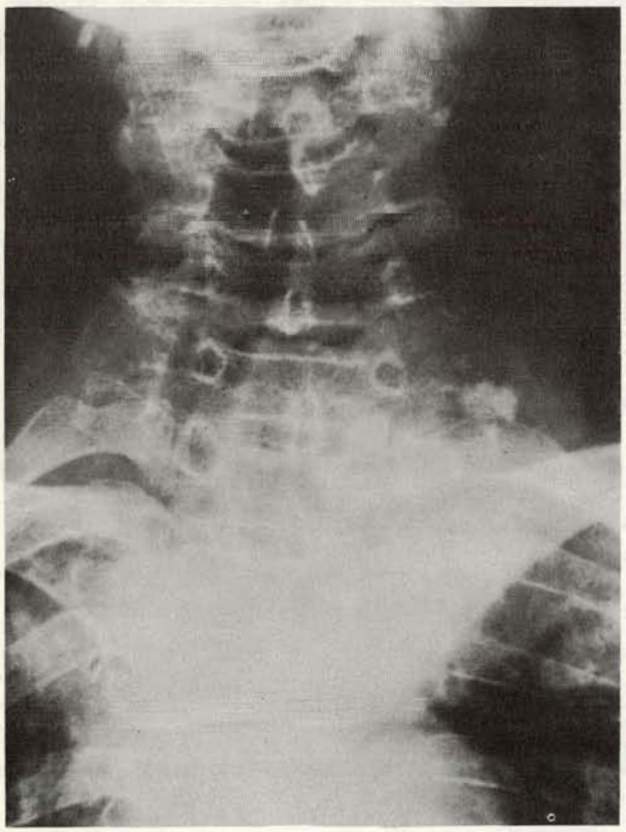
1) That of deciding within the 2 months following treatment whether a second dose would be of value. After 2 months, there is nearly always a definite improvement, which sometimes continues until the patient is cured. On the other hand, the improvement sometimes stops and the patient remains improved but not cured. From a biologic point of view there is often at this time a discrepancy between the results of a further tracer study and the clinical findings, and between the iodine uptake and the blood chemical PBI. We have studied (in about 200 cases) the prognostic value of a tracer study done within 2 or 3 months of the first treatment. When the uptake at this time is lower than normal, the clinical state becomes hypothyroid in 18% of the cases, normal in 57% of the cases, and remains slightly hyper in 25%. When the uptake is normal, 10% of the cases become hypothyroid, 55% become normal, 23% remain slightly hyperthyroid, and 12% grossly hyperthyroid. When the uptake is higher than normal, 5% become hypothyroid, 27% normal, 52% remain slightly hyperthyroid, and 16% grossly hyperthyroid. When the uptake remains unchanged, none becomes hypothyroid, 15% become normal, 54% slightly hyperthyroid, and 31% remain grossly hyperthyroid.

2) Estimation of the weight of the thyroid is another problem. Estimation based on palpation is always uncertain and sometimes impossible when a part of the thyroid is retrosternal. In such cases, we have found a pneumothyroid-radiographic technique to be very helpful. This was inspired by the work of Franco and Quina.[2] A sufficient amount of oxygen is injected into the pretracheal space, and straight roentgenograms and tomograms are taken (Figure 29A-C).

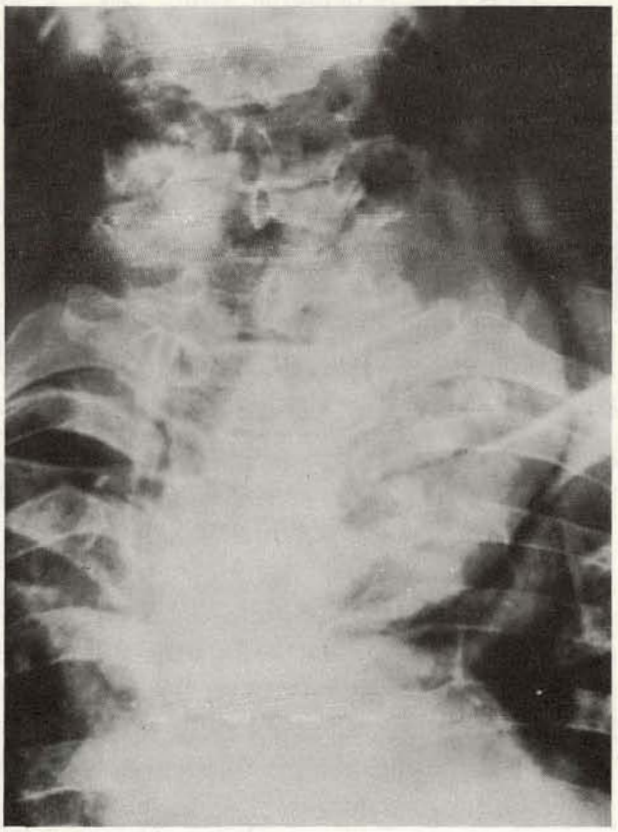
DR. SONENBERG: It was stated that there appears to be no common denominator. I just wondered if there isn't. Two things that come to mind now are what Dr. Quimby and what Dr. Childs said, that the one correlation they were able to make with successful



A



B



C

Figure 29. A. Injection of air into pretracheal space. B. Roentgenogram taken before injection. C. Roentgenogram taken after injection.

cases was with the effective half-life. One of my modest friends, Dr. Rall, took this into account when he worked up the cases, and I wondered if he had any further comment on that now, since his calculation is significantly different from what you have up there.

DR. RALL: This is, I think, a major point on the effective half-life, which can vary from 1 day to 7 days, and could have a big bearing on it. It has a bearing in another way, i.e, if the time uptake is measured. Six hours may be the peak for someone with a very fast turnover and not the peak for someone with a much slower turnover and uptake. On the other hand, if you measure it at 1 or 2 days, you may get the peak of the slow turnover and be way down on the scale for the high turnover. So the effective half-life does influence, to a great extent, the figure you record as the uptake. From this figure, if you do tracer studies beforehand, you can calculate the μc deposited in the gland. I want to emphasize that this is important. We tried to take it into account without measuring over the gland for a period of several weeks, which is necessary, by just measuring the amount of perceptible iodine in the blood, which is a function of the rapidity of turnover, and by empirically correcting the number of μc to be deposited in the gland. We have not analyzed actually the results of treatment after using this formula to see how much it improved it.

I think one other comment I might make is, that it seems to me worthwhile to consider whom you are treating. If you are treating younger individuals who are in reasonably good shape, one may, I think, temporize with hyperthyroidism for some period of time in an effort to arrive at the minimal dose. On the other hand, if you are treating elderly patients with complications and with other serious diseases, it seems to me one's desiderata are different, and one should then attempt control with a single dose. So I would suggest that perhaps there are different dosage criteria to be applied to different patients. Our experience has been almost exclusively with patients in the older age group and with other serious diseases. Hence, we felt a rather high incidence of myxedema is not at all deplorable, whereas continuation of the hyperthyroidism for a relatively long period of time might be otherwise.

DR. WERNER: On the other hand, how well does the effect anticipated from a tracer dose correlate with that of the treatment dose?

DR. RALL: It depends upon your reading. When we tried to analyze not the effective half-life but the blood level, the correlation coefficient was of the order of 0.75.

DR. MILLER: I swore I was not going to say anything about this and I will try to make it short. It strikes me there is one thing very much needed in this discussion, and that is not what people do, although this is important, but why. We started our work back with Mayo Soley in 1945. I very naively approached this problem in terms of total dose at that time, then being a radiologist at heart, and tried to decide what type of dose we were giving. This would answer all questions—as I say, I was very naive. Time went on and we made the studies on half-life, total turnover, and total long-term studies on uptake, calculated all these doses (this work has all been published) and came very quickly to the conclusion that there was very little correlation no matter how you cut it. Then, still in this naive period, just before I spent 6 months of the most unhappy time of my life, I tried to

make a division between those patients who were seriously ill, moderately ill, and mildly ill, and I found great difficulty with that. In point of fact, we found it impossible because there were no criteria by which we could make these distinctions. Then, of course, one asks the next question; if you can't make distinctions, can you make the distinction between those who are ill and those who are well. Since there are no objective criteria by which you can do this, and no operational definition by which you can, you get to the point where the whole thing begins to be opinion. If this is true, I think much greater variations should be expected since it is a function of opinion and not objective analysis. So, in short, we ended up on dose calculation by looking at what we had done and finding that it was really fairly simple. We went through the data on all the patients and found the dose that resulted in hypothyroidism. Then we looked over the data again for the dose given patients who required more than one treatment. The dose used, then, lies between these two extremes.

DR. WERNER: I hoped the conclusion would be that any method gives the same results as any other. This seems to be the fact.

DR. BERMAN: I would like to make two comments: one with respect to the discussion on the general factors involved in radioiodine therapy, and one with respect to Dr. Quimby's results.

Dr. Stanbury outlined a number of factors that may account for the clinical results of radioiodine therapy. A number of treatment schedules have also been described that are based on only one or two factors, such as the number of mc administered, the effective half-life of radioiodine in the thyroid, etc. Yet, these simple schedules seem to yield statistically the same clinical results as do very careful kinetic studies and dosimetric calculations. This implies that some variables that play an important role in the correlation between radiation delivered and clinical effect are as yet not defined properly. In view of this, it may be useful to differentiate two phases of the problem. On one hand, it is necessary to treat patients routinely by the simplest and most effective method possible. On the other, it is still necessary to measure and control as many of the known variables as is possible so that the data may be useful in the interpretation of the undefined factors.

Dr. Quimby pointed out that some hyperthyroid patients with relatively long effective half-lives of radioiodine in the thyroid do not respond to large doses of radiation. The effective half-life of radioiodine in the thyroid, aside from the physical decay of the isotope, is usually a composite of a number of variables. If the end of the radioactivity curve in the thyroid is chosen to represent the effective half-life, two parameters of iodine metabolism dominate it most: the renal excretion and the thyroid uptake rate of iodine. For example, if there were no renal excretion (neglecting fecal excretion) of radioiodine, the effective half-life of the isotope in the thyroid would equal its physical half-life. The amount of renal excretion, however, depends on the rate of thyroid uptake since the two processes compete for iodide. It follows, therefore, that a long effective half-life can be caused by a very high rate of iodide incorporation in the thyroid. The turnover rate of iodine in the thyroid may have but a minor effect on the effective half-life and could show up more in the earlier portion of the curve or in the radioactive PBI build-up in the blood. It is possible, there-

fore, that the patients described by Dr. Quimby may have very rapid rates of iodine metabolism, even though their effective radioiodine half-lives in the thyroid are long.

C. Gland and general body radiation from current I^{131} dosage schedules.

DR. WERNER: We shall now turn to the subject of the general effects on the body of I^{131} therapy. I hope that the radiobiologists will tell us why one patient responds while another does not when the same treatment schedule is used. Dr. Quimby.

DR. QUIMBY: As a matter of fact, Dr. Werner asked me to discuss both the dose to the gland and the dose to the patient. There has been a good deal already said about the dose to the gland, and in view of all the different methods that people have used to adjust dosage, it seems that there is not much remaining to say. I do have several illustrations that summarize some of the things we have been talking about, and you might look at them and see a little more about why so many uncertainties arise.

Figure 30A is essentially the formula that Dr. Sinclair gave you this morning in which we have put a combination of factors to get rid of the separate β and γ components. So we have a constant factor, effective half-life, and concentration of the isotope in the gland. The effective half-life varies between 3 and 8 days, but in our series of patients about 85% are between 5 and 7 days. The percentage uptake varies between 35 and 95; 85% of the cases of hyperthyroidism are between 60 and 80; the gland size varies between 50 and 150 g, and the error in estimate is plus or minus 50%. With all this in mind, let us suppose that we have decided that we would like to administer a dose of 7000 rads to the gland. You can do it in rads or you can do it in terms of μc, you can do it in any way you like, but the result will come out to the same degree of uncertainty. Let us say we have an effective half-life of 6 days, and that the tracer uptake was 70%. If we are going to get 7000 rads to the gland, the formula is as shown, and the calculated dose is 5 mc to be administered.

Let us see what this means in terms of what the patient will get. This is a mathematical calculation on the basis of having gotten the effective half-life on a tracer dose and tracer uptake. Here are the things that might happen. In the first place, the tracer and therapy uptakes are by no means always the same, and in the terms of Figure 30B, they were sometimes greater and sometimes less, not often by more than 10%. The effective half-life on the tracer dose and on the therapy dose may differ; it is likely to be less on the therapy does but not always, and it may vary by as much as a day. I have been very liberal in stating that the estimated gland size may be not wrong by more than 25%; most of you have already said it is probably worse than that. These may cancel each other out or they may add up. The uncertainty of the average dose may be at least 50%, so the 7000 rads that we started out with may be 4000 or may be 10,000 or may be anything in between. This possibly explains why with the record of 100 patients that I showed before, it does not seem to make very much difference what the dose is. This is the average dose based on uniform distribution within the gland, and since Dr. Sinclair spoke this morning there has been very little said about the fact that the dose distribution is really not uni-

form within the gland. Table 1 gives a ratio of maximum to average dose; in the toxic diffuse goiter Dr. Sinclair's maximum dose averaged about three times the mean. In the copy of the paper I saw, there were not very many cases but they were fairly well distributed in these three types; in the toxic nodular, the maximum average is about 7.5 times the mean, but you will remember that he had a tremendous range of relation between maximum and mean, and there is no information about the minimum dose.

So we wish to give a dose of 7000 rads, and we calculated the required mc on the information that we have; we come out with something between 4000 and 10,000 on an average. We look at these things and wonder whether we know anything at all about dosage. I have no idea what the answers are. We have talked about all the variables, and I thought that since we must do something about dosage we might average up our uncertainties this way.

The other aspect Dr. Werner asked me to talk about was the dose to the whole body (Figure 30C). Dr. Sinclair did speak about that this morning too. The best work I know of in the study of whole-body dose is the work published by Seidlin, Yalow, and Siegel.[3] Their work was done mostly on cancer patients, but they did include a series of 13 hyperthyroids, and they studied the blood levels over a period of time; i.e., they took uptakes and then they took blood levels at 24 and 48 hrs. and at least 2 subsequent periods. They then plotted a curve and determined the area under the curve as being proportional to the dose.

It is only by some such continual study of dosage integration, that we can get the dose to the whole body. It is not possible, so far as I can see, to get it by any one measurement, whether it is clearance, protein-bound iodine, or anything else. You have to follow it over a long period of time to see just what there is circulating through the body and then make another calculation to determine what part of the dose, the amount circulating in the blood, is effective. The authors quoted come out with an average blood dose of about 1 rad per mc administered. But this varies between 0.25 rad and 2 rads per mc administered, depending on a lot of things, e.g., on how fast the turnover is, the size of the patient, and so forth. However, for the hyperthyroid situation, this is a perfectly adequate value with which to work; between 0.25 rad and 2 rads, and take an average of 1 rad per mc whole body or blood dose. This will be reasonable. To the soft tissues, about half of the dose to the blood, because the β rays will not deliver the full dose to the other soft tissues.

The reason for worrying about whole-body dose is that these levels, in hyperthyroid therapy, cannot cause any damage to the patient himself; anything that we might call damage; the dose will never be enough. What we are worrying about, I take it, is genetic damage. The average gonadal dose in I^{131} treatment for toxic goiter, with the single dose we have talked about, would be about 1 to 6 rads to the gonads, spread over a period of not more than a month, depending on the rate at which the iodine is removed from the body, and not repeated for 2 or 3 months. The maximal permissible dose to the gonads or to the blood-forming organs is 5 rads in a 1-year period for radiation workers. So this is of the order of occupational exposure. It is not occupational exposure to be sure, but it is sup-

D(gland) = about 17 x T(eff.) x C rads. T(eff.) in days. C in μc/g.

T(eff.) varies between 3 and 8 days. 85% of cases probably between 5 and 7 days.

Percentage uptake varies between 35 and 95. 85% probably between 60 and 80.

Gland sizes vary between 15 and 150 g. Error in estimate of size $\pm$ 50%.

To administer an <u>average</u> dose of 7000 rads to a 50-g gland,

with T(eff.) = 6 days and tracer uptake = 70%:-

$$7000 = 17 \times 6 \times \frac{\text{mc adm.} \times 1000}{50} \times 0.7$$

$$\text{mc adm.} = \frac{7000 \times 50}{17000 \times 6 \times 0.7} = 5$$

Figure 30 A. I^{131} dosage in hyperthyroidism. Dose to the gland.

Difference in uptake on therapy and tracer doses — $\pm$ 10 per cent.

Difference in T(eff.) on therapy and tracer doses — $\pm$ 1 day.

Error in estimation of gland size — $\pm$ 25% (or more).

Combinations of these may counterbalance each other, or may be additive.

Uncertainty in <u>average</u> dose may be $\pm$ 50% (or more).

The proposed 7000 rad average dose may be between 4000 and 10,000 rads <u>average</u>.

Uneven distribution of I^{131} in gland results in uneven dosage (Sinclair).

In toxic diffuse goiter maximum dose averages 3 x mean.

In toxic nodular goiter maximum dosage averages 7.5 x mean.

No data concerning minimum dose.

Figure 30 B. I^{131} dosage in hyperthyroidism. Possible errors in determination of dose.

(Information from study by Seidlin, Yalow, and Siegel.)[3]

No simple formula; dose distribution based on repeated blood measurements and graphic integration of data.

<u>Average dose to blood</u> — about 1 rad per mc administered.

Varied between 0.25 and 2.10 rad/mc adm. in cases studied.

<u>Average dose to soft tissues</u> — about half of blood dose.

Thus average gonad dose in I^{131} treatment of toxic goiter, with 2 - 12 mc administered per dose, is about 1 - 6 rads, spread over a period of about one month and not repeated for three months at least.

The "maximum permissible dose for occupational exposure" to the gonads or to the blood-forming organs is 5 rads in a one-year period.

Figure 30 C. I^{131} dosage in hyperthyroidism. Dose to blood and soft tissues.

posed to be, at least exposure in a class with diagnostic radiology, exposure which is of some use to the patient. We have the levels, then, that we have to think about administering to the gonads.

DR. WERNER: Do you think it useful to continue to calculate the radiation dose delivered to the thyroid?

DR. QUIMBY: There are so many variable factors that the rads don't mean too much. It is hard to say. I think we should stop trying to be exact, for I wonder if we are not fooling ourselves when we try to be. The rads in Figure 30A were calculated as accurately as any dosage could have been. The effective half-life was determined on the therapy dose by one person always. The gland size was determined by one person. The whole thing was done over a long period of time with great care.

DR. HASTERLIK: I should like to ask Dr. Quimby—don't you think the gonadal dose would be somewhat higher than you mentioned? You have only calculated the tissue dose from the blood dose. On the other hand, there is going to be a considerable fraction of a mc that will be in the bladder for a period of time, lying closely adjacent to the ovaries in the female. Has this been taken into account in your calculations?

DR. QUIMBY: No, this would bring it up somewhat. It still, however, would be at a low level. Remember that a mc in an hour at 1 cm gives 2.6 rads.

DR. HASTERLIK: It might double it.

DR. QUIMBY: It might double it in the female. I doubt if it would be that much in the male. A small change in distance produces a large change in dose.

DR. MARINELLI: Concerning the genetic effect, should the reproductive life of the patient be considered in this regard, Dr. Glass?

DR. GLASS: This would be of great importance, I think. During the coffee break I was talking with several people, and the point was made that the great majority, probably 50% or more, of the hyperthyroid patients who are treated are over the age of 40; of the remainder, probably at least half are between the ages of 30 and 40. So you can eliminate about 75% of the cases, I should think, from genetic considerations. In the others, I think there might be a reduction on the basis of impaired fertility. I do not know of any statistics to support this.

DR. WERNER: I would like to ask in the discussion of damage to future generations, what radiation doses might lead to an increased rate of mutation.

DR. GLASS: I am prepared and expect to talk about this later in this meeting. Perhaps it would be better to wait.

DR. WERNER: There is one problem involved, though. We have to try to decide whether I^{131} has advantages or disadvantages over other modalities such as surgery. So I think you ought to give us a little preview, if you want to do that. It is an important consideration because there is a growing tendency throughout the country to say, "Well, we have gone this far, we are not so much worried about cancer, and we can treat younger people. We can treat children in their teens." And the question is whether this is leading to the same kind of difficulty that the Committee of the National Academy of Sciences has

been stressing. Can you give us a brief summary?

DR. GLASS: Suppose we use the figure that Dr. Quimby just gave you—an average of around 5 r from such a treatment. The probability of getting mutations in the gametes of an individual subjected to ionizing radiation is according to our best estimate around .0025 mutations per r per gamete. That is certainly subject to an error of estimate of at least 1 order of magnitude on either side; in other words, the true value may be 10 times smaller than that or 10 times larger. A child then, coming from a person irradiated with 5 r would have 5 times that probability of carrying a mutation. This certainly is not a very large increase, and it is safe to say that a relatively small proportion of the population is being subjected to any particular kind of treatment, as with I^{131}. The genetic damage that would be done even from a dose of 200-300 r to a person who does become a parent is not going to increase perceptibly the probability of a tangible genetic effect in the offspring. There may be hidden mutations that would show up later on, but these would be evident only in a statistical study and therefore are not important since they merge with the effect upon the population as a whole. The dosage that is being given this way to the population as a whole is really a relatively small one.

DR. STANBURY: I think the question might be more clear, at least to me, Dr. Glass, if you added the answer to this question. Suppose this was not a small section of the population, but supposing that for this or other reasons an entire breeding population were exposed uniformly to this dose of radiation of the gonads. What would the net result in terms of mutations be at the 12th generation?

DR. GLASS: The Committee made some rough calculations of that general sort, and came up with the answer, again subject to at least 1 order of magnitude of uncertainty on either side, that you might expect 5 million induced mutations in 100 million babies in a population exposed to 10 r. That's about 5% with a mutation. That is directly related to the previously mentioned rate of .0025 mutations per r. Five million in 100 million is .05. Divide by 10 to get it down to the rate per roentgen, and then put it on the basis of the gamete instead of the baby, two gametes being required to make a baby. You get .0025/r.

DR. TUBIANA: What would be the number of normal mutations or natural mutations in that number of people?

DR. GLASS: The number of mutations that are normally occurring per generation?

DR. TUBIANA: Yes.

DR. GLASS: This is subject to a still greater degree of uncertainty, but it is probably around 1/2, or maybe even 100%. In other words, in 100 million babies, 40-50 million mutations, or maybe even 100 million. So if a dose of 10 r is about 1/4 to 1/8 of the doubling dose, as we estimated, and if that 10 r will produce 5 million mutations, then the spontaneous rate would be about 20 to 40 million mutations, with a considerable measure of uncertainty. It might be as high as 1 mutation per baby.

DR. RAWSON: Is it not true that the doubling rate would be the doubling of those that were radiation-induced to start with?

DR. GLASS: No. We don't know what proportion of the mutations occurring spontane-

ously in the human species is due to the background radiation, and what proportion is due to other things. In the fruit fly, only about 0.1 of 1% of all mutations is due to the background radiation, but there is reason to suppose that in organisms with a longer length of life, the proportion caused by background radiation is greater. Some geneticists have even suggested that all the spontaneous mutations occurring in the human species are due to background radiation, which is what your question implies. Most of us would not accept that as a really reasonable guess, but perhaps the background does produce 1/3 or 1/5 of all mutations that occur in man.

DR. MILLER: What is the evidence for this? Infection, decreased oxygen supply to the fetus, and all sorts of things play a part in producing mutations. The reason I bring this up is that the ones that were published in the NAS report as being due to radiation are not all due to that agent. Those that were originally radiation-induced would be doubled with a doubling dose. But if only 0.1 of 1% were due to radiation, then the doubling dose would be the doubling of the 0.1 of 1%, not 3 or 4%.

DR. GLASS: The difficulty is simply in understanding the definition of the doubling dose. By the doubling dose the geneticist means the radiation dose that will double the spontaneous mutation rate, irrespective of what produces that spontaneous rate.

DR. GORDON: I would like to ask a question. In regard to that figure you gave of 5 million mutations in a 100-million population, is that in 1 generation, 10 generations, 12, or what?

DR. GLASS: That is in 1 generation.

DR. MILLER: The dose to the gonads of the patient who is ill comes in here for discussion. Suppose in a given case the dose to the gonads was high, but still the radioisotope treatment was the treatment of choice, would the fact that there was a chance of genetic damage determine whether these patients should be so treated?

DR. WERNER: Would you take into account how many of these patients had 2 and 3 doses, not just 1?

DR. GLASS: I would have to guess, not being able to find any information on that in the paper by Stanley Clark, which is the paper that was relied upon mainly at that time for the calculations of the NAS Committee[4] of the dosage to the population from medical sources—I have taken 16,000 simply because it is more or less an even fraction of the population of the United States, and I have been able to gather today that it is perhaps not terribly far off from the right figure. If 16,000* persons are actually treated annually with I^{131}, representing .01 of 1% of the total population, then the dosage is 31 r per year per person. Those individuals receive in 1 year about the equivalent of the doubling dose, which we think lies somewhere between 30 and 80 r. Thinking now not in terms of all mutations that might be produced, whether they had such effects as shortening of the life span, or small reductions of intelligence, such things as you could determine only statistically, physiologically, or by an intelligence test—but taking only tangible genetic defects, such

*Estimated number of individuals treated by all the participants of this conference.

as organic anomalies and the like, it may be estimated that there is about a 2% probability of these occurring in the population in each generation. (The total frequency of tangible defects is about 4 to 5%, and Neel thinks that probably half of these are attributable to genetic causes.) Then the effect of this dosage (31 r per year per person) would increase the probability of their own children having tangible medical defects to only 2.2% in the first generation and to only 4% when the full effect is reached. That is, if this dose is about equal to the doubling dose, it would give ultimately an increase from 2 to 4% of tangible genetic defects, and perhaps 0.1 of that would be demonstrable in the first generation. You see, the shift even over all generations is not very large and probably could never be detected in the descendants, and certainly the effect in the first generation is so negligible that we no longer need to be concerned about it.

If you increase the dose per person, while the amount of radioisotope used for the entire population stays the same, the dosage is then given to a smaller fraction of the population. If you increase the dose per person by 10,000, you will increase it to 31 r per year, because the annual dosage delivered from I^{131} to the entire population was estimated to be .0031 r per person. The smaller the fraction of population actually getting the dose, the more each individual will get. In Stanley Clark's patients, the dosage of I^{131} was averaged over the entire population of 160,000,000 people.

DR. SINCLAIR: Would it not be better to start with 16,000 people you do actually irradiate and assume an average dose for them instead of taking Stanley Clark's figures? You have all the data.

DR. WERNER: That is the same point I would like to make. These are individuals who are exposed to radiation from I^{131}—based on 1 dose, 2, or 3 doses—granted they are older. The reason not very many younger people are treated is because many clinics still maintain an age distinction, and the big question is what will happen when this age distinction is abolished.

DR. SINCLAIR: I think the same estimate can be made more simply. Your average may apparently be made up from the dose per person given I^{131}, the number of people involved, and the number in the total population. At least the figure you end up with is approximately what you would expect on this basis if 16,000 people get 1 dose of iodine per year.

DR. GLASS: If I understand you correctly, two things are being confused here. One is the probability of mutations within the entire population; the other is the probability of mutations within the offspring of the particular individuals who are being treated. The figure I was talking about is the probability of mutations within the offspring of the individuals who are being treated, not in the whole population.

The other figure that I put on the blackboard (0.0025 mutations/r/gamete), applies to the entire population. It was in terms of the number of mutations per roentgen per gamete. This new figure [0.005 mutations/r] is the same thing, except that now it is in terms of the mutation rate per baby per roentgen. Calculating then from the dosage estimated by Clark of the I^{131} administered to the population, you would come out with 50,000 mutations in 100 million babies, of which the great majority would be types of mutations that

would not involve any tangible defects. You might get 500 additional cases of tangible defects in the first generation and ultimately 5000 per generation. That would be for each r. This would be for the estimated amount for exposure of the population to I^{131} in 1954.

DR. POCHIN: Would this be another way of putting it, to say that if you have 16,000 patients per year and you give them 3 rads each, and they represent 0.001 of the population, that to the population as a whole you are adding an average of 3 millirads per year which can be compared with natural radiation of 100 millirads per year and represents a 3% increase?

DR. GLASS: Yes, that calculation is correct. The average natural background in the United States is calculated as being composed of about 3.1 r over a 30-year reproductive lifetime, which is the unit geneticists prefer to talk about. Compared to this, luminous dials of watches and other instruments contribute about 0.03 r, fallout about 0.085 r at the current rate of testing, and the medical uses of X radiation, radium, and radioisotopes, according to Stanley Clark, were estimated to contribute a total of 4.6 r, of which 0.1 r was attributable to I^{131} and slightly more than that to P^{32} used in therapy. I noticed in consulting Clark's paper that he made no correction whatsoever for the age distribution of the patients being given the I^{131} and P^{32}, for either diagnostic or therapeutic treatments, nor did he make any correction for age distribution for X-radiation therapy with the sole exception that he eliminated all cancer treatments on the grounds that those individuals were too old to be in the reproductive population. On the basis of a more careful study of that paper, these figures are all probably much too large from the genetic point of view. In any event, it would seem that this dose, in so far as the entire population is concerned, is a large proportion, 1/30, of the total medical exposure and is actually only about 3 times as much as people are getting from luminous dials, or just about the same as from the fallout.

DR. FURTH: I would like to raise a question about the validity of the conclusion that there is no threshold for the amount of radiation that will induce mutations.

DR. GLASS: This is one assumption that I think every geneticist is quite convinced is valid. All the data on all organisms support it; there is no threshold as far as genetic factors are concerned.

DR. MILLER: Certainly the exposure of the luminous dial workers is bad. As to the fallout, it is bad. The natural background is bad. In the NAS report, the medical exposures were sandwiched between all exposures that were bad. Therefore, medical exposures are all bad. Doesn't one sort of naturally draw that conclusion from this type of presentation?

DR. GLASS: One could make the assumption that all radiation that is unnecessary is therefore bad. So far as the genetic effect is concerned, one might say that all mutations, with very rare exceptions, are bad, and the damage done by any agent in terms of the mutations it produces is to be weighed against the compensations that are obtained. Geneticists would certainly not maintain that because the harm is great, we should necessarily stop giving treatments or exclude the use of X radiation in diagnosis. Yet if there were other ways of achieving the same ends without producing mutations, I am sure the geneti-

cists would approve.

DR. MILLER: The point I am bringing out is that disease is also bad, yet from the reaction of the public and of the press, it certainly looks as though medical exposure to radiation is all bad. I think this is a very unfortunate method of presentation.

DR. GLASS: The reaction of the public to any presentation of scientific material is likely to be, so far as I can see, "all bad." I said something over a television program about radiation from luminous dials in order to put the amount received from fallout in the proper perspective. The consequence was not at all what I intended. There was great alarm about the danger from luminous dials.

DR. FURTH: In your calculations you figured that the number of tangible genetic defects would go up to 2.2% and finally wind up at 4% in all descendants. Does this mean that at some later periods the percentage of tangible defects will get considerably above a 4% average; or is this 4% based on the original first generation?

DR. GLASS: The 4% is the final equilibirum value that would be reached.

D. Usefulness of radioisotopes of iodine other than I^{131}.

DR. WERNER: Years ago Dr. Chapman used I^{130} in the treatment of hyperthyroidism. At the present time Dr. Berman, Dr. Becker, and others are using another isotope, I^{133}. I will ask them to say a word about this agent.

DR. BERMAN: The possible use of various radioiodine isotopes in the treatment of hyperthyroidism was considered as a result of the studies reported earlier. Again, the criterion for the use of an isotope was the minimal radiation to the blood of the patient for a desired dose to the thyroid. It was assumed that on a rad basis, all isotopes are equally effective, regardless of geometry, irradiation rate, energy of particles, etc.

Four hyperthyroid patients were treated with I^{133} (half-life, 21 hrs.). Radioiodine kinetic studies were done on these patients before treatment, and the estimated dose was calculated from the kinetics. The blood radiation to each of the patients for each of the isotopes relative to I^{131}, for a fixed thyroid dose, is shown in Table 22. As can be seen, I^{133} delivers the lowest dose to blood for all patients. The estimated number of rads delivered during treatment to the thyroid (T) and blood (S) of each patient are also given.

I^{133} was supplied to us by the Brookhaven National Laboratory. Initially, it has an I^{131} (8.1 days) and I^{135} (6.7 hrs.) contamination. When a proper time is allowed to elapse, the I^{135} content becomes negligible, and I^{133} may comprise 10-20% of the total number of mc. Because of the I^{131}, the actual advantage of the isotope is lower than pure I^{133}, as shown in Table 22.

This work is still in progress. It is hoped that in addition to reducing radiation to the blood, we may be able to evaluate the number of rads necessary to treat hyperthyroidism using I^{133}, the relative effectiveness of β particles of various energies (.484 Mev for I^{133} against .195 Mev for I^{131}), and the possible biologic effect of high irradiation rates.

So far, I^{133} seems to be a desirable and practical isotope to use.

Table 22

BLOOD TO THYROID DOSE RATIO FOR VARIOUS IODINE ISOTOPES, NORMALIZED WITH RESPECT TO I^{131}

Patient	Gland weight (g)	Hyperthyroid patients						T (rads)	S (rads)
		I^{124} T 1/2 = 4 d E_γ/E_β = 2.45	I^{126} 13 d 1.12	I^{130} 12.5 hrs. 7.95	I^{131} 8.1 d 2.04	I^{133} 21.0 hrs. 1.20	I^{131} / I^{133} mixture		
B.R.*	25	.96	1.07	1.04	1	.87	.92	14,700	21.3
C.L.	45	1.08	.84	1.45	1	.66	.79	8,063	9.1
G.R.	40	.93	.91	.74	1	.59	.73	8,960	23.4
M.A.	30	.80	1.19	.51	1	.38	.48	11,525	22.0

*Kinetics of therapy altered from tracer.

DR. BECKER: We have recently been faced with the problem of treating a group of hyperthyroid patients of the type mentioned earlier by Drs. Keating and Rall. These patients demonstrated very rapid turnover rates and very high blood levels of radioactive iodine. Dosimetry calculations of the type just presented by Dr. Berman showed that these patients would receive exceptionally high doses of radiation to the blood from I^{131} if it were administered conventionally. By using I^{133}, however, calculations have shown a varying advantage in reducing radiation to the blood. The degree of advantage in using this short-lived isotope varies with the kinetics of iodine in the individual patient.

I should like to present pertinent data from 4 patients who received I^{133} as treatment for hyperthyroidism. All received intravenous tracer doses of about 100 μc of I^{131}. Frequent determinations were then made of the activity in the neck region and in the blood. Thyroid weight was estimated by palpation, and dosage was calculated by the methods outlined previously to deliver about 9000 rads to the thyroid. Actual dosage delivered was calculated from the behavior of the therapy dose.

The first patient, F. M., is a 56-year-old woman who when first seen had a 4-month history of moderately severe hyperthyroidism. Laboratory data included a BMR of +54 and a chemical PBI of 15.4 mcg%. The behavior of a tracer dose of radioiodine can be seen in Figure 31. Within 1 hr. after administration of the tracer, almost 100% of the dose had accumulated in the patient's thyroid. At the 24th hr., the amount in the neck had decreased to 60%, and at the 48th hr., it was down to 45%. The protein-bound I^{131} showed a similarly rapid rise to unusually high levels, reaching a maximum of 5.5%/L of the administered dose by the 36th hr. All of the radioiodine in the blood was protein-bound within 1 hr. Calculations indicated that 10.3 mc of I^{131} would be required to deliver 9000 rads to the thyroid and would, at the same time deliver over 46 rads to the blood. A dose of 15.4 mc of I^{133} would deliver the same radiation to the thyroid, but decrease the total radiation to the blood by half. The latter dose was given, and the actual dose delivered to the thyroid proved to be 11,500 rads.

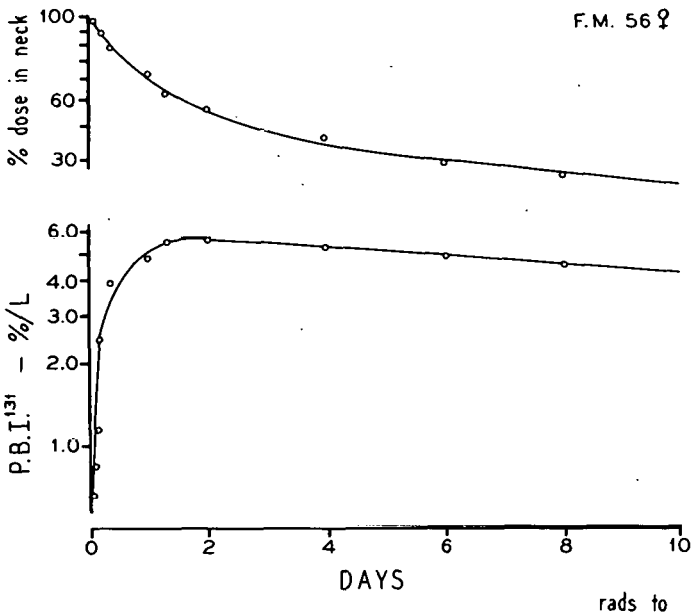
The patient had a partial remission of her disease and required retreatment 4 months later.

The second patient, H. G., is a 52-year-old woman who developed Graves' disease while taking desiccated thyroid for well-documented hypothyroidism.

Laboratory data included a BMR of +35 and a chemical PBI of 13.8 mcg%. Tracer studies (Figure 32) showed that almost 100% of the dose was present in the patient's neck by the 3rd hr., with 74% present in the neck at the 24th hr., and 53% at the 48th hr. By the 4th hr., 83% of the iodine in the blood was protein-bound. A peak level of the PBI^{131} of 5.4%/L was reached at the 72nd hr.

To deliver 9000 rads to the thyroid, it was calculated that 7.4 mc of I^{131} would be required with a consequent blood radiation of 32 rads. A dose of 13.8 mc of I^{133} was given with consequent radiation to the blood of 30% less than might be expected with I^{131}.

The patient noted slow gradual improvement following therapy and was thought to be euthyroid 4 months later.



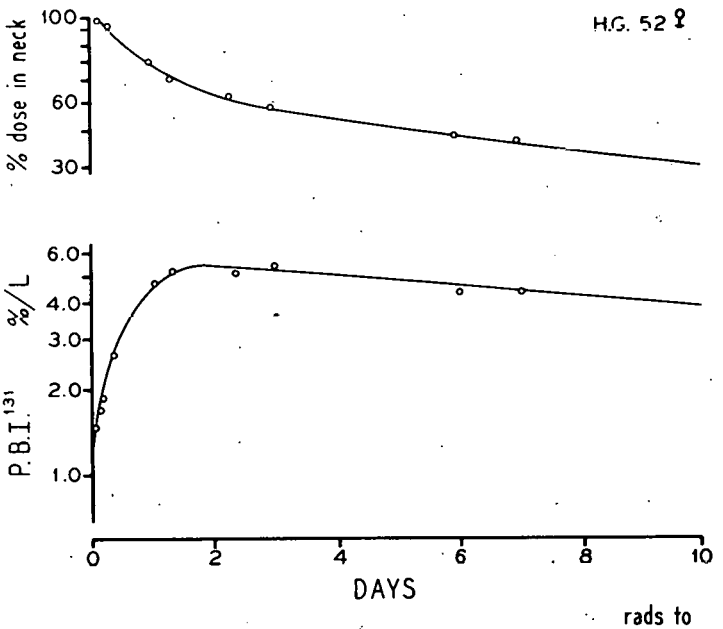
			Mc.	rads to Blood
Thyroid weight	30 gms	I^{131}	10.3	46
Thyroid radiation	11,525 rads	I^{133}	15.4	22

Figure 31. In this and Figures 32, 33, and 34 the neck uptake and protein-bound I^{131} are plotted on the ordinate on a semi-logarithmic scale. Time, in days, is represented on the abscissa. The table lists the number of mc of the two isotopes of iodine calculated to deliver 9000 rads to the thyroid and the consequent blood radiation from each isotope. The actual dose of thyroid radiation received (as calculated from the behavior of the therapeutic dose) is also listed as is the estimated thyroid weight.

The third patient, M. B., is a 49-year-old woman with a 2-year history of relatively mild hyperthyroidism. Tracer studies (Figure 33) showed 90% of the dose in the neck at the 3rd hr., with 74% in the neck at the 24th hr., and 65% at the 48th hr. By the 5th hr., 70% of the radioiodine in the blood was protein-bound. Calculations suggested that a slight advantage in terms of radiation to the blood had been achieved by using I^{133} (23 rads to the blood with I^{131}, 21 with I^{133}).

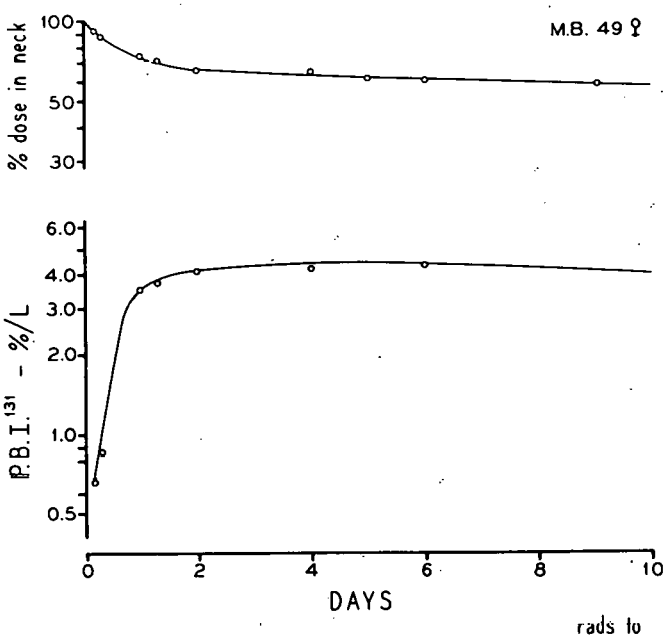
The patient felt better within a few weeks after receiving the therapeutic dose and has continued well until the present, 3 months later, when she is thought to be euthyroid.

The fourth patient, E. C., is a 36-year-old woman with a 3-year history of the symptoms and signs of severe thyrotoxicosis. Her BMR was +80, cholesterol 125, and chemical PBI 19 mcg%. Tracer studies (Figure 34) showed rapid pickup of radioiodine by the thyroid, reaching 93% of the dose by the first hr. and 100% by the second. In contrast with the pre-



			Mc.	rads to Blood
Thyroid weight	40 gms	I^{131}	7.4	32
Thyroid radiation	8970 rads	I^{133}	13.8	23

Figure 32. See legend for Figure 31.



			Mc.	rads to Blood
Thyroid weight	25 gms	I^{131}	5.4	23
Thyroid radiation	14,700 rads	I^{133}	11.7	21

Figure 33. See legend for Figure 31.

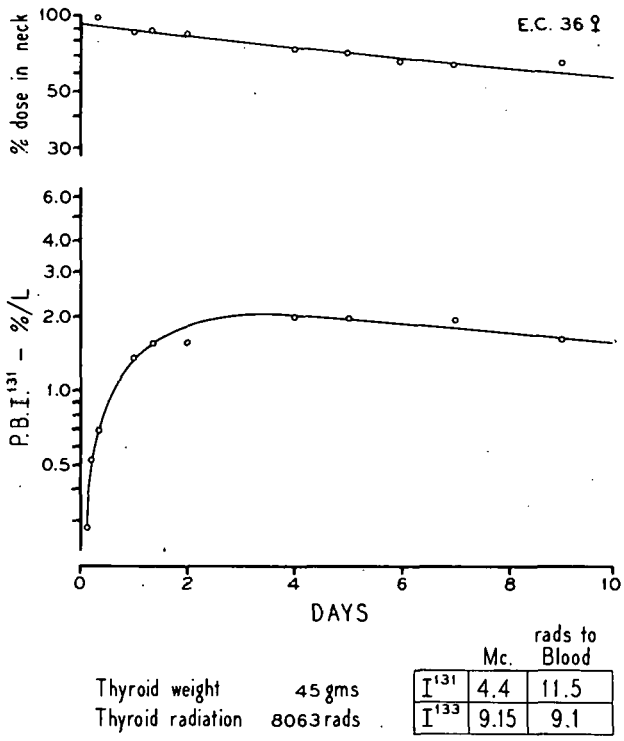


Figure 34. See legend for Figure 31.

vious patients, the thyroid radioactivity decreased more slowly. Thus at the 24th hr., 88% of the I^{131} was in the neck, and at 48 hrs., 85% was present. Five hours after administration of the tracer, 90% of the iodine in the blood was protein-bound. The PBI^{131} reached a maximum level of 1.9%/L by the 4th day.

As can be seen from Figure 34, dosimetry calculations showed a relatively slight advantage in giving I^{133}. However, 9.15 mc of I^{133} were given with a total of about 8000 rads delivered to the thyroid. The patient first noted improvement 4 months after treatment, and since then has had appreciable diminution of all symptoms. When last seen 6 months after therapy, the patient appeared to be euthyroid.

In none of the 4 patients studied was there any evidence of symptoms that were in any way suggestive of radiation sickness nor did any of the patients show symptoms or signs of thyroiditis.

These preliminary case reports suggest that in selected patients, particularly those with rapid turnover rates and high blood levels of radioactive iodine, a short-lived isotope of iodine, I^{133}, has a varying advantage in decreasing the radiation delivered to the blood, while delivering the same radiation dose to the thyroid.

DR. POCHIN: I should like to mention a 2-hr. uptake test that we use with I^{132} where the slowness of uptake into the thyroid gives a very appreciable advantage in addition to

that due to difference in half-periods between I^{132} and I^{131}. The two are compared in Figure 35, showing the dose to the thyroid and ignoring the discharge from the thyroid. In comparing I^{131} and I^{132}, the relatively slow rise of radioiodine concentration in the thyroid produces an appreciable alteration in the calculation for rads to the thyroid per μc.

$$D = \frac{PK}{100G} \int_0^{\infty} (1 - e^{-\log_e 2 \frac{t}{T}}) e^{-\log_e 2 \frac{t}{S}} dt$$

$$= \frac{P K S^2}{100 \log_e 2 \, G (S + T)}$$

for P% uptake in G g gland with T as time constant of uptake and isotope of halfperiod S, K rads/hr per μc/g; neglecting discharge of radioiodine from the gland.

For I^{131} S = 192 hr. K = 0.43
For I^{132} S = 2.3 hr. K = 0.96

For children, taking P = 45%, G = 5 g, T = 3 hrs.

I^{131} 33 rads for 3 μc
I^{132} 0.4 rads for 3 μc

For adults, taking P = 30%, G = 20 g, T = 6 hrs.

I^{131} 5.5 rads for 3 μc
I^{132} 0.04 rads for 3 μc

Figure 35. Calculations of thyroid β and γ irradiation from test doses of I^{131} and I^{132}.

For example, in children (Figure 35) if you take a normal, or what is said to be a normal uptake in children, of 45% of the dose with a 5-g gland and a rather rapid uptake into the thyroid, you will get something like 33 rads per 3 μc test dose of I^{131}, and about 0.4 rads with I^{132}, which is an advantage of 80-fold for I^{132}. For adults with a rather slower uptake into the thyroid, the advantage is something like 140-fold. The greater counting advantage per μc of I^{132} balances its faster decay, so that equal doses of I^{132} and I^{131} will give about equal counting rates 2 hrs. later. I would have felt that using a test dose of say 3 μc of I^{131} in children, a nonhomogeneity factor of something like 3 for uneven distribution within the thyroid would bring the dose to 100 rads at some points and well within reach of figures of 200 rads or more, which have been suggested as possibly carcinogenic in children. We have checked whether any of the tellurium distils over into the dose flask and have not found it to do so. I do not know your conditions of supply. With our tellurium we have been unable to find it chemically in the distillate, and we have been unable to find any loss of radiotellurium from the source.

DR. RALL: It is my understanding with the I^{132} generator that we have been using,

that the very strong garlic odor which the patients complain about represents the biologic manifestation of stable tellurium which is carried over. Isn't that so?

DR. CHILDS: Apparently with the tellurium generator some of the stable as well as radioactive tellurium is carried over into the I^{132} fraction because of incomplete re-precipitation of the tellurium. We have stopped using this generator as a source for I^{132} for patients because of this and other problems. I believe the generator is being re-designed.

DR. WERNER: Is there anyone else with experience with either I^{132} or I^{133}?

Part II — Complications of I^{131} Therapy

A. Hypothyroidism.

DR. WERNER: We had planned to have a session on hypothyroidism and recurrence in later years after I^{131} therapy, but I think the figures have been pretty well brought out; is there anyone who has less than 7% incidence of hypothyroidism?

DR. FEITELBERG: Our study of the incidence of myxedema by years is presented in Table 23. It is based on 1611 patients on whom we have a follow-up of from 2 to 10 years.

Table 23

INCIDENCE OF MYXEDEMA IN PATIENTS TREATED AT THE MOUNT SINAI HOSPITAL, NEW YORK, FOR HYPERTHYROIDISM WITH I^{131}, AND FROM WHICH CURRENT FOLLOW-UP DATA ARE AVAILABLE. YEARS LISTED ARE THE YEARS OF TREATMENT.

Year	Total treated (No.)	Myxedema	
		(No.)	(%)
1947	14	2	(14)
1948	60	6	(10)
1949	132	19	14
1950	238	16	7
1951	350	25	7
1952	339	17	5
1953	281	14	5
1954	197	6	3
Total	1611	105	6.5

We had lost track of about 1400 patients. Our original incidence was over 10%; it has dropped to 3 to 5% in recent years. The average is about 7%, in agreement with most reports. We came to realize, however, that there is one obvious factor in our statistics that works against us: patients with myxedema are generally more faithful attendants of the clinic; they continue to need our help, or believe that they do. Cured patients have fewer motives to follow our invitation to revisit us. It is probable, therefore, that we lose more cured patients and retain more of the myxedemas. If this is a relevant factor, then we probably did relatively better in the past years than it appears and have not learned as much as the statistics seem to indicate. Roughly speaking, this consideration indicates that the incidence of myxedema has been actually less than 6 to 7%, but certainly not less than 3 to 5%.

DR. WERNER: I just want to bring out one point which is that we have to talk about the early incidence of myxedema and the late incidence of myxedema; I think that was touched upon previously by someone. In short, early in our experience we found our incidence of hypothyroidism to be about 7.6% a year or two after I^{131} was given (Table 24).

Table 24

PERMANENT HYPOTHYROIDISM — 78 OF 525 PATIENTS

Years after I^{131} therapy	No. of patients
0 - 1	40
1 - 2	1
2 - 3	12
3 - 4	12
4 - 5	3
5 - 6	3
6 - 7	3
7 - 8	3
8 - 9	0
9 - 10	1
Summary	
Within 1st year	40 (7.6% of 525 patients)
After 1st year	38 (7.2% " " ")
Total	78 (14.8% " " ")
Type of goiter before treatment	
Toxic diffuse	76
Toxic recurrent	1
Toxic nodular	1
Total	78 (14.8%)

Then when these patients were followed carefully through the years, it was found that as late as 10 years after I^{131} therapy, patients up to then documented as euthyroid by all criteria were still becoming hypothyroid. I believe the incidence of myxedema will have to be reported in terms of a very careful follow-up. Also, I would stress that one must use all available tests or one is apt to miss these people. One has to do an uptake, a serum precipitable iodine level, and often subject the patient to a trial of thyroid and cessation of the trial in order to confirm the diagnosis. Many of these patients, and I have tried this many times, look absolutely normal, so that the surgeon or some trained observer when called in will pass them by as not being hypothyroid. One gets to know these patients, or becomes suspicious, and then finds they are truly hypothyroid with a good response to thyroid therapy. I wonder if others have had the same experience.

DR. GORDON: I would like to document the same observation. When we presented our first 350 cases about 3 yrs. ago, both in the literature and at the Oak Ridge Symposium, our overall post-treatment myxedema rate was 2.4%. At present when we add up almost 3 times that many patients, it is about 4%, and this increase is due to some extent to these cases, to which Dr. Chapman referred earlier, of late myxedema that appears several years after therapy.

DR. STANBURY: There are a lot of patients wandering around who appear perfectly normal, but when one determines a PBI or an uptake on them, he finds that they have a genuine severe hypothyroid state.

DR. CHAPMAN: We have seen a lot of such people. I was just commenting on a fellow who had a PBI of 1 to 2, a low uptake, and a low BMR; he did not complain very much, he looked hypothyroid and he was, but such patients are not complaining too much about it. They clearly are in a state of hypothyroidism without being in complete myxedema. In other words, they are manufacturing some hormone and get along with it. When you put them on a little thyroid, they may or may not feel better; it is variable.

DR. WERNER: One hypothyroid patient came into the hospital feeling fine until he came down with pericardial effusion and cardiac tamponade.

We should record the recurrence rate, also, after I^{131} therapy and a long-term follow-up. I think we have very few patients who have had recurrences after they remained euthyroid over 1 yr. We have 1.1% of our 525 patients.

DR. DOBYNS: Will you define the basis on which these patients were judged euthyroid and then judged to have recurrence and what the intervals of time really were? Recurrence is so rare that these changes must be defined clearly to be convincing.

DR. WERNER: If they have been euthyroid for 1 yr. and then become hyperthyroid again. In other words, we try to compare those figures with those of surgery where, over a 15- or 20-year follow-up period, the incidence of recurrence is about 10%. We had 1.1% or 6 patients in 10 yrs.

DR. CHAPMAN: We have 3 documented cases, euthyroid for many months to a year, with normal indices, then the disease came back again.

DR. CLARK: We have 3 that were euthyroid by all criteria; 1 for 2 yrs. and 2 for 3

yrs., then they developed classical signs and symptoms of hyperthyroidism.

DR. WERNER: The chances are, in all probability, as far as recurrence rate goes, that this is much less likely to develop after I^{131} than it is after surgery.

B. Iodinated compounds in blood after therapy and their relation to thyroid storm.

DR. WERNER: We want to go on to the question of what is released by the thyroid into the blood after I^{131} therapy, such as thyroglobulin and other compounds that one sees in patients with thyroid cancer after I^{131} therapy. Also we should discuss whether the increase in PBI after I^{131} treatment is enough to explain the several reported deaths from thyroid storm; there are two in the literature in which death was reported to occur about 7 days after the therapy was given. Whether that was sheer coincidence or whether there could have been a causal relationship, is a subject for speculation. We have had 1 patient at our institution who, on the 4th day after I^{131}, went into unquestionable storm. Whether this was fortuitous or whether there was a relationship is unknown. I have asked Dr. Rall if he would discuss this.

DR. RALL: I don't know that there is a great deal I can say about the iodine compounds employed. I can just report the clinical experience at Memorial Hospital when I was there. We did not see any storms after I^{131} treatment. On the other hand, there is certain proof that if patients with severe Graves' disease and some other complications are not hospitalized but are treated with radioiodine, they may develop storm. It certainly is a normal sequence of events with very severe Graves' disease, because certainly I^{131} will have no effect within a week or two so far as decreasing thyroid function.

We might first review the iodine compounds that may be detected in the blood. The major thyroid hormone in blood is thyroxine, which comprises at least 90% of the total. Triiodothyronine can usually be detected as a radioactive substance in amounts of 1 to 5% of the total. Recently, 3-3' diiodothyronine and reverse T3 or 3, 3'-5' triiodothyronine have been reported to occur in the blood. Thyroglobulin has been found in the blood, and Compound X. I might make a brief comment as to the circumstances in which these various iodinated materials may be seen.

In Graves' disease, unless the iodinated compounds are labeled with massive amounts of radioiodine, we have only seen thyroxine and triiodothyronine in the blood, usually in a ratio (radioactive) of 20:1. As Benua and Dobyns have noted, triiodothyronine is usually maximal at an earlier time than thyroxine and decreases more rapidly. Their data suggest that triiodothyronine is more likely a thyroidal precursor of thyroxine than that it is formed peripherally from thyroxine.

In euthyroid individuals, thyroxine is again the main iodinated constituent of blood. In subjects with cancer of the thyroid, the iodinated materials in blood become more complicated. Thyroxine is always seen and triiodothyronine may be seen, occasionally in amounts up to 10% of the total serum radioactivity. In addition, Compound X has been observed in

the serum of about 65% of patients with cancer of the thyroid. Compound X is an iodinated protein with many similarities to albumin and, in fact, it is very difficult to separate it from serum albumin. It is not, however, a simple iodinated albumin but a different and special protein. It can be hydrolyzed to yield monoiodotyrosine and an iodinated thyronine. Many more data are available on this interesting subject but they are not really pertinent to this discussion.

Thyroglobulin deserves a special word. We have only seen it after destructive doses of radioiodine. In general, a dose of about 3000 r to thyroidal tissue in the second 24 hrs. after the administration of the radioiodine is required to produce significant amounts of thyroglobulin in the serum. This somewhat cumbersome way of expressing the radiation was necessitated by the fact that at the time we did this study, we could be more sure of our figures on the second day than on the first. Hence, we may find thyroglobulin in the blood of any type of patient, euthyroid, hyperthyroid, or cancerous, if the dose of radiation is large enough and there is any active thyroid tissue.

3-3' Diiodothyronine and 3,3'-5' triiodothyronine (reverse T3) have been identified, and their biologic activity has been investigated by Roche and Michel. They have reported that in rats, as much as 25% of radioactivity in blood may be in the form of the former compound. Reverse T3, on the other hand, is rarely present in a quantity exceeding 5% of the total serum radioiodine. There is now some disagreement as to the biologic activity and importance of these compounds.[5] We have been unable to identify these materials in any of the patients we have studied, although the separation of the compounds is difficult. At the present time, I am afraid we cannot give any clear idea of either the presence or physiologic significance of these compounds in the human being.

DR. WERNER: One question—at what days after I^{131} therapy in Graves' disease do you get a rise in PBI, and at what day is the maximum reached?

DR. RALL: When we do get thyroglobulin, it usually appears about the second day, reaching a peak at from 5 to 7 days, and then declining. That is very close to what Reese found with the PBI changes.

DR. DOBYNS: In the course of doing butanol extractions preliminary to the daily quantitative chromatographic fractionations of the free iodinated amino acids in treated patients, we have observed that the extractability falls appreciably after a time. It usually occurs about the 7th to 9th day. I hesitate to say for the record that the nonextractable portion is thyroglobulin, but it behaves in some respects like thyroglobulin. We cannot predict which kind of patient will show decline in extractability. It is usually found in patients with larger treatment doses. Presumably, the decrease in extractability of radioactivity coincides with deterioration of the gland.

DR. STANBURY: I think it is unlikely that there would be very much 3-3' diiodothyronine in the peripheral blood because in the half a dozen or so patients we have studied this material is degraded with remarkable rapidity. At the end of an hour, less than 25% of the administered radioactivity is in this form.

C. Recurrent tissue after therapy.

DR. WERNER: The question of the appearance of nodular tissue after I^{131} therapy came up. We have had 2 patients in our series who have had no palpable glandular tissue for several years after treatment, who then developed a recurrence of palpable tissue thereby raising the question of radiation effect. Dr. Frantz would like to discuss these cases.

DR. FRANTZ: The first case was a woman of 65 treated for hyperthyroidism with an I^{131} uptake of 53%. The gland was described by Dr. Werner ". . . a big firm gland, 3 x 2 x 2 cm, and nodular." A total of 8.5 mc was administered in 2 doses, October, 1948, and March, 1949. Two months after the first dose, Dr. Werner described the thyroid as follows: "Gland firm, with 1-cm nodule in palpable 2.5 x 1.5 x 0.5 cm remnants bilaterally." The gland remained hard and palpable for 1-1/2 yrs. At 2 yrs. and 9 months after treatment, the gland was said to be unpalpable and remained so until 4-1/2 yrs. after treatment, when a recurrent nodule was first palpable on the left side. There was, therefore, an interval of somewhat over 2 years in which it was not possible to palpate the gland. Operation was then advised, but the patient refused surgery for 2 years. She finally submitted to it when the nodule became larger. At surgery, a 1-cm nodule was found in the left lobe. The rest of the gland was described as small and multinodular, the nodules varying from 3- to 5-mm in size.

One nodule was removed from each lobe. Both of these proved, on histologic examination, to be adenomas. One had fairly active-appearing cells which, however, did not suggest malignancy. This was the nodule from the left lobe. The other nodule showed involutional change.

It is my assumption, therefore, that these were probably originally "hot" nodules and were responsible for her hyperthyroidism. In other words, these adenomas were present before therapy, and the I^{131} cannot be indicted in this case as having initiated a neoplasm. When the nodules again became palpable, I assume that in one, at least, this was due to compensatory hypertrophy. The increase in size of the other nodule might have been due to hyperinvolution.

The second case was a woman of 60, also treated for hyperthyroidism. Her I^{131} uptake was 61%. At this time, Dr. Werner made a clinical diagnosis of "toxic nodular goiter," and because she refused operation, the patient was treated by I^{131}, a single dose of 5.9 mc. Three months after treatment she was euthyroid, and the thyroid gland had decreased in size. By 15 months, it was no longer palpable, but a nodule became palpable 3 years and 9 months after treatment. During all this time she remained euthyroid. At operation, 4 years after therapy, the nodule proved to be one of multiple Hürthle cell adenomas in a clear-cut Hashimoto struma. Some of these adenomas displayed somewhat atypical cells, but I am not inclined to consider them malignant. We know that in Hashimoto struma there is a fairly high incidence, not only of adenomas, but also of carcinomas. To attribute these adenomas, therefore, to the effect of radioiodine would, I think, be unjustified. All that can be

said, therefore, about these two cases is that nodules that were present before treatment disappeared temporarily and then reappeared a few years later while both patients were still euthyroid.

These patients were operated upon because of our fear of the possible carcinogenic action of I^{131}. In this connection, it is well to review our past experience with patients treated by surgery for Graves' disease. The amount of tissue removed varied according to the surgeon's judgment at the time of operation. No matter how much or how little was taken out, the surgeons got good results in at least 90% of the cases. In the late follow-up of these euthyroid patients, we have all seen some with recurrent nodules. We have regarded these nodules without alarm as being due to simple compensatory hypertrophy. With the advent of I^{131}, however, we have become concerned about the possible malignant character of any nodule that appears after this therapy. I would agree that if I^{131} treatment had been given for a toxic diffuse goiter, it would be highly instructive, if not mandatory for the patient's safety, to remove any definite circumscribed nodules that might appear later. The two cases cited, however, were nodular before treatment was instituted so that I^{131} can hardly be said to have caused the appearance of the nodules de novo.

D. Course of ophthalmopathy after I^{131} therapy and after surgery.

DR. WERNER: Comparable figures on the incidence of eye changes, as we will hear later from Dr. Dobyns, are extremely difficult to secure. In our clinic we use a nomenclature that was planned to represent the clinical appearance of the patient. "Noninfiltrative" means that the patient had proptosis but no evidence of edema; and "infiltrative" means that there was muscle involvement, chemosis, or other evidence of the very severe type of involvement that often leads to destruction of the eyes. These 2 categories are commonly recognized, although in all probability the mechanisms responsible for both are the same. After accumulating our data, we were quite disappointed not to find comparable surgical figures.

At any rate, 163 of our 525 patients had the eye changes of which we just spoke. These were classified (Table 25) with the help of Dr. Robert Day, an eye man especially interested in our material. Ninety-two patients were described as "noninfiltrative" and 71 as "infiltrative." Included in the 71 are most of the patients that the surgeons did not want to operate upon because of the presence of these eye changes. It was extremely interesting to find out first, that in the noninfiltrative group, 6 of the 92 patients showed edematous or infiltrative changes after I^{131} therapy, but since only 1 wound up with evidence of permanent injury other than protrusion of the globes, we put down as improved or static 91 or 99% of the group. In the infiltrative group, we had 71 patients. Here, with patients, as I said before, who were not candidates for surgery, 90% did quite well; they either showed significant improvement or were no worse as a result of I^{131} therapy. On the other hand, there were 7 of this group who developed severe trouble after the administration of I^{131},

with permanent eye changes in the form of muscle fibrosis or weakness. One older man developed optic neuritis and is almost completely blind. The total doing poorly, therefore, is only 1.3%, of which none required orbital decompressions or lost their eyes. Actually these figures are comparable or perhaps even better than those obtained as a result of surgery. I hope Dr. Dobyns in his discussion on the course of ophthalmopathy after surgery will make some estimate of surgical results. I do think the figure of 1.3% of patients becoming "worse" should be confirmed by more information, not only obtained from I^{131}-treated patients, which I hope will be brought out this morning, but also from surgery. The subject is now open for discussion.

Table 25

CLINICAL COURSE OF OPHTHALMOPATHY — 163 OF 525 PATIENTS

Noninfiltrative — 92 patients		
Improved		2 (2% of noninfiltrative group)
Static		84
Change to infiltrative		6 (6% " " ")
Improved	3	
Static	2	
Worse with muscle fibrosis	1	
Improved or static		91 (99% " " ")
Infiltrative — 71 patients		
Improved		6
Static		58
Improved or static		64 (90% of infiltrative group)
Worse		7 (10% " " ")
Muscle fibrosis or weakness	7	
Optic neuritis and amblyopia	1*	
Summary		
Both types of ophthalmopathy		
Improved		8 (1.8% of 525 patients)
Static		148
Worse		7 (1.3% " " "

*Also included under "muscle fibrosis."

DR. JAFFE: How many patients, if any, developed this complication after I^{131} in which there was no evidence of exophthalmos prior to I^{131}?

DR. WERNER: An analysis of our cases of ophthalmopathy in regard to time of onset is shown in Table 26. Most of the cases had eye changes prior to I^{131}, but 10 patients developed either infiltrative or noninfiltrative ophthalmopathy after I^{131} therapy. Eight patients had a change from a mild noninfiltrative to a severe infiltrative form after I^{131}. There was a total of 14 or 2.7% of the patients with onset of infiltrative changes after I^{131}.

Table 26

ANALYSIS OF OPHTHALMOPATHY AND TIME OF ONSET
163 OF 525 PATIENTS

Type of ophthalmopathy	Time of onset				Change after I^{131} to infiltrative ophthalmopathy
	Before I^{131}	After I^{131}			
	No. patients	Hyper.	Eu.	Hypo.	(No. patients)
Toxic diffuse					
Noninfiltrative	47	1	1	0	4
Infiltrative	43	2	2	1	--
Toxic recurrent					
Nonilfiltrative	36	0	0	0	2
Infiltrative	17	1	1	0	--
Toxic nodular					
Noninfiltrative	7	0	0	0	0
Infiltrative	3	0	1	0	--
Total	153	4	5	1	6

Summary

Patients with onset after I^{131}		10
Noninfiltrative	2	
Infiltrative	8	
Noninfiltrative becoming infiltrative after I^{131}		6
Total with onset of infiltrative ophthalmopathy after I^{131}		14 (2.7% of 525 patients)

DR. McCULLAGH: Were the eyes of these patients all examined consecutively, whether or not they showed signs in the beginning?

DR. WERNER: Yes, every patient was examined carefully by Dr. Day; examined clinically and with the exophthalmometer and then examined on follow-up visits.

DR. McCULLAGH: What criteria do you use for separating the infiltrative from the noninfiltrative?

DR. WERNER: As I said, clinical criteria; if there is chemosis, muscle weakness, especially diplopia, or if there is corneal ulceration, they are called "infiltrative."

DR. McCULLAGH: Do you put in the infiltrative group all the ones that show bulging of the lids, for example?

DR. WERNER: If there is significant infiltration of the lacrimal gland; most with simple proptosis we call nonfiltrative.

DR. McCULLAGH: You mentioned the patient who had optic neuritis and who was becoming blind. Did that patient have very severe proptosis and conjunctival edema? Did the patient have marked or visible changes in the ocular fundi? Was there choking of the discs?

DR. WERNER: That patient started out perfectly well so far as the eyes were concerned. He had also diabetes and pernicious anemia. He was regulated, however, so far as the diabetes was concerned. Suddenly, after several weeks, he started to develop suffusion of the conjunctivae and diplopia, and then became amblyopic. There was no choking of the discs. The amblyopia remained. We wondered whether this occurred as part of his diabetes or was due to his anemia, but everyone finally concluded that it was more likely due to I^{131}.

DR. McCULLAGH: But he did have hypermetabolism.

DR. WERNER: He had hyperthyroidism.

DR. McCULLAGH: We do not have accurate enough statistics, unfortunately. We have only recently started to get consistent measurements on all patients. I do not believe that our figures differ materially from those shown. We have had a relatively large number of patients treated with propylthiouracil, and we believed that their eyes behaved the same as did those of postsurgical cases.

DR. RALL: I cannot say much except that we followed a small series for a while with measurements at rather frequent intervals after I^{131} therapy. Without having the statistics with me, my impression was that the majority of them showed protrusion of the eyes after therapy which was very similar, although somewhat slower in developing, than what Brown Dobyns found in patients who had surgery. It is an old story, and everyone here knows it. In many instances, there would be a measurable increase in proptosis when the eyes appeared to be improved. Nevertheless they did show increased proptosis in the majority of the cases.

DR. DOBYNS: I am skeptical about trying to compare the effects of surgery with the effects of radioiodine on exophthalmos. We all gain impressions. Frankly, I do not have any figures to present on the radioiodine nor on the surgical patients. We see a considerable number of these patients with eye problems because of our attempts to assay a factor in the serum. Some have been treated and others we treat with radioiodine or surgery. We are seeing more and more radioiodine-treated cases. There is no question; very severe progressive exophthalmos does arise following radioiodine therapy.

If you go back and review the old literature before the turn of the century, when the surgeon was not so bold about doing thyroidectomies, there are many reports describing enucleations, corneal ulcerations, or loss of vision associated with severe thyrotoxicosis. Progressive exophthalmos is not a disease that necessarily follows correction of hyperthyroidism. Graves' disease is a disease with multiple facets; goiter, hypermetabolism, exophthalmos, and emotional instability. You may initially have a goiter and no hypermetabolism, at which time the diagnosis probably will be colloid goiter. Perhaps after some months or years, thyrotoxicosis will make an appearance or the patient will bloom out with the eye problem. You may see a patient with hypermetabolism without a goiter; you may see the eye problem alone; you may see a patient that has been observed solely by the

ophthalmologist, because the only symptom is ophthalmoplegia and called orbital myositis. Similarly, destruction of the thyroid cures hyperthyroidism, but it does not cure the cause of Graves' disease. The eyes may progress whether surgery or I^{131} is used.

To illustrate how one of these things can come alone, I should like you to see Figure 36. This is a photograph of a man who had protrusion of one eye 4 years ago. The first eye was 8 mm more prominent than the second. A tarsorrhaphy was performed. His first radioiodine uptake was 22%. He had no hyperthyroidism nor goiter until a few months ago. He now has auricular fibrillation and a goiter of considerable size. His I^{131} uptake has risen progressively. The second eye has now protruded as far as the first. This is a moderately extreme example of an eye problem that existed for 4 years before the hypermetabolism or anything else came into the picture.

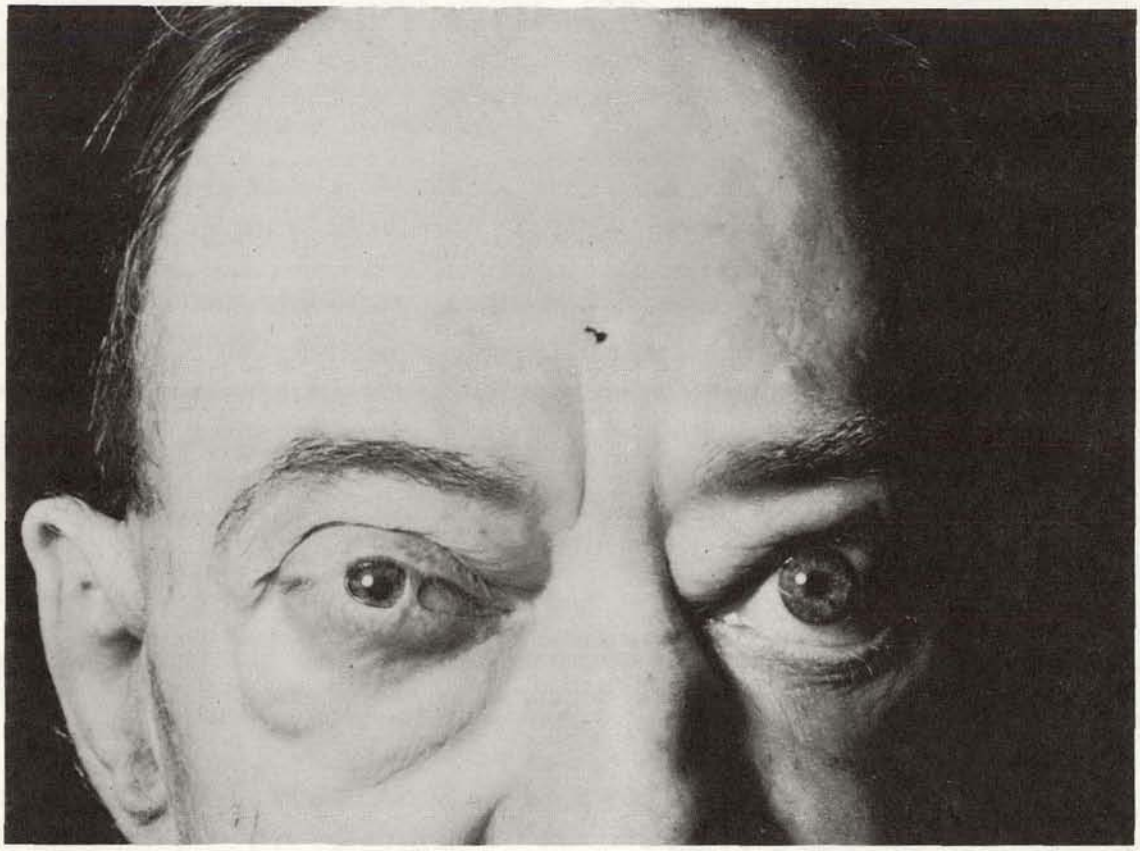


Figure 36. Patient in which there was protrusion of the eyes prior to diagnosis of hyperthyroidism or goiter.

I am certainly not convinced that radioiodine therapy is more kindly to the eyes than surgery. But I do feel strongly that hypometabolism is a serious threat to a patient who has such an eye problem. In the hypothyroid state, water storing occurs in the tissues. This, superimposed upon an eye problem, makes the situation considerably worse. If one removes

water from a myxedematous or moderately hypothyroid patient, considerable slack becomes available in the orbits. Desiccated thyroid is of far less or of only questionable value in the euthyroid patient. If one follows the progression of the eyes with many, many measurements, it will be found that the slight slack that has been acquired by giving desiccated thyroid will soon be taken up by the progression of the disease, and any curve describing the progression of measurements will follow essentially the same course as it had before.

I cannot, in my own mind, accept the ideas of some concerning complete ablation of the thyroid as treatment of exophthalmos. I think that when hyperthyroidism comes along, it should be treated. I think also that in a very large number of patients the problem of progressive exophthalmos will subside spontaneously, regardless of what is done for the patient. In the treatment of the hyperthyroidism, I prefer radioiodine in some of these patients because I think it is less risk to the eyes to give the patient a drink of radioiodine, particularly if he has very prominent eyes, than it is to use an anesthesia mask over the face in the presence of a tendency toward exposed corneas. I hasten to admit that we haven't sufficiently good concrete information about the biology of this problem to advocate strongly any special form of therapy. It is a self-limiting disease and will follow its own course. Only time will tell in any given patient whether that course will turn toward improvement before damage is sustained to the eyes.

DR. RAWSON: May I ask Dr. Dobyns a question? Do you mean that the reason you use radioactive iodine as a therapeutic agent in patients with rather severe exophthalmos and hyperthyroidism who come to surgery, is to avoid keeping the mask on the face during the operative procedure?

DR. DOBYNS: That is part of the reason. As a matter of fact, you will remember that about 10 years ago it was suggested that letting a patient down slowly with radioiodine might be more kindly to the eyes. In other words, it would slowly correct the hyperthyroidism without some sudden and perhaps detrimental imbalance. That philosophy I have continued to follow and hence, I use radioiodine.

DR. RAWSON: That is really why you give radioiodine?

DR. DOBYNS: That is why I have in the past. I think we can treat them either way.

DR. RAWSON: If you think that surgery would not do any more harm, I am sure there is a mechanical means of protecting the eyes against the mask that could be worked out.

DR. DOBYNS: I agree.

DR. WERNER: A point I would like to make is that unless you have adequte figures from two different methods, by whatever criterion, and I suggested this as a proposal for comparison, you can't make a statement. You have an impression, but there are enough figures from surgery, if the cases were collected and classified properly, to make the comparison to see whether the spontaneous course, if you will, is identical following one method of therapy with another; or whether there are significant differences.

DR. DOBYNS: On the basis of the data that have been recorded, I would say that such an analysis would be rather futile, because the data must all be collected by the same ob-

server. There are all degrees of this problem. Even among your own patients I am sure that you found difficulty trying to decide whether you should include this mild case or that one. Some patients have only extra ocular muscle weakness. Others have angry eyes with measurements of protrusion less than the average normal individual. Still others have extremely prominent eyes with only mild or no irritative features. There are almost as many shades of difference as there are patients.

DR. WERNER: We classified cases only as a matter of clinical convenience because of the popular impression that if one has what we call noninfiltrative opthalmopathy, the course will be benign; if one has the other form, the course will be severe. It is our personal belief, and I think that of everyone around us, that it is all one disease and as you have expressed, the eye changes are simply expressions of the same pathologic mechanism. But we are essentially out to show how many finally wound up with permanent handicaps, what we call "worse." This is an obvious and simple end-point that requires no subjective discussion and is entirely open to objective appraisal. This number adds up to 1.3% of our series, and it can be simply ascertained in other series with very little confusion or extra effort. Dr. Sloan was the only one I found who made any effort to state what happened after surgery in these terms. Out of 613 patients he found 22, I think about 3%, who did badly. He did not break down his series into categories. I must repeat that unless we have certain criteria by which to follow patients, we are going to go, as you say, by impression, and I think the problem now calls for something a little more objective.

DR. KEATING: I fear that I am on Dr. Dobyns' side of this argument, for a number of reasons, but mostly because I think that the disease, exophthalmos, is so varied in its manifestations that one will never appreciate all aspects of it by simply taking a surgical, medical, or radiologic series of cases in themselves. There are some patients with exophthalmos, appearing as a manifestation of Graves' disease, who do not come to operation and who do not receive radioiodine. Somehow or other, even though we may not know how to do it at the moment, we must manage to take account of these patients. In the old days, much experience accumulated on the effects of surgery on exophthalmos; these effects have largely been forgotten. But my preceptors remembered them, and I was fairly well indoctrinated with the point of view that their lifetime experience had taught them, namely, that, contrary to the teachings of Hertz and others in the 1930's, the condition of the average patient with severe hyperthyroidism and Graves' disease, an elevated basal metabolic rate, a prominent goiter and prominent exophthalmos could be predicted with reasonable certainty to improve with respect to the clinical appearance of the eyes upon resection of the goiter and consequently relief of the hyperthyroidism. A real contribution was made by Hertz and colleagues when they called attention to a special group of patients with Graves' disease who constitute exceptions to this generalization in several important respects; i.e., these patients were not intensely thyrotoxic and had small thyroid glands. In addition, they responded in what we might call a "supernormal" way to the administration of iodides. These are the patients, as Hertz maintains, whose eyes could be expected to become worse after thyroidectomy, and the eyes of a good many of them did. It should be added, parenthetical-

ly, that the eyes of such patients also may become worse, and probably with the same frequency, after the use of radioactive iodine.

Perhaps the next step was made by Mayo Soley, who showed that virtually every patient who undergoes thyroidectomy, whether his disease becomes clinically worse or not postoperatively, has a measurable, objective increase in the forward protrusion of the globes. This brings us to an important point that I think may be part of the difference of opinion that has been expressed here. Every patient with Graves' disease has eyes further displaced postoperatively, whether or not he has exophthalmos of a clinically significant degree. Even if he has adenomatous goiter without hyperthyroidism, thyroidectomy may cause his eyes to protrude further, so that this process, which Soley first described and Dobyns confirmed, is really a manifestation of some ancillary effect upon the water balance of the globes, or at least so I interpret it. Nevertheless, it may still be a very important observation, indicating why the patient with the Hertz or hyperophthalmopathic type of condition becomes worse clinically after operation. That is, for some reason the globes are unable to tolerate this unavoidable increased forward displacement, which may be a nonspecific consequence of thyroidectomy for any kind of goiter.

I think another difficulty may be involved in referring to the earlier cases, as has been proposed, and in digging out a series of cases from the pre-antithyroid era to see what thyroidectomy accomplished. It is this: there is good evidence that Graves' disease itself may have undergone some kind of change. Twenty-five years ago, a much more severe and intense variety of this condition was being observed than the one we see today; furthermore, as a disease, its incidence was much more common than that which we encounter today.

DR. POCHIN: If myxedema is really simply additative in its contribution to exophthalmos, that ought to be easy to pick up in all these patients with thyroid carcinoma whom we pitch in and out of myxedema at the time of successive radioiodine doses. Have we any data on that, any measurements of the eye of a patient before inducing myxedema and after causing myxedema?

DR. DOBYNS: We published such data in 1946.[6] The eyes are found to be increased in prominence when myxedema develops. You can make the eyes go in by giving thyroid. In spontaneous myxedema, they also recede considerably when thyroid is given.

DR. POCHIN: How many millimeters—2, 3, 4?

DR. DOBYNS: Two or 3.

I think we should make a universal plea that all persons who treat Graves' disease either by surgery or radioiodine should alert themselves to the signs and symptoms that raise the suspicion of a future eye problem. They should then be very **sure** that these patients are followed carefully and not permitted to go into a hypothyroid state. In spite of all the efforts that we have made, we see these patients sometimes slip down to a lower metabolic level than they should have.

Not infrequently an attending physician may be concerned about the eyes becoming worse while actually the apparent worsening is due to hypothyroidism. When myxedema

or severe hypothyroidism is corrected, the eyes recede so much that there is often dramatic improvement. Thus, one water-loading effect has been superimposed on another.

Figure 37A illustrates the effect of hypothyroidism. It is the picture of a man with signs of progressive exophthalmos and severe thyrotoxicosis before he was treated. He had diplopia and signs of pressure behind the globes and cardiac failure. He was treated with radioiodine. The whole problem became worse when he failed to report for follow-up (Figure 37B). The eye problem had become much more bothersome. Fortunately, when the hypometabolism was corrected, the problem with the eyes was not only significantly improved but far better than it had been when he had had severe hyperthyroidism. Now, 2 years later, his eyes have regressed 6 mm in prominence.

DR. CLARK: We have 2 cases that got very bad after treatment with I^{131}. These had failed to return for check-ups and had developed hypometabolism. In spite of intensive therapy, they did not improve, one requiring orbital decompression. For several years we have made it a practice in our post-thyroidectomy patients with mild exophthalmos, or in individuals we think might develop post-therapeutic exophthalmos, to start them on thyroid extract (1-2 grains every day) and Lugol's solution immediately after surgery and to keep them on these drugs for a long period of time. So far, that regime has been very encouraging. I am wondering if it would not be a good idea to follow the same regime in patients treated with radioiodine. They could be started about the time they were approaching a euthyroid state. It is certainly true that many cases will disappear and you can't follow them carefully. If they were on a small dose of thyroid it would prevent some of these bad hypometabolic states that arise.

DR. FREEDBERG: That may be the reason why we haven't seen anything suggesting exophthalmos in 200 cardiac patients in whom we have induced myxedema. We have measured their eyes with the exophthalmometer. They are on 6 or 12 mg of desiccated thyroid a day. They are distinctly hypothyroid, but it may be that that small amount of thyroid is the reason for the difference between Dr. Dobyns' calculations and ours.

DR. DOBYNS: Dr. Freedberg's patients with cardiac disease cannot be compared with those under discussion because they did not have Graves' disease.

DR. FURTH: May I ask two questions—first, what are the anatomical changes in what you call ophthalmopathy? Second, has anybody in recent years studied the biology and pathology of experimental exophthalmos? Following thyroidectomy, all rats become "popeyed." Thus, there is an excellent opportunity for study of exophthalmos under controlled conditions.

DR. POCHIN: Any condition which involves forward displacement of the eye, and anything or any change behind the eye that pushes the eye forward causes "exophthalmos." The change may be one of about 50 different things, and they all produce "exophthalmos." You can get a muscle action displacing the eye forward. I think it is certainly unwise to use the term exophthalmos to relate to one pathologic condition, or to think of one pathologic condition as its cause. About the former question, I don't quite know what to say except that clinically there appear to be two groups: those in which the eye muscles have an

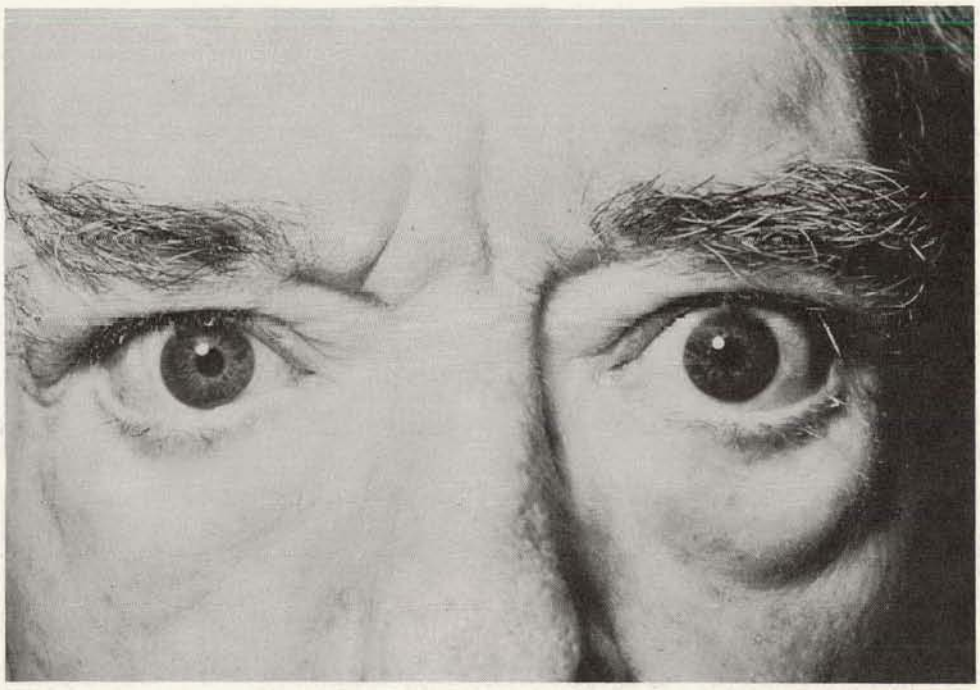


Figure 37A. Photograph of hypothyroid patient with signs of progressive exophthalmos and severe thyrotoxicosis prior to treatment with I^{131}.

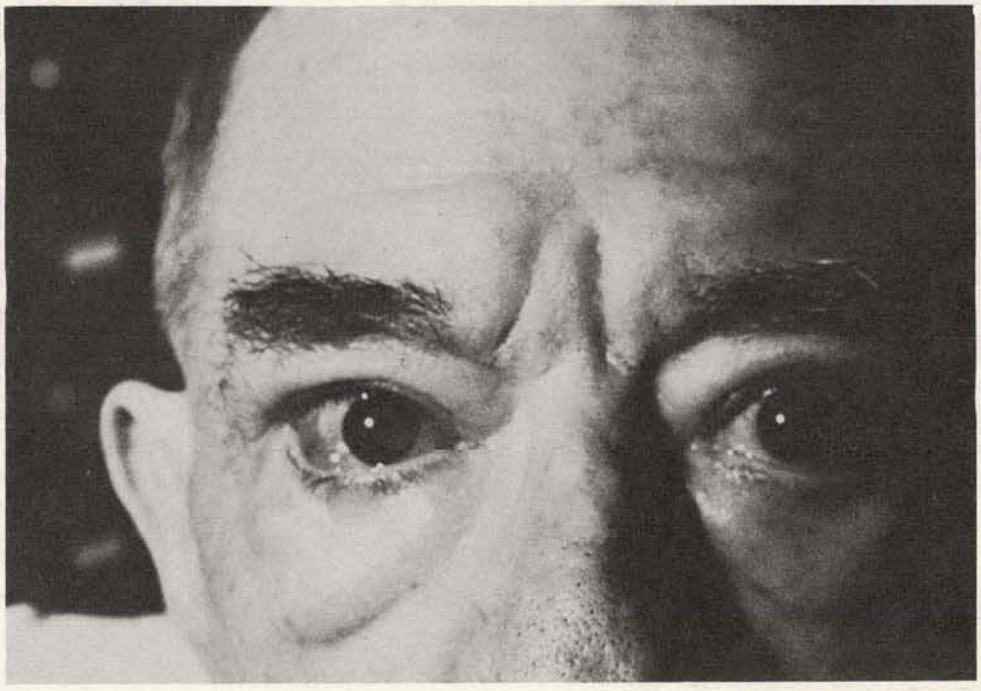


Figure 37B. Photograph of same patient as shown in A, after treatment with I^{131} and after he had failed to return for follow-up examinations.

increased water content and increased fibrous tissue content, going on sometimes to calcification, and those in which there is a change of retrobulbar tissues associated with increased fat content; and there are different clinical correlations of these two groups.

DR. WERNER: This is what we tried, in a clinical sense, to do with our classification. An increase in the content of the orbit, the fatty content only, is seen with the noninfiltrative type of involvement.

DR. FURTH: I do not know what you mean by "infiltrative." Is the fatty infiltration mere adiposity (as in pancreas, for example)? I did not seem to have phrased my question well. One can very readily produce, in any animal, exophthalmos, e.g., by radioiodine. Here is an opportunity to study the natural history of this change; the matter of dose, the sequence of anatomic and functional changes with persistence of exophthalmos, hypothetical therapeutic measures, etc.

DR. DOBYNS: I think we have been a little unfair, Dr. Furth. We dive into a subject and discuss it. Many of us are particularly interested in the thyroid and we perhaps skimmed over the background. Some of the things you refer to have been done and are being done, and the problem is still highly confusing. I do not blame you for questioning the term infiltrative, because I have the same feeling about it. The last thing I would like to say is, I think it would be nice if Dr. Pochin would clarify our various interpretations of his earlier work in which the matter of fatty infiltration or fatty deposition in the orbits was described and was later variously interpreted by others. Do you regard the anatomic change as being deposition of fat or is it merely edema in fat?

DR. POCHIN: This was a question of straightforward numerical observation. We examined at postmortem any patients with hyperthyroidism that we could lay hands on.[7] Of those, 4 out of the 12 had exophthalmos of the type you would call noninfiltrative in this particular notation. In the whole group, and not merely in those with exophthalmos, as compared with subjects dying without thyroid disease, there was statistically a greater quantity of ether-extractable tissue in the orbit, and a greater proportion of ether-extractable tissue in various components of the orbit, notably the muscle and the lacrimal gland. There was therefore apparently an absolute increase of something ether-extractable through orbital tissue, so it looked as though those could be described as having an excess of fat in the orbit, and this, of course, was in a wasting disease.

DR. WERNER: Did you attribute the increase in exophthalmos to fat rather than water?

DR. POCHIN: There was no increase in water in the orbit either as suggested by absolute figures or as indicated by the proportional figures.

DR. WERNER: Did you have sections of the orbital contents?

DR. POCHIN: We have some histologic preparations, but there was nothing conclusive that one could say from the histologic evidence.

DR. WERNER: Were there fatty and cellular infiltations of the muscles?

DR. POCHIN: Certainly there was an increase in the amount of lipoid deposited between muscle fibers in the eye muscles,[8] but there is a great deal in normal eye muscles.

Round cells are always present in eye muscles of hyperthyroid patients and were present in this group. The tie-up between the position of the eye, as measured postmortem with the exophthalmometer and the degree of the increase in retrobulbar tissue, was fairly good,[7] so it looks as though there is a correlation between bulk and the corresponding prominence of the eye. Of the excess bulk, the majority was lipoid. We have not a competent assessment of round cell infiltration but that would be a small factor in the volume change. It looked as though the amount of lipoid scattered throughout the eye muscles corresponded to the degree of prominence of the eye.

DR. WERNER: At the risk of being tendentious, I would still like to suggest since we have indices, however faulty, in surgical series done by men who are in a position to follow their patients, that one or several series be followed with the view of finding out the life history of the ophthalmopathy, just as we have done after I^{131}.

DR. KEATING: My answer to that is that it would be an excellent idea, but at present I dare say there are very few surgical series that would be uncontaminated by the factor of selection, because surgeons are now pretty well sensitized to this matter of severe exophthalmos and are quite unwilling to operate upon patients who have it.

DR. WERNER: I think that is a valuable comment, because that is exactly what happened to us. Nevertheless, it would be quite interesting to know what is happening to those people they do operate upon.

DR. McCULLAGH: It seems to me that we are still a little confused on the matter of communication, and perhaps of semantics. We continue to say "exophthalmos" when we mean the eye changes of Graves' disease, and we say "exophthalmos" when we mean proptosis from other causes, too. It is confusing. The question arises repeatedly whether hypothyroidism causes exophthalmos. I think that myxedema, whether it is from primary or secondary hypothyroidism, doesn't cause exophthalmos of the type we are talking about in Graves' disease; neither do pituitary tumors. The whole picture of exophthalmos as it exists in severe form seems to me to have almost nothing at all to do with the function of the thyroid gland per se. We see it advancing to a severe degree long before hyperthyroidism occurs; we see it advancing to severe proportions in the face of hyperthyroidism; and, we see it advancing in the so-called "euthyroid" state. We know from the earlier literature that exophthalmos of the type that is seen in Graves' disease got so severe that before the days of thyroid surgery, radioactive iodine, or other measures, the eyes were lost completely. It appears to me that we just don't know the cause of exophthalmos at all, whether it is pituitary or hypothalamic or the things we all have in the backs of our minds. I doubt very seriously whether we are not just keeping a smoke screen going when we talk about hypothyroidism in relation to aggravating the fundamental cause of the exophthalmos of Graves' disease.

DR. WERNER: What we have said at this meeting is that we do not know the past or the present life history of ophthalmopathy, and that at the moment, in choosing between modalities of therapy, when there are complicating eye troubles, we have nothing but our instinct to guide us.

E. Miscellaneous.

DR. WERNER: We want to try to find out about miscellaneous complications, parathyroid injury, and so forth. We have seen 2 patients with pleural effusion shortly after I^{131} therapy. I wonder if anyone has had such an experience.

DR. JAFFE: We have had 2 patients with pericardial effusion. I do not know whether it was the result of the I^{131} therapy or part of their hyperthyroidism. We wrote to about 8 different people throughout the country, and only Dr. Haines and one other person had observed pericarditis with effusion as part of hyperthyroidism in the past. Dr. White, Dr. Levine, and a few others said that they had never observed it.

DR. WERNER: Pleural complications were mentioned as a possible complication of I^{131} therapy at the American Cancer Society meeting where it was brought out that the radiation might induce injury to the pleura. Is that your impression, Dr. Rawson?

DR. RAWSON: I do not remember that.

DR. WERNER: Someone at the meeting said that there had been several flareups in thyroid cancer treated with I^{131}.

DR. RAWSON: I understand that certain people have seen isolated lesions apparently begin to grow on ablation of the thyroid.

DR. McCULLAGH: I have an example of a complication that might be of interest. One patient was a woman who went into thyroid crisis after a very large dose; it would be of interest to me to know if others have had the same experience. Dr. Rall spoke about this, and I was very much interested to hear him say that he thought it might occur if the patient was seriously debilitated or had an additional serious metabolic disorder.

This woman (Figure 38) had hyperthyroidism without very high basal metabolic rates; +38, +50, and so on. She had, however, extreme muscle weakness; she could not get up out of a chair, nor go up an ordinary step without help. Her hyperthyroidism persisted for over a year in spite of a total dose of 93 mc of I^{131}. The last dose given was 25 mc. In a few days she became extremely ill; her pulse was 150 per minute and she developed a fever for about 5 days, as high as 105° F. She began to vomit. She was extremely restless and sleepless and in a state of mild delirium. She was given I. V. iodine and various means of support and recovered from the crisis, but her hyperthyroidism remained until after thyroidectomy.

Another man that I want to mention had something that you may or may not be willing to accept as a thyroid crisis, as the result of radioiodine. He was a farmer, 44 years of age, with severe hyperthyroidism and severe diabetes. He also had quadriplegia as the result of an accident. He was given a relatively small dose of radioactive iodine, I believe just 7 mc, and the following day he developed a temperature of 104.5° F. and a pulse rate of 160 to 180. He died about 24 hrs. after radioactive iodine was given despite all the measures we could supply. In a third patient the complication might be classed as failure of treatment (Figure 39). I would like to hear some comments on this. The patient was seemingly well clinically and received an 8-mc, a 6-mc, and a 4-mc dose of I^{131}. The radio-

active iodine uptakes never came down, a situation in some ways comparable with that seen in the patient who still has continuing hypermetabolism. About 17 months after the first dose the patient did not have a true hypermetabolism, only about +12, but was sick, clinically hyperthyroid. Is this a recurrence or is it a continuation of the disease?

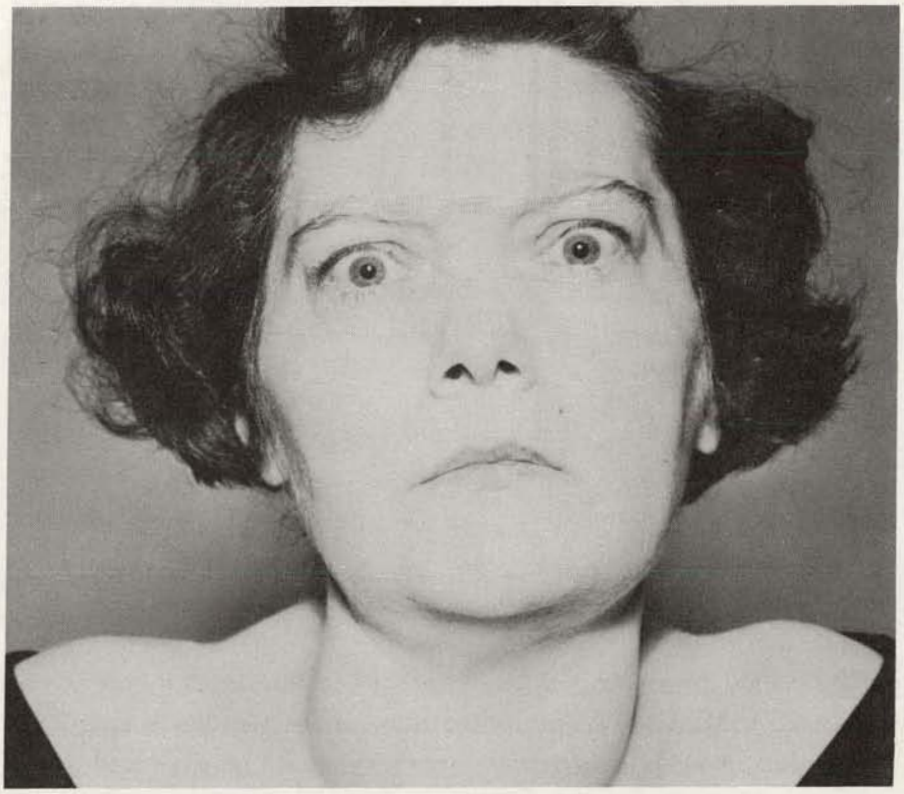


Figure 38. Woman having moderately severe Graves' disease and large diffuse goiter who had thyroid crisis following I^{131}.

DR. DOBYNS: Was the therapy discontinued before you gave radioiodine, or had the patient been completely untreated up to that time?

DR. McCULLAGH: This patient had had propylthiouracil.

DR. WERNER: Have there been any cases of parathyroid injury, storm, and so forth? We have had 2 patients with symptoms suggestive of storm.

DR. CLARK: We have had 4 cases with symptoms suggestive of storm.

DR. FEITELBERG: We studied serial thyroid sections from a patient who died 6 weeks after a large dose of I^{131} for cancer therapy. All normal thyroid tissue had advanced necrosis. No changes whatsoever could be observed histologically in the parathyroid gland.

DR. WERNER: Are there any other complications? We mentioned leukemia.

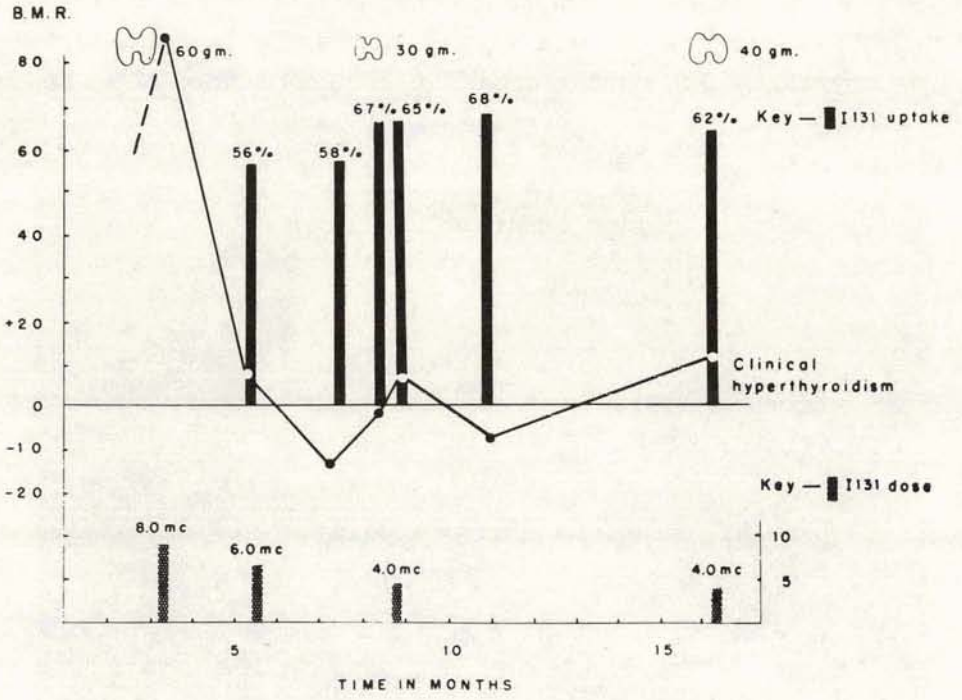


Figure 39. Graves' disease with recurrence of hyperthyroidism after I^{131}-induced remission.

DR. POCHIN: I thought you might be interested in the figures referring to those leukemias. As mentioned yesterday, from my memory of the incidence spontaneously of leukemia, the 4 cases described in this group yesterday would be expected purely by chance to be on something of the order of 100,000 years of follow-up; whereas this group's total experience would represent 63,000 patient-years. I would guess the 4 cases were random. But I do think it is rather important that any isolated cases of leukemia following radioiodine should be reported, so that we continue to know whether they are, in fact, random.

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Part III — Results of Other Modalities of Therapy

A. Current results of surgery.

DR. WERNER: We will now go on to the current results obtained by means of surgery.

DR. CLARK: I think most of you are familiar with the results obtained with surgery, but I would like to review them briefly because it is quite important when one is trying to decide on surgery versus iodine therapy for thyrotoxicosis to be familiar with what one might expect from surgery. Upon examination of the literature, it is somewhat difficult to make an accurate estimation of the results from surgery, because most of the publications are from large centers where there are very fine internists and good surgeons who are experienced in doing thyroidectomies. It is possible, if one included the results from small communities where a surgeon did 3 or 4 thyroidectomies a year, that the results would be poorer and the complications much higher.

Table 27 shows a composite of some of the published work with regard to mortality. The ranges are from 0 to 3.1%, with an average of 0.7%. You talk to the surgeons around the country, and I think mortality from thyroidectomy has declined in recent years, many surgeons having large series of thyroidectomies without any mortality. If one reviews the deaths very critically that are reported in the literature, he will find that most of them are attributable to cardiac complications or thyroid storm. Today, I don't think that many individuals with thyrotoxicosis and severe cardiac complications are being operated, but are being treated with I^{131}. Also, with the advent of the antithyroid drugs, patients can be prepared much better for surgery and one should never have a postoperative thyroid storm. Actually, the mortality statistics are quite good, but as long as we are doing surgery for thyroid disease, there is going to be a small mortality. I do not care who the surgeon is or where the surgery is done, there will be an occasional case that is lost.

Thyroid crisis is reported as 0.1 of 1%. This is very low, but with proper preparation of patients one should never have a postoperative thyroid storm. If a storm occurs, it means the patient has not been properly prepared and has been subjected to surgery too soon.

Vocal cord paralysis averages about 1 to 2%, and most instances are unilateral. Permanent bilateral paralysis is very infrequent.

The incidence of hypoparathyroidism is reported as 0.2 to 5%, with an average of

Table 27

MORTALITY FOLLOWING THYROIDECTOMY BASED ON DATA OBTAINED FROM SURVEY OF THE LITERATURE

0 - 3.1%
Aver., 0.7%

Group	No. cases	%
A	611 (D) 496 (T.N.)	0.0 0.4
B	487 (D) 315 (T.N.)	0.61 1.58
C	1630	0.24
D	655	.9
E	315	0.0

about 1%. One may get temporary hypofunction of the parathyroids that will disappear in a few weeks.

Secondary operations have about 4 times a higher incidence of recurrent nerve injury or hypoparathyroidism than that following primary operation. This is the reason why most surgeons are very hesitant to advise surgery for recurrent thyrotoxicosis.

Persistent or recurrent thyrotoxicosis varies from 1 to 27.9%, with an average of 5.6%. Because of the high incidence of complications associated with secondary operations, such patients are better treated with radioiodine.

The incidence of hypothyroidism in the literature runs from 0.2 to 29.7%, with an average of around 6 to 7%. It may be seen from what has been said with regard to hypothyroidism that the overall incidence is probably a little bit lower following surgery than following radioiodine. In our own group, it runs just about the same.

It is obvious from what I have said that surgery does carry a certain risk, but with a skilled surgeon, well trained in thyroid surgery, it is certainly minimal.

B. Current results of chronic antithyroid drug therapy.

DR. WERNER: Dr. Vander Laan will discuss the current results obtained by means of chronic antithyroid drug therapy.

DR. VANDER LAAN: I have been assigned the opening part of the discussion of antithyroid drugs. Three possible uses for antithyroid drugs are quite clear: 1) they are used widely in the preoperative preparation of patients; 2) they may be used with I^{131} for the severe cases in which one wishes to hasten a return to good health; and 3) they may be

used definitively in treatment. About the last point, there is the widest possible divergence of opinion.

With regard to the merits and demerits of treatment, probably toxicity has come up as the main problem. Dr. Storrie and I reviewed this subject last year in Pharmacological Reviews.[1] We elected to include only series of 30 patients or more because so much that is reported in terms of individual cases relates only a fragment of the total experience of the individual. Of the common drugs in use, propylthiouracil and tapazol, there seems very little to choose regarding toxicity; the overall incidence of serious effects is below 1%, and although deaths have been reported from each of these agents, they are of very low order. Holliday,[2] in England, reviewed the total number of cases of agranulocytosis due to antithyroid drugs. He accepted about 27 as valid instances up to the time of publication sometime in 1951.

I think one of the important points that was made a long time ago and is still generally disregarded is that most of the toxic effects of antithyroid drugs occur during the first 2 months of treatment. I would think that in the preoperative use of these drugs one can hardly escape with a shorter period of treatment if the goal is to avoid thyroid crisis entirely and restore the patient to good health. I presume that will also be true of the adjunctive use of I^{131} for antithyroid drugs. For the most part, 2/3 of the toxic effects occurring in the first 2 months will have been encountered by the time the drug has been abandoned as an adjunct to I^{131}. Toxicity is a very minor consideration in terms of one's choice of treatment. The other greater disadvantage that is commonly brought out is the long period of treatment. I used the antithyroid drugs only for years; then I^{131}. I began to be impressed that it was a lot easier to manage hyperthyroidism when I used antithyroid drugs solely. I should like to present a few illustrations to show the type of experience on which this opinion is based.

The data in Table 28 are somewhat old and, of course, the death rate is much too high.

Table 28

GRAVES' DISEASE TREATED SURGICALLY
1933 – 1940[3]

Total number of cases	149
Number observed 6 mos. or longer	130
Deaths	2.7 %
Persistent or recurrent hyperthyroidism	8.5 %
Hypothyroidism	13.9 %
Tetany	2.7 %
Laryngeal paralysis	4.7 %
Total	32.5 %
Recovery with no complications except exophthalmos	69.2 %

This is the experience at the Peter Bent Brigham Hospital. This was in Dr. Cutler's time; he was interested in thyroid surgery. Half of the cases were done by the house staff, and half by the senior staff. Three of the 4 deaths occurred in house staff cases, but apart from the death rate, it probably does not vary a great deal from the overall report that Dr. Clark gave, and I think the relatively low recurrence rate for hyperthyroidism is associated with a relatively high hypothyroidism rate.

Table 29 shows data obtained as a result of Dr. Astwood's work at New England Center Hospital, in the treatment of hyperthyroidism with I^{131}. There were 101 cases that Anderson[4] reported; that was a rather selective series in that it was comprised of difficult cases; 72 of the 87 analyzed had had previous treatment before I^{131} was given; 56

Table 29

NEW ENGLAND CENTER HOSPITAL — I^{131} TREATMENT OF HYPERTHYROIDSM

Selected series — 101 cases (Anderson's analysis 1949-53)

11 - required re-treatment later
3 - lost to follow-up
87 - analyzed

72 - previous treatment
56 - antithyroid drugs
15 - surgical
1 - iodine only
15 - no previous treatment

	Av. dose mc	Recovery mos.
56 - 1 dose (57%)	7.5	2.4
22 - 2 doses	17.9	7.4
9 - 3 to 7 doses	48.1	18.4

3 recurrences at 4, 7, and 8 months

5 transient hypothyroidism (after 1 dose) average 12 mos.

5 permanent hypothyroidism (to develop

Unselected series — July 1954 - 1955 (Cassidy)

54 cases

28 well with 1 dose
6 myxedema (1 dose)
20 multiple doses

with antithyroid drugs, 15 surgical, and 1 iodine only. I thought it would be of interest to break down these figures. Of these cases, 56 recovered with 1 dose, an average of 7.5 mc, and their recovery time was 2-1/2 months. Twenty-two had 2 doses, 17.9 mc total, and the recovery time was 7-1/2 months. Nine received 3 to 7 doses, with an average dose of

48 mc, and an average recovery time of 18-1/2 months. The next cases Dr. Cassidy and I treated. These were unselected. Twenty-eight recovered with a single dose, and we had 6 with myxedema. Thirty-four had 1 dose, and 20 had multiple doses. I think the recovery time was approximately the same as in the recurrent series. Perhaps it does not make much difference whether they are recurrent cases or unselected ones so far as overall results are concerned.

I think the amount of time it takes to get a person well with this treatment is rather impressive, of the order of 40% of the patients require multiple doses, and about 10% become myxedematous. I believe more patients will be sick longer, i.e., there will be more patient-sick days with radioiodine treatment than with antithyroid drugs. Our experience with the 101 unselected cases on antithyroid drug treatment, is shown in Figure 40.[5]

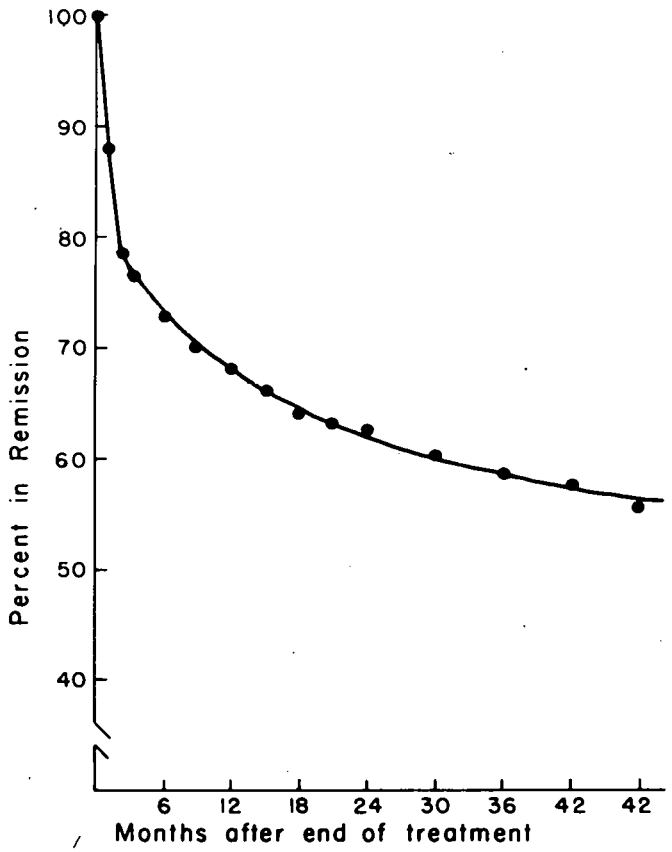

Figure 40. Per cent of patients in remission who had been treated with antithyroid drugs.

This illustration shows a decay curve for a group of patients who had recovered from hyperthyroidism, or returned to the euthyroid state following a single course of antithyroid drugs lasting at least 6 months. One sees 80% remaining well or in remission at the end of 2 months, and then a gradual falling off, as time elapses.

Table 30 shows the number of remissions obtained with prolonged antithyroid-drug therapy. On the left is shown what actually was observed and on the right what might have been accomplished had all the patients with relapses at the end of a 6-month course been

Table 30

NEW ENGLAND CENTER HOSPITAL — ANTITHYROID DRUG TREATMENT OF HYPERTHYROIDISM

Actual	Maximum
101 cases - 1st course 56 remissions 45 relapses	101 cases - 1st course 56 remissions 45 relapses
33 cases - 2nd course 12 remissions 36.4%	45 cases x 36.4% = 16 remissions 29 relapses
12 cases - 3rd course 3 remissions 25%	29 cases x 25% = 7 remissions 22 relapses
71 (70.3% remissions)	79 (78% remissions)

Remissions — 4 years after treatment ended.
Treatment courses — 6 months minimum.

retreated. By the time 3 courses were given, 70% of the patients remained in a lasting remission. These are unselected cases, and we didn't differentiate between nodular and hyperplastic goiters. All cases of hyperthyroidism were treated with antithyroid drugs. These are patients who were in remission at least 4 yrs. and at most 10 yrs.

The last thing I would like to present is a study (Figure 41) on a group of patients who had been treated from 6 to 10 yrs. before they were called back, and uptake studies were done.[6] The mean uptake was just below 40%. The patients were given 0.2 g of thyroid a day for 3 weeks, and the uptakes were repeated. There were 2 cases with uptakes so low that thyroid was not given. We observed that in 10 of the 12 there was a substantial fall in iodine uptake after 3 weeks of this treatment; in one a rather dubious fall, and in one, who was euthyroid, there was no effect. We did not increase the dosage or continue the treatment period. I think this is one more indication that normal pituitary-thyroid relationships return in the control of thyroid function. We have used the same test to distinguish euthyroidism, with goiter and high uptake, from hyperthyroidism, and in my experience this kind of response never occurs in a person recognizably hyperthyroid. So it is my belief, and I am sure I am alone in it, that nearly 70% of patients obtain a good result from antithyroid drugs, and this is lasting. This is the most physiologic of any of the treatment methods evolved and is generally the most available, requiring no special equipment. Finally, it

offers the least amount of risk and the quickest return to health. For these reasons, it is my opinion that antithyroid drugs deserve serious consideration in the choice of therapy of hyperthyroidism.

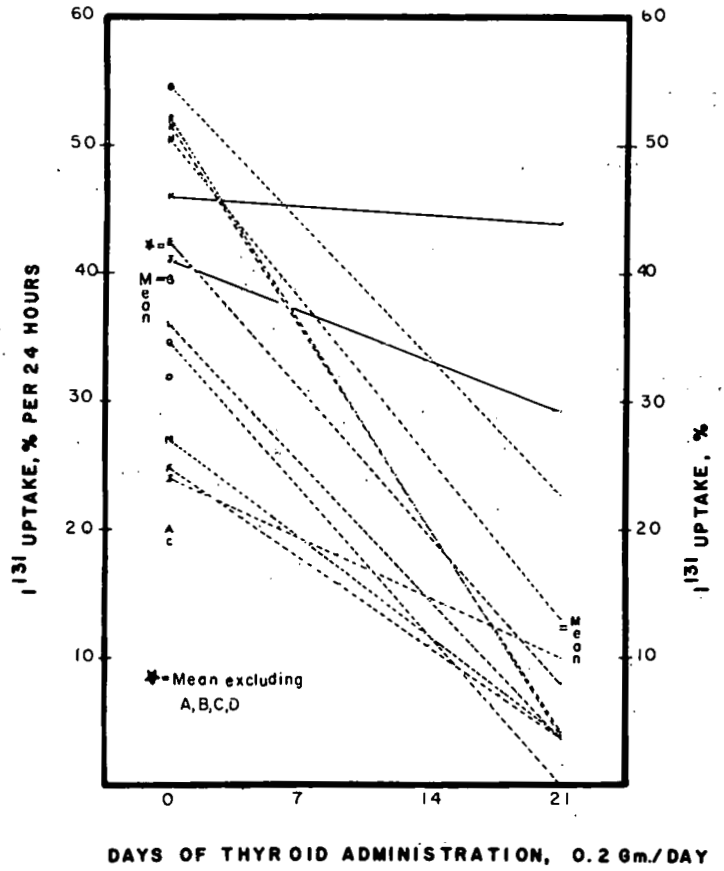

Figure 41. Uptake of I^{131} in patients maintained for 3 weeks on 0.2 g of thyroid per day. This study was conducted on individuals who had been treated for hyperthyroidism 6 to 10 years previously.

C. Late sequelae of X irradiation to the head and neck region in children.

DR. WERNER: Dr. Clark will now speak about thyroid carcinoma in children consequent to irradiation of the head, neck, and upper chest region.

DR. CLARK: We do have a little evidence that an association may exist between prior irradiation about the head and neck and the development of carcinoma of the thyroid in the young individual.

I think you all remember that this association was first suggested by Duffy and Fitzgerald.[7] They found that 10 out of 28 patients 18 years of age had been subjected to irradi-

ation of the thymus between the 4th and 16th month of life. The incidence they describe may have actually been higher. Their data were obtained by questionnaire, and there were several who did not reply. We have learned that careful and persistent questioning of the parents is often necessary to elicit a previous history of irradiation. It cannot be done by questionnaire.

Reinhoff, talking recently at the Southern Surgical Association, recorded 9 of 17 cases at Johns Hopkins under 20 years of age who had previously received radiation to the thymus, tonsils, adenoids, or polyps of the upper respiratory tract.

Warren Cole and Majorakis at the University of Illinois have 10 patients 15 years of age or younger with carcinoma of the thyroid, and I think they reported that all of them had had prior radiation around the head and neck. Recently, Simpson, Hempelmann, and Fuller[8] at the University of Rochester made a survey of 1722 children who received X-radiation therapy to the thymic region between 1926 and 1951. They studied 1400 of these. Table 31 shows their results in summary. In their treated children they expected 2.6 cancers and observed 18; for thyroid cancer they expected .06 and observed 7; for leukemia they expected .6 and observed 7. In the untreated siblings they expected 2.8 cancer and observed 5; for thyroid cancer they expected .08 but did not observe any; for leukemia they expected .06 and did not observe any.

Table 31

RESULTS OF A SURVEY OF 1722 CHILDREN TREATED IN THE THYMIC REGION WITH X IRRADIATION

	Treated children		Untreated siblings	
	Expected	Observed*	Expected	Observed
All cancers	2.6	18	2.8	5
Thyroid cancers	0.06	7	2.08	0
Leukemia	0.6	7	0.06	0

*Includes only cancers identified as such by original pathologist.

We have at the present time 19 cases of cancer of the thyroid in children 15 years of age and under. All 19 have had prior irradiation; 4 for "so-called" enlarged thymus, 3 for cervical adenitis, 9 for enlarged tonsils and adenoids, and 3 for chronic pulmonary conditions.

A brief summary (Table 32) of 13 of the children reveals that the time from the radiation to the time carcinoma was diagnosed was 6.9 years. The total doses ranged between 200 and 725 r about the head and neck. We thought from the data obtained from the radiologists that had treated these children, that it was entirely possible that the thyroid area was included in the portal of irradiation. The dosage, as you can see, is small, and wheth-

Table 32

LIST OF CASES OF CARCINOMA OF THE THYROID IN CHILDREN AND ADOLESCENTS WHO RECEIVED IRRADIATION

Case	Sex	Age received irradiation	Age carcinoma diagnosed	Time from irradiation to diagnosis	Location of irradiation	No. treatments	Total dose (r)	Portals	Reason for irradiation
K.D.	F	2 mos.	7 yrs.	7 yrs.	Chest	1	210	5 x 5	Enlarged thymus
J.S.	F	3 mos.	7 yrs.	7 yrs.	Chest	4	400	-	Enlarged thymus
K.S.	F	8 mos.	8 yrs.	7 yrs.	Ant. upper chest	2	200	-	Enlarged thymus
M.N.	F	5 yrs.	11 yrs.	6 yrs.	Neck	4	200	10 x 10	Cervical adenitis
S.L.	F	4 yrs.	12 yrs.	8 yrs.	Right upper neck	3	300	3 x 3	Cervical adenitis
M.K.	F	6 yrs.	15 yrs.	9 yrs.	Neck	3	-	-	Cervical adenitis
J.M.	F	10 mos.	4 yrs.	3 yrs.	Head and neck	3	600	8 x 10	Enlarged tonsils and adenoids
D.S.	F	3 yrs.	8 yrs.	5 yrs.	Head and neck	3	-	-	Enlarged tonsils
M.B.	F	3 yrs.	10 yrs.	7 yrs.	Head and neck	3	624	6 x 8	Enlarged tonsils
P.W.	M	4 and 6 yrs.	14 yrs.	8 or 10 yrs.	Right and left nasopharynx	6	725	8 x 10	Enlarged tonsils
M.D.	F	4 yrs.	10 yrs.	6 yrs.	Tonsillar area	4	300-400	8 x 10	Enlarged tonsils and adenoids
T.A.	F	3 yrs.	10 yrs.	7 yrs.	Face and ant. chest	4	550	10 x 15	Sinusitis and peribronchitis
E.W.	F	4 yrs.	14 yrs.	10 yrs.	Ant. upper chest	4	300	Large	Pertussis

er this is a factor in the increasing incidence of carcinoma of the thyroid in young people, we are not prepared to say at this time. I think that the association is striking and I think we should all be very cautious about giving radiation for benign conditions about the head and neck to children. At this time the thyroid gland is very hyperplastic and the cells may be more susceptible to small doses of radiation than in later life.

D. Biological effects of radiation from a genetic standpoint.

DR. WERNER: Dr. Glass will now tell us in further detail about the biologic effects of radiation from a genetic standpoint, which is important to us in our appraisal of the role of I^{131} in the treatment of hyperthyroidism.

DR. GLASS: The data we have on the relation of mutation rate to dosage of ionizing radiations are derived from studies on microorganisms, including bacteria and molds, on various green plants, on fruit flies (Drosophila), and on mice. When one finds so general, if not universal, a relationship, the burden of proof must fall on those who would claim it does not apply to man, too.

Whether or not any radiation is applied, organisms exhibit a certain frequency of spontaneous mutation. The linear dosage curve, when extrapolated downward to zero dose, points to the level of spontaneous mutation on the ordinate as its origin. Now suppose one assumes there is a threshold somewhere between the end of the experimentally observed curve and the origin, as indicated by the dotted line in Figure 42. It must follow, not only that at very low levels (below the threshold) individual quanta are incapable of bringing about a mutation, but also that there is a region (just above the threshold and between it and the long, experimentally demonstrated, linear part of the curve) where individual ionizations have a higher efficiency in producing mutation than at higher doses. In other words, each ionization produced over this short intermediate part of the range would have to produce more than one mutation. There is no evidence from any experiments done on any organisms that you ever have a higher efficiency than unity in this relation of dose to effect. And from this physical consideration plus the fact that in all the organisms that have been studied, from bacteria to mice, you do get this extrapolation to zero at the origin, geneticists are convinced that the linear proportionality holds for all organisms and can confidently be presumed to hold true for man. They have no data, naturally, for man in this respect, and even for the mouse there are only two points on the curve, but they show the same proportionality as far as they go. For plants, the dosage curve has been extended down to about 15 r, and for microorganisms it has been extended down to about 5 r.

Another point that has come up and caused some misconception is that of the possible occurrence of beneficial mutations. This I think we can set aside, not only because, although beneficial mutations undoubtedly do occur, they are extremely infrequent, and certainly not as high as 1% of all mutations (probably not more than 0.1% of all mutations), but also because the data we have are based on increase with dosage of definitely deleterious

mutations. In the fruit fly, for instance, the dosage curve has been worked out on the basis of mutations that have lethal effects, or on visible mutations, i.e., the mutation's visible morphologic effects, which practically always have adverse effects either upon the viability or the fertility of the organism. In the mouse, the data are based on visible mutations of lowered viability. In bacteria, the data are based on biochemical mutations that either produce a loss or an impairment in efficiency of enzymes that control particular steps in the metabolic path.

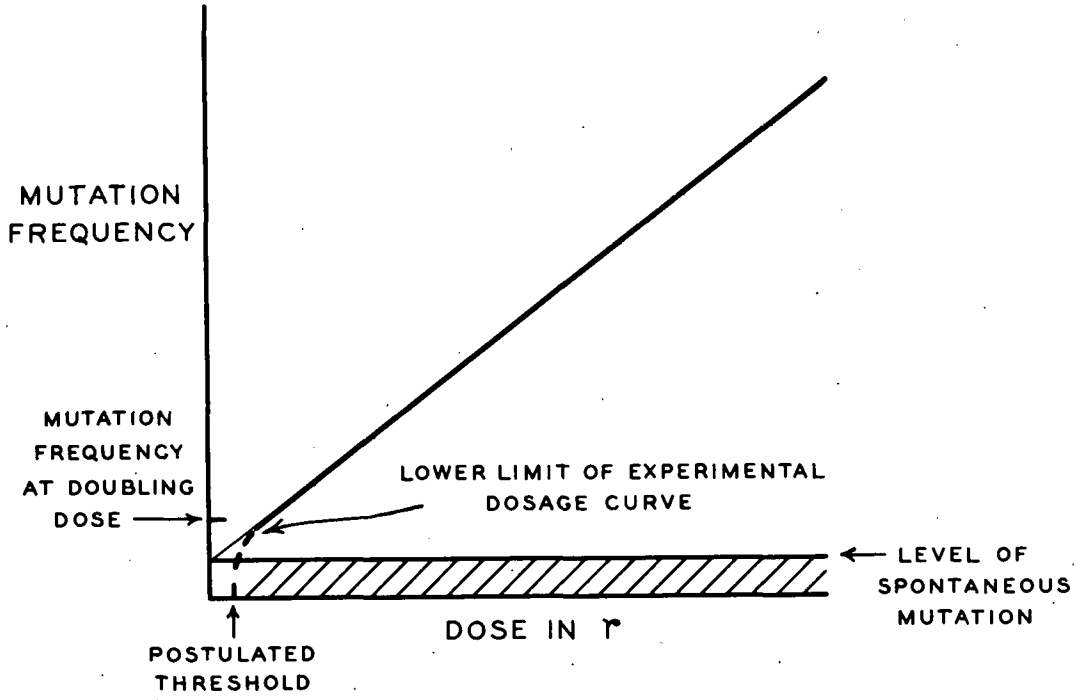

Figure 42. Frequency of mutations in living organisms. The dosage curve for the effect of ionizing radiations has been extrapolated to zero.

I think it is very important for us to recognize that the data upon which the Genetics Committee of the National Academy based its conclusions as to the physical properties of ionizing radiations and the exposure of the population of the United States to them, were especially prepared for the Committee by two biophysicists, Drs. John S. Laughlin and Ira Pullman, who did a splendid job of collecting what material was available and evaluating it. When it came to radioisotopes, they had essentially just one published source, namely, the paper by Stanley H. Clark.[9] So what the Committee has said about radioiodine is based simply on this one set of figures. It is up to you, it seems to me, to tell us if the figures are wrong, in your estimation. They may well be. Clark based his calculations on a figure of 557 curies of radioiodine shipped by the Atomic Energy Commission during 1954. He made the assumption that the same amount had been used annually in the period since then.

He assumed that of that 557 curies, approximately half would undergo physical decay before it was used on patients. That would reduce it to 278.5 curies. Of that remaining amount of radioiodine, he assumed that one-half would be excreted within 24 hrs., mostly via the urine, and would therefore be important only in terms of the dose to the gonads while circulating in the blood stream through the bladder and kidneys. Clark assumed that 10% of the physical energy from that quarter of the total amount of radioiodine would be delivered effectively in β radiation to the gonads. He assumed a distance of 7 cm for the average distance between the bladder-kidney region and the gonads. Finally, the other quarter of the total 557 curies he assumed is absorbed by the thyroid, has an effective half-life of 6 days, and an average distance from the gonads of 56 cm. Adding all these together, he calculates, for the entire 160 million persons in the United States, a γ dose of .0011 r per yr. and a β dose of .002 r per yr., a total of .0031 r per yr. If this dosage, then, were continued over a 30-year period for the entire population, irrespective of what individuals it was given to, it would amount to .09, which is approximately 1% of the recommended 10-r limit set for the entire population.

I round off the .09 r to 0.1 r for the I^{131} 30-year average dose, which is about 1/30 of the dose estimated to be the total medical dose from all sources of ionization. It is somewhat less than the radiation dose from P^{32} and about the same as the dose from fallout at present levels. In comparison with the natural background (which is not included in that 10-r limit), it is about 2%.

We can estimate the number of mutations occurring in the entire population that will sooner or later have some kind of detrimental effect—we are not now talking about the tangible genetic effect—it would be .005 detectable mutations per r unit per infant. This will then give for the calculated dose of I^{131} to the population: 50,000 mutations per 100 million babies. In case you want to figure the effect also in terms of the additional cases of tangible defects in the first generation, it would result in 500 additional cases to be added to the roughly 4 to 5% of births now occurring with tangible defects of this sort.

This calcuation relates particularly to the probability of exposed persons having children with tangible genetic defects. If 160,000 persons were actually treated, forming 0.1% of the total population, and if all these individuals were in the reproductive part of the life span, the dose per yr. per person is 3.1 r, about 1/10 of the doubling dose. So that the 2% probability of getting children with tangible genetic defects will be increased very slightly in the first generation and will rise ultimately to 2.2%.

Let me now give you just a few more calculations that I think may possibly be illuminating. These are based on data given us a short time ago. The average dose of I^{131} to the gonads in treatment of cases of hyperthyroidism was given as 1 to 6 rads by Dr. Quimby. This seemed to me to run a little above the level of Dr. Werner's data. He cited figures from 1 to 8 mc for the first dose, with increasing amounts per dose when patients received up to as many as 6 doses.

DR. QUIMBY: That 1 to 6 rads was for a single dose and did not take into consideration any subsequent ones.

DR. GLASS: Yes, it did not take into account that subsequent doses might generally be larger. So I proposed to use 6 rads as the average value for purposes of calculation.

Take the effect on the population of treating 100,000 persons under 30 yrs. of age—you can easily make the proper corrections if you include people up to 40 by just dividing the number from age 30 to 40 by 1/2, since after the age of 30 the reproductive potential would be reduced by approximately 50% from a genetic viewpoint. I take 100,000 persons merely because it is a round number and because there are approximately 100 million persons of reproductive age under 30 in the population at the present time who would have to be replaced to keep the population in a steady state. We take 6 rads, multiply by the probability of getting a mutation in a gamete (.0025/T), times the number of individuals, and the result is 1500 mutations in the population. The Committee has calculated that 10 rads applied to the entire population would produce 5 times 10^6 mutations. The ratio of 1500 to 5 million is 3 in 10,000. In other words, this would be .03% of the number of mutations expected to be produced by the radiation limit that was recommended by the Committee. But the rate of 100,000 persons under 30 yrs. is not an annual one; it is spread over 30 years. It would be 3333 persons treated per yr. From what we heard earlier in this meeting, I think that is probably an underestimate of the number of individuals that might be treated annually with I^{131} at the present time. If the age limit for treatment is lowered, it might be considerably too low. Let's just calculate what it would be if we treated 100,000 persons annually.

DR. QUIMBY: I don't think that's fair at all, because I don't think that by far the greater number of people treated were over 30 years to begin with.

DR. GLASS: This is a purely hypothetical calculation. Just suppose 100,000 persons below the age of 30 were treated annually.

DR. QUIMBY: There is a great big IF in that.

DR. GLASS: I am just trying to give you some figures to play with. What you are going to do with them is up to you. If you treat 100,000 individuals under the age of 30, annually, the dosage to the population would still be only 0.9% of the permissible limit. In other words, radioiodine could be used on individuals under the age of 30 up to a level of treatment of the population of 100,000 persons annually, without increasing the mutation rate more than approximately 1% of the permissible limit. This is not very much but you must remember that there are a lot of other sources contributing to the total radiation to the population. If everybody thinks it is all right for us to go up to 1%, the total will run up considerably, particularly since the peaceful uses of atomic energy are likely to produce more widespread exposure of the population to radioactive wastes.

On the basis of the calculation just made, I would repeat what I have said, that I don't think there is any very sizable danger from the genetic point of view in the use of radioactive iodine on the basis of what I would suppose to be a reasonable number of cases, somewhere under 100,000 per year.

Suppose we take next the possible effect of a dose of 36 r upon the individual and his own children and descendants. This might be one of those individuals who had 4 to 6 treat-

ments over a period of several years, which is roughly in the range of what we consider to be the doubling dose. We think the doubling dose for human beings probably lies between 30 and 80 r, although it might be as low as 10 r. This is one reason for the considerable caution we take in making our estimates. Let us then say the dose of 36 r is between 1 and 3 times the doubling dose. Then let's calculate the probability of finding tangible genetic defects in the offspring of such an individual. The 2% that you would expect, the 2% probability that applies to the general population, would, if this is a doubling dose, be increased ultimately to a probability of 4%. But if the doubling dose is actually 10 r and 36 r is 3 times the doubling dose, then the probability of getting tangible genetic defects in the descendants would go up to 8%. That would be about the highest figure, the extreme prediction. These defectives would not all be produced in the first generation. If you want the figures for the first generation, the increase would be to about only 2.2%, assuming that this is about the doubling dose, and to 2.6% if this is 3 times the doubling dose.

One more calculation might be rather interesting since these doses already discussed are, of course, relatively low doses that are given to individuals treated for hyperthyroidism. Earlier we heard mention of large doses given individuals with carcinoma who nevertheless later produced offspring. There was one case, I believe, in which the female had received 50 mc and the male 500, and they produced 2 children after that.

Suppose we take it as 75 and 750 r to avoid doing the arithmetic over. Using the same probability of a mutation per roentgen, .0025 per r per gamete . . . the doses were measured in millicuries, and I think we can accept an r per mc. In any event, we can equate an r and a mc for this whole-body relationship. The probability of mutation per gamete per r unit is .0025. That would mean 2.06 mutations of all sorts per child. These are not tangible genetic defects, these are mutations of all sorts, tangible and intangible, which might ultimately have an effect upon the population. We really need be concerned only with the effect upon the F_1 progeny, since here you are irradiating a very small number of individuals. The later descendants are going to be lost in the general population, and you need be concerned only about the probability of mutations in the immediate children of such parents. We may then estimate that the combined dose of ionizing radiation is at least 10 and may be as much as 40 times the doubling dose. The chance of a tangible genetic defect in the F_1 then, assuming the lower ratio, would increase from 2% to 4%, and assuming the higher ratio would increase to 10%. This would be the probability of getting tangible genetic defects in the children of individuals given this much radiation, and this worst likely outcome would about double the probability that already exists from all causes (5%). I do not know whether you think the possibility of raising the frequency of tangible genetic defects in the children of such individuals to 10% is grave or not. I doubt that doubling the probability is sufficient to warrant therapeutic abortion.

DR. WERNER: Thank you, Dr. Glass.

Part IV — Selection of Modality of Therapy in Hyperthyroidism

A. Age limit for I^{131} — pro and con.

DR. WERNER: We must now turn to the question of an age limit for I^{131} therapy in hyperthyroidism, based on what we have just heard and on the question of later cancer. Dr. Keating.

DR. KEATING: Despite what has been said here, I think I shall probably leave the meeting with the same impression I had when I came, namely, that the question of the selection of treatment for exophthalmic goiter, at this precise point in space and time, is not one that can be settled on a permanent and definite general basis. Instead, it must be settled on a particular and specific and possibly even individual or at least institutional or community basis.

I wish first to review the historic background of the point of view that I have been asked to present. We first used radioiodine in Graves' disease in August, 1946, within a month after the agent was first released by the Manhattan District. At that time we knew even less about radioiodine than we do now, if that anachronism could be possible, and we had access only to the elegant pioneering papers on the clinical use of the material which had come from San Francisco and Boston. Also, at that time—and this is important—patients with Graves' disease had access to two efficient methods of treatment: thyroidectomy and appropriate medical treatment with antithyroid drugs. When we began to use radioiodine we preferred initially to administer it to those patients who had complications or disease that made them poor surgical risks or medical care problems. As soon as the efficacy of the new agent became obvious, its use was extended to patients with recurrent disease without complications and, later on, to patients without complications or recurrence but who were more than 45 yrs. old. I personally feel the limits that we impose upon selection of patients to receive radioiodine are based upon a number of considerations which, it must be emphasized, are tentative and are predicated largely upon ignorance, and on opinion. First is uncertainty regarding the question of carcinogenesis. Second is the necessary assumption that should carcinogenesis of a significant degree be encountered, there will be a long latent period before it becomes manifest. This latent period might be very long, for example, in the case of carcinogenesis of the skin, and taking into account the unique biologic history of thyroid cancer. Third is the concern about sterility and genetic mutations, which, I hope, have been laid decisively to rest at this meeting. Fourth is the matter of public relations. It is not enough to have data that satisfy you as a clinician or investigator. We must take into account the impression our policy or decisions will have upon the patient, his relatives and friends, and the general public. It may not be enough for us to be reasonably certain that there will exist an acceptably small probability of leukemia, tumors, or other types of cancer in a population if we treat enough people who have lumps. If we treat enough people with lumps, we know that we shall be faced with the seri-

ous problem of having to explain this rather esoteric theoretic consideration to a patient with a lump who subsequently proves to have had metastatic cancer all along. Lastly, I think, a good case must be made for considering very carefully any and all reasonable alternatives to the policy of treating a nonmalignant disease with ionizing radiation.

Evaluation of the risk of therapy with radioactive iodine, therefore, must inevitably involve consideration of the risk of alternative forms of treatment as well. In the case of thyroidectomy, the risk may vary, as Dr. Clark has mentioned, from one institution to another. However, more than 25 yrs. ago Dr. J. deJ. Pemberton showed that the mortality for patients with Graves' disease operated upon under optimal conditions and after adequate preparation with iodides was no greater in the aggregate than the mortality rate to be expected from a comparable series of euthyroid patients with nodular goiter. He showed further that a substantial proportion of the mortality rate following thyroidectomy for Graves' disease could be anticipated to arise from a small group of patients who could be selected preoperatively. These so-called high-risk patients were, of course, the first we selected to be treated with radioiodine after it became available. It may be partly on this account that we have had no deaths from thyroidectomy for Graves' disease since 1945, although we have treated by one means or another perhaps 2500 patients for this condition from that time to the present. While the incidence of complications of Graves' disease varies with the surgeon and the technique, it similarly is higher among patients with recurrent disease, very small thyroid glands, or very serious complications. The recurrence rate also may be reduced by selecting for operation only patients who do not have complications, small glands, or recurrent disease.

It seems to me, therefore, that as long as we are able to provide our patients with a minimal risk of mortality, morbidity, and recurrence by means of surgical treatment, we may be justified in foregoing, at least for selected patients, the inviting prospect of completely bloodless therapy for exophthalmic goiter, so long as we are faced with the likelihood that a genuine risk of carcinogenesis still accompanies treatment with radioactive agents. However, the foregoing is a highly personal and local decision. It must be predicated upon the notion that the surgical mortality rate will be virtually zero. We might be prepared to treat with radioiodine any patient with Graves' disease if we were confronted with a surgical mortality rate of 2%, for example. A detailed discussion of differences in mortality rates is a consideration proper for surgical and not medical groups, and I shall not attempt it. However, I am sure that our surgical colleagues would agree that if all operations on the thyroid gland were done by qualified specialized surgeons, as opposed to general ones, surgical house officers, or general practitioners, the surgical mortality rate accompanying thyroidectomy throughout the country would be much lower than it is.

DR. FEITELBERG: Dr. Keating and I were asked to present the pro and contra of keeping a lower age limit for patients to be treated with I^{131} for Graves' disease.

Dr. Keating's arguments for maintaining an age limit are so balanced and thoughtful that I really cannot see any point on which we basically disagree. He states that on the basis of available data, or, as he so poignantly and justifiably states, on the basis of ab-

sence of reliable and conclusive data, the decision depends on personal and local factors. When somebody says that 2 and 2 are 5, we can say that he is either an ignorant person or a fraud—we can take a strong stand. We can argue about possible conclusions when factual or logical conditions are more uncertain. But under such circumstances, the attitude of a scientist is characterized by the withholding of an opinion and by a continued effort to obtain additional data, often with the aid of a working hypothesis only. In clinical work, such a scientific attitude is not possible. Faced with a critically ill patient, a definite action is required. When we are confronted with a 30-year-old patient with severe hyperthyroidism, we cannot let him die while we accumulate experimental data. We must treat him, either with antithyroid drugs, radioiodine, or by surgery. We are in agreement with Dr. Keating that in light of our present information, the decision is essentially between surgery and radioiodine. The advantage of radioiodine is low morbidity and mortality. We had only 1 death in 3000 cases and this was possibly due to the choice of I^{131} therapy, although the evidence points rather to extraneous causes. The advantage of surgery is the known absence of carcinogenic effects. Conversely, the disadvantages of I^{131} are the possible carcinogenic and genetic effects, and the disadvantage of surgery is operative mortality.

We have increasingly good reasons to disregard the genetic effects of I^{131}. But we have no good data on the extent of the carcinogenic effect. Estimates of elapsed time for its peak incidence vary between 10 and 20 yrs.; it is too early yet, whatever value we take, to evaluate our data. No incidence of malignancy in patients treated with I^{131} for Graves' disease has been reported yet.

We know a little more about mortality following surgery, although this varies over a wide range. Let us look at 3000 patients that we have treated with I^{131} and assume a possible 2% mortality, which is one of the figures discussed by Dr. Keating. If we had referred all these patients to surgery, 60 of them would have died. I agree unhesitatingly with Dr. Keating, that for a 2% surgical mortality, we would prefer I^{131} therapy at present. Good surgery, however, gives a lower mortality; but even if this were only 0.25%, 7 of our patients might be dead. We must remember, on the other hand, that we are not discussing all of our patients, but only the younger group. Most of us agree that poor surgical risks of any age should be treated by I^{131}. The number of our patients who might have died is therefore less than 7.

From the point of view of conventional ethics it is unquestionably advantageous to keep a reasonable age limit, since surgery is the established and conventional treatment. If we lose patients by surgery, we commit, at worst, a sin of omission. Should we find an increased incidence of malignancy in our patients treated with I^{131}, our sin will be the worse one of commission. What we must accept is that we have no path of innocence open to us, as the pure scientist has. We are not allowed to remain contemplative and inactive; all we can do is to choose between the two kinds of "sin."

I wish I could give you substantial arguments on why we have decided against observing an age limit of two score and present stronger reasons than Dr. Keating did for his opposite point of view. All I can do is to mention the various thoughts that have entered into

our largely arbitrary and emotional decision. We were impressed by the fact that we have not been losing any patients and by the complete absence of morbidity attributable to the curative procedure. We have felt that the practice of dropping the so-called age limit from 50 yrs. to 40, sometimes to 30, approached a reduction ad absurdum. (We have kept rigidly a line at 18 yrs., the period of adolescent growth, where susceptibility to carcinogenesis appears to be great.) We were also concerned with the growing number of "exceptions" that were made by groups advocating an age limit. There is no question that really poor surgical risks should be treated with I^{131} at any age, in spite of any carcinogenic odds. But contraindication to surgery was becoming rather loose. I would like to mention one situation as an example of such looseness: "Patient refuses consent to surgery." Did the patient just say, "I am scared?" Was the matter discussed with him in a short interview, or was concerted pressure applied to him and his family over days and weeks?

Since the whole decision is so nonscientific, we were also influenced strongly by the consideration that unless we built up a large amount of patient material, the availability of data required for a well-founded decision will be delayed by decades.

It is hard to predict how long it will take to obtain valid information on increased incidence of malignancy in patients treated with radioiodine. If there is a marked increase, we should know it within the next 10 to 20 yrs. If there is none, it will take longer to substantiate such a negative finding; 20 yrs. at least. Actually, we shall not be able to feel relaxed about this until about 30 yrs. from now, when the presently younger patients will provide evidence to those of us who used post-adolescence as age limit.

When we have valid information on the incidence of malignancy in I^{131}-treated patients, the decision will be simple; if the incidence is equal to or smaller than that for sugical mortality, I^{131} will be the therapy of choice. If the incidence is greater, the alteration of life expectancy by the two procedures will have to be estimated and the choice made on such bases. But then—if there is still a difference of opinion—I shall be able really to argue with Dr. Keating on the basis of scientific arguments, rather than emotional opinions.

DR. WERNER: It is clear that the question of an age limit is open to discussion. We did not bring out the use of I^{131} in conjunction with antithyroid drugs, or in some instances iodine therapy. The drugs may be given either before the contemplated I^{131} therapy or shortly after the I^{131}. In this way, one is able to keep the patient reasonably euthyroid either from the start of therapy or shortly after the therapy. If one stops drug therapy at intervals, one can keep the patient euthyroid for all but brief periods when I^{131} is given if needed. In those clinics in which I^{131} and antithyroid drugs are administered, there is the general impression that larger doses of I^{131} are required for a successful outcome than when no adjuvant therapy is used. This may be due in part to blocking of recirculation of I^{131} but may also represent an increased resistance to the radiation effect.

DR. DOBYNS: Because of the large bizarre nuclei that we found a number of years ago in thyroids of animals and human beings which had received large doses of I^{131}, we decided to make quantitative measurements of the desoxyribosenucleic acid (DNA) in the cells of irradiated thyroids. We observed that antithyroid drugs caused latent changes

(which were produced by small doses of I^{131} and were not otherwise detectable) that become evident when such a stimulus was brought to bear on the gland.

Varying doses of I^{131} were given to large groups of rats. Later, some were given thiouracil. A temporary period of thyroid enlargement followed a 2-week period of iodine-deficient diet preliminary to the administration of I^{131}. Later, when thiouracil was given, glandular hypertrophy was found to be impaired in proportion to the dose of I^{131} that had been given. Presumably, cells were not multiplying normally under this stimulus following very subtle damage. The first histologic evidence of damage in animals given only I^{131} was not detected until doses as high as 50 μc were used, but the failure in hypertrophy occurred following lower doses of I^{131}. Although hypertrophy did not occur, bizarre nuclear forms did.

DNA was measured in individual cells by means of the Feulgen staining and microspectrophotometric technique. The DNA in individual cells has been plotted against nuclear size in Figure 43. In a nonirradiated nonthiouracil-treated animal, as seen in the upper left square, the amount of DNA in each nucleus and the size of the nuclei are uniform. Thiouracil treatment without radiation, as seen in the upper right square, increases the DNA but not over 2 units because at this point the cell divides. If 10 μc of radioiodine is given and thiouracil is not given, there is no significant change from normal. But if thiouracil is added to this irradiation effect, which alone causes no histologic evidence of damage, one finds a large number of cells with abnormally large amounts of DNA and markedly large nuclei. Some of the nuclei had become irregular in shape. After a 30-μc dose of I^{131}, the functional quality was probably slightly impaired so that a self-induced stimulus (functional thyroid insufficiency) produced the bizarre nuclear forms. It is assumed that this is a situation in which DNA is building up the nuclei and cell division has either been thwarted or forced to follow an abnormal course.

This to us is one basis for caution in giving radioiodine to human beings. Superimposing antithyroid drugs on radiation damage should draw even more caution.

DR. WERNER: What about the time factor compared with that for patients?

DR. DOBYNS: I assume that you mean to ask how much time has elapsed between the dose of I^{131} and the finding of the bizarre nuclei. We have not looked for the changes in less than 4 months but they are present by that time. I should like to say that in some patients, in which there is inadequate treatment and follow-up, one sometimes finds that another physician has been treating the patient with antithyroid drugs for quite a period. If we are going to give radioiodine, I think we should treat them adequately that way and settle it.

DR. VANDER LAAN: I am not convinced that patients recover from hyperthyroidism after radioiodine therapy so fast as the present discussion seems to indicate. The data I presented, and those from Dr. Chapman's experience, indicate that months may elapse before health is restored.

DR. WERNER: Patients get well from a single dose; that I think has been well presented by many groups. The hyperthyroidism continues unabated for 4 to 6 weeks in most,

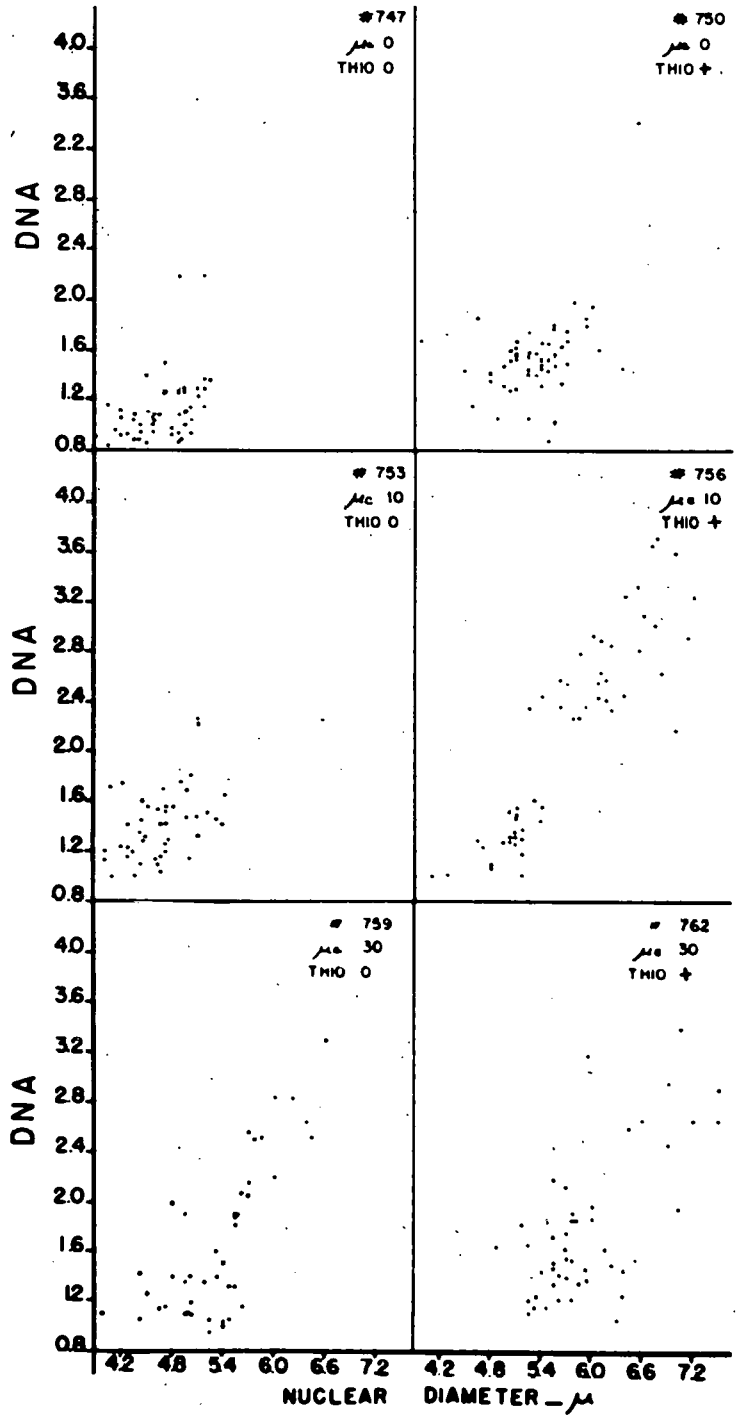

Figure 43. The DNA content and nuclear volume of individual thyroid cells from rats treated with I^{131}, thiouracil, or I^{131} and thiouracil.

and if remission is to result, there is an abrupt decrease in toxicity and the patient becomes euthyroid. These events have nothing to do with the percentage of remissions.

DR. VANDER LAAN: It has been longer than that in our experience.

DR. SONENBERG: With respect to I^{131}, our experience has been similar to Dr. Vander Laan's, insofar as it takes more than 4 to 6 weeks. I have the impression that his point of view has not been aired adequately. I think you have a 40 to 70% chance, if I remember the figures, with 1, 2, or 3 courses, of getting a permanent remission with antithyroid drugs. It might be a good compromise to try a patient on one of the drugs and see if he falls into this 40 to 70% group, and then make your decision on the 30 or 60% that remains.

DR. TRUNNELL: I will third the motion, since Dr. Sonenberg has already seconded it. Not only do I think it is a good idea; we have been doing just that for the last 6 yrs. with all new hyperthyroid patients. They get a trial of antithyroid drugs first. After they are euthyroid, they are maintained on the antithyroid substance for varying periods, usually another 1 or 3 months. Then the agent is discontinued, and only if they relapse do we come to a decision about surgery or radioactive iodine.

DR. KEATING: I do not need to argue the point, in behalf of Drs. Vander Laan, Astwood, and Trunnell, that antithyroid drug therapy can be an efficient way of controlling Graves' disease. I simply wish to insist that the same rigorous tests be applied to the general results of antithyroid drug therapy that we feel obliged to apply to the results of surgical treatment of the thyroid gland or to the results of therapy with radioiodine. It seems to me that in hands other than those of clinicians particularly interested in antithyroid drugs, the results of treatment often have not been too satisfactory. Many patients that we see with Graves' disease appear to have had their disability unduly prolonged because someone attempted (usually in an improper way and contrary to published directions on the subject) to treat the patient for a protracted period with an inadequate dose of an antithyroid drug. The net result of such drug therapy (in terms of the physician who occasionally treats exophthalmic goiter) is exactly like the net result of operations on the thyroid gland by those who do such work only occasionally: it is likely to prove less than satisfactory. I would not object to treating patients with antithyroid drugs were I able to follow the condition of such patients as carefully as I should wish to, and it might be that the results would be superior to those in current general surgical experience. But I should be very concerned in such cases about how long this type of treatment took, what the net expense to the patient was, and so on.

DR. WERNER: I would like to point out that in the New York area at least, we have supposedly a high level of practice. Nonetheless, the number of patients who have had an irregular and at times unsupervised course with antithyroid drug therapy is not inconsiderable. These patients are seen hyperthyroid at one point and hypo- the next. I think it is hard enough when you start to follow people, and I have had this experience since shortly after Dr. Astwood made known his work. It is hard enough to keep them coming regularly for follow-up visits in order to regulate dosage, so that variable control is inevitable. Al-

so, one of the most discouraging aspects is the disappointment engendered when, at the end of a given period of time, a patient who has been kept well, stops the drug and relapses. I think these disadvantages have to be considered in the choice of therapy.

B. Toxic nodular goiter.

DR. WERNER: I will ask Dr. McCullagh, who has had considerable experience with toxic nodular goiter, to speak on this subject.

DR. McCULLAGH: We have treated toxic nodular goiter with radioactive iodine for some years now, beginning, as many of you have, with those patients who seemed to be particularly unsuitable for surgery. This is about what we saw. We do not look on radioactive iodine therapy as the treatment of choice for toxic nodular goiter. We look on toxic nodular goiter as a separate disease from Graves' disease. This could be a very long argument that I will not go into now, but I want to call attention to the fact that one of the main reasons why we believe this is true, is the great variation in the reaction to radioactive iodine. In our experience there is a difference in size of the dose of I^{131} required to control hyperthyroidism in the two conditions. I think Dr. Chapman's experience is not the same as ours in this regard. One outstanding characteristic of nodular goiter is that no matter what dose of radioactive iodine is given, hypothyroidism is not produced. We have not seen a single instance of hypothyroidism following doses up to 50 mc or more in toxic nodular goiter, one patient receiving 70 mc.

So there are two things I wish to speak of briefly; the first is dosage of I^{131} to treat nodular goiter. Our thesis is that within fairly wide limits, the greater the dose the faster the patient gets well. This I believed quite firmly until some months ago, but I feel now that our argument in support of this is not quite so strong as it was. I leave you to judge. The reason we came to give bigger doses was that after some experience with Graves' disease, we found that our average full dose was less than 14 mc; and after treating 60 or more patients with nodular goiter having hyperthyroidism, we found that our average dose was about 34 mc. We now have treated about 150 cases of toxic nodular goiter, but only about 100 have been followed long enough to permit any conclusions. Some patients appeared to respond almost not at all to doses up to 15 mc, but when given 30 mc they soon were well (Figure 44).

There is a great deal of difference as a rule, as I think you all know, in the uptake of radioactive iodine in Graves' disease as compared with that in toxic nodular goiter. In Figure 45 are shown 100 cases of Graves' disease, and 67 cases of toxic nodular goiter. You see at a glance that in Graves' disease a very large proportion had a very high uptake, whereas in toxic nodulars almost all have relatively low uptakes, and the larger proportion have uptakes below 45%.

DR. DOBYNS: Have you taken the Graves' disease cases with incidental nodules out of the group of toxic nodular goiter?

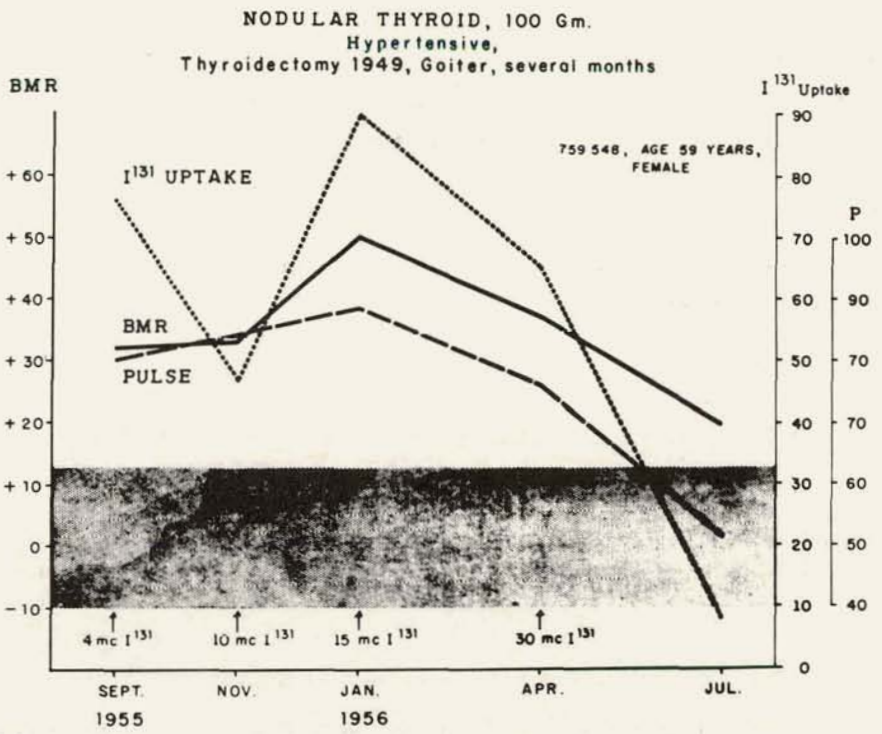

Figure 44. Effect of a dose of 30 mc of I^{131} upon a patient with toxic nodular goiter.

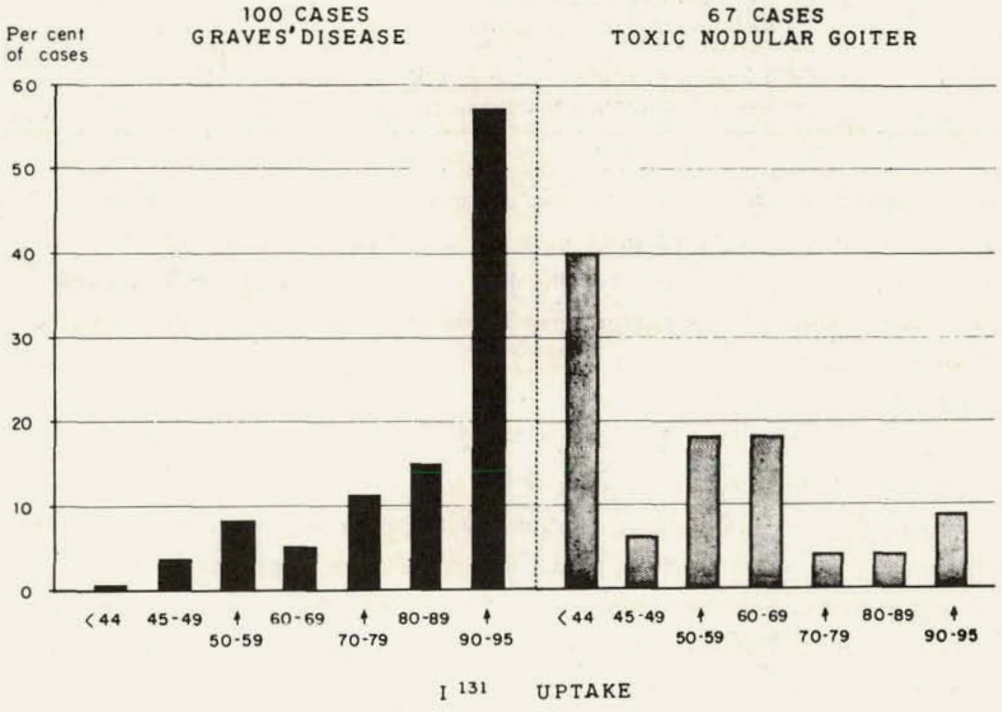

Figure 45. Uptake of I^{131} in 100 patients with Graves' disease compared with that in 67 patients with toxic nodular goiter.

DR. McCULLAGH: We have diagnosed all patients with clinical hyperthyroidism and exophthalmos as having Graves' disease. I recognize that this, in some ways, is a weakness because you might say that it is a foregone conclusion that it is Graves' disease if there is exophthalmos. We have not excluded those who showed some nodularity of the gland nor those in whom nodules became apparent after treatment.

Twenty to 50 mc of radioactive iodine were given to patients (Table 33) at 2-month intervals, depending upon the uptake and the clinical status; many had large glands. Of 45 patients, 31 were euthyroid within 4 months. Fourteen patients were not controlled within 4

Table 33

TREATMENT OF TOXIC ADENOMATOUS GOITER WITH RADIOACTIVE IODINE

Dosage:	20-50 mc at 2-month intervals, depending on the I^{131} uptake and clinical status.
Results:	(1) Of 45 patients - 31 were euthyroid within 4 months.
	(2) Of 14 patients not controlled in 4 months - 6 were controlled within 7 months; 6 were euthyroid 9, 9-1/2, 10, 12, 16, and 18 months; and 2 were toxic at 6 months and did not return.
	(3) Of 31 patients who received 20-40 mc of I^{131} - 22 were euthyroid within 4 months.
	(4) Of 14 patients who received 50 mc of I^{131} - 9 were euthyroid within 4 months.

months; 6 were controlled in 6, 9, 10, 12, and 16 months, and 1 in 18 months. Of 31 patients who received 20 to 40 mc, 22 were euthyroid within 4 months, and of 14 who received 50 mc, 9 were euthyroid within 4 months. So this is one of the reasons I say that 50 mc is more effective than a somewhat smaller dose Data on patients separated according to dose are also shown in Figure 46.

DR. BERMAN: Fifty-mc total dose?

DR. McCULLAGH: Fifty mc as a single dose.

DR. BERMAN: Do they get it after the first 2 months again?

DR. McCULLAGH: Yes. We think we have some evidence, also in single cases, that the big doses do produce a faster result than we get with smaller doses (Figure 47). The patient was thought to have Graves' disease, but there was some doubt, so we hesitated, of course, to give big doses. Here, 6 mc was given in March and 12 in May, with no improvement; 40 mc was given in July. This was followed by a fall in pulse and BMR, and the uptake returned to normal values.

Figure 48 illustrates a similar instance; 10 mc was given in April. The patient was

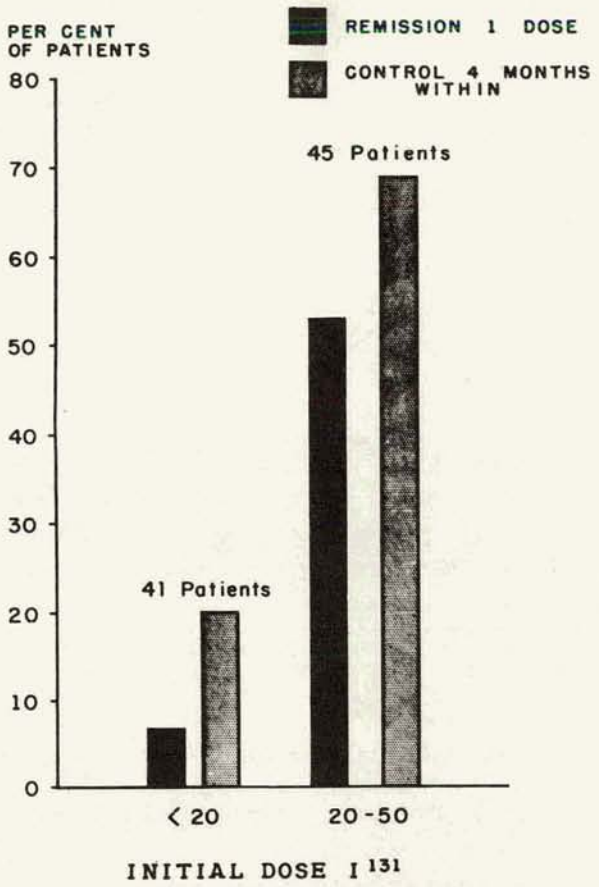

Figure 46. Effectiveness of large doses of I^{131} in patients with toxic nodular goiter.

actively hyperthyroid in June. Forty mc was given, and by September the patient was well.

DR. WERNER: There must be a geographic factor that we have to take into account to explain the difference between your experience and ours with toxic nodular goiter. As you can see in Tables 34 and 35, very few patients required more than 3 doses, and the total dosage given was less than 10 mc in 3 of 4 patients entering remission. In fact, an incidence of hypothyroidism comparable to that with toxic diffuse goiter was observed. Seven of 9 patients becoming hypothyroid received 9 mc or less. So I think we are dealing with a different type of disease than Dr. McCullagh has seen in an endemic goiter area.

DR. FEITELBERG: I agree with you that there is apparently a marked local difference because we have seen a large number of nodular goiters and the average dose administered per gram required turned out to be 130 μc. This is not significantly different from the dose for diffuse goiter.

DR. CHAPMAN: Perhaps there is some difference between your series in New York and the series in Cleveland, in what you personally classify as nodular goiter. In Boston,

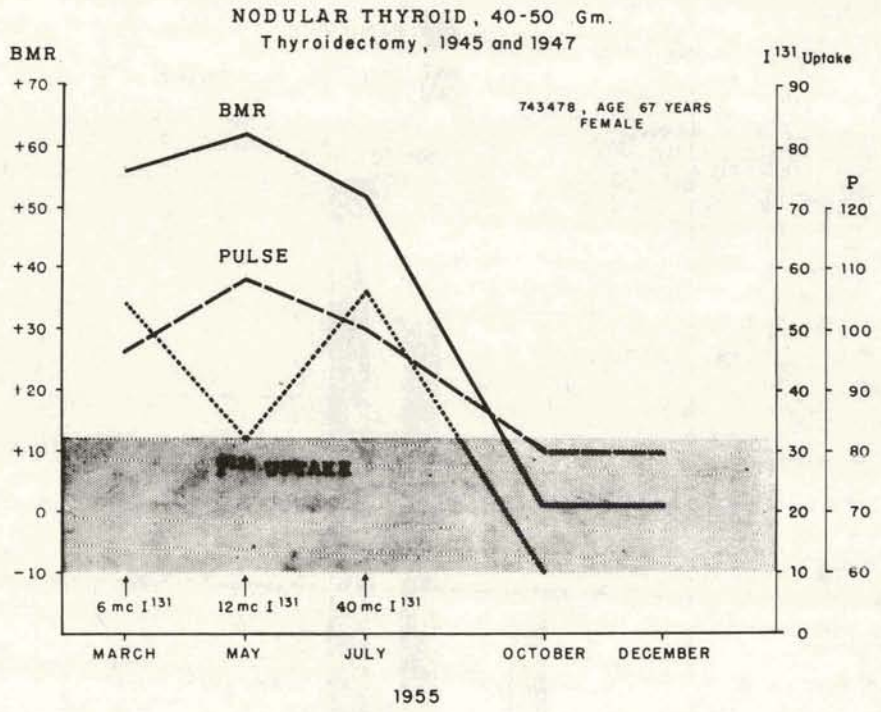

Figure 47. Effect of a dose of 40 mc of I^{131} upon a patient with a toxic nodular thyroid.

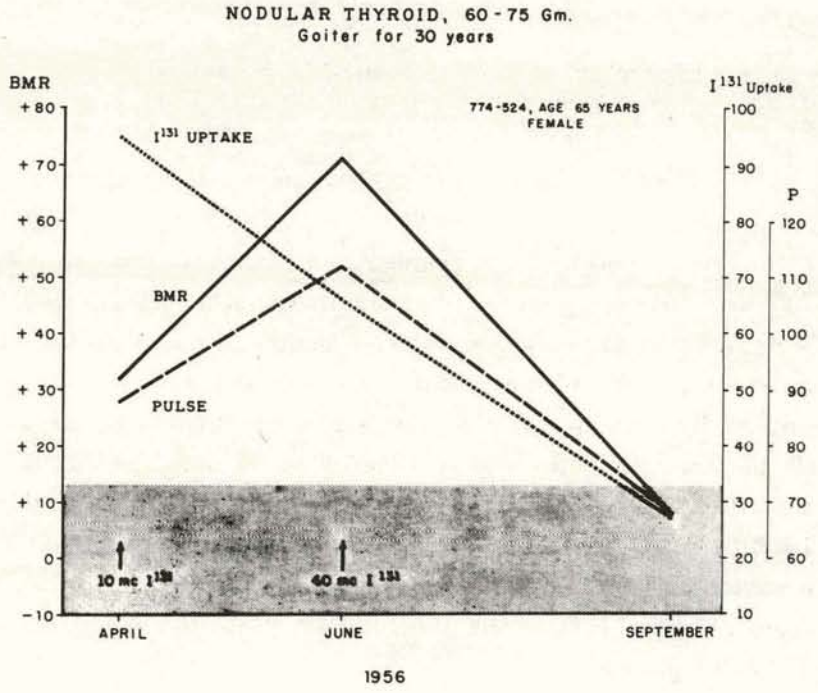

Figure 48. Effect of a dose of 40 mc of I^{131} upon a patient with a toxic nodular thyroid.

Table 34

NUMBER OF DOSES OF I^{131} ADMINISTERED TO PATIENTS WHO BECAME HYPOTHYROID (78 OF 525 CASES)

No. of doses	Type of goiter		
	Diffuse	Toxic recurrent	Nodular
	(No. patients)		
1	29	22	4
2	5	5	3
3	3	1	1
4	0	0	1
5	2	0	0
6	0	1	0
Over 6	1	0	0
Total	40	29	9

Table 35

AMOUNT OF I^{131} ADMINISTERED TO PATIENTS WHO BECAME HYPOTHYROID (78 OF 525 CASES)

Dosage mc	Type of goiter		
	Diffuse	Toxic recurrent	Nodular
	(No. patients)		
0 - 3	11	5	0
4 - 6	22	17	3
7 - 9	4	3	4
10 - 14	0	3	0
15 - 25	0	0	1
Over 25	3	1	1
Total	40	29	9

our experience is precisely the same as Dr. McCullagh's. We had 50 patients with nodular goiters, 43 of them are recorded in our 10-year paper. In these nodular goiters no hypothyroidism nor myxedema was produced after treatment. The treatment doses were all larger than required for diffuse goiter. After the treatment, when the patients were euthyroid by all criteria, we still could palpate nodular tissue. This was a very important point —we felt clinically—that given nodular goiter, with its natural course, its histology and

pathology, and with avascular material, you just know you aren't going to change the necrotic material that is in there. You just can't change it with radioactive iodine. So I think this is one of the criteria. When a goiter that is said to be nodular disappears entirely, it is possible that it was what we call a diffuse goiter with lobulations or, as Dobyns calls it, a diffuse goiter with incidental nodules. In other words, the two disease entities are distinct, although certain individuals, I think, might confuse the two. It is a matter of semantics, really.

DR. WERNER: I appreciate your point. I am well aware that the lobulations of toxic diffuse goiter may appear like nodules in toxic nodular goiter. However, we lean over backwards to avoid this error, and, in those instances where surgery is elected, almost always are confirmed in our findings. I want to ask Dr. Rawson if he would like to express an opinion as to whether there is any difference in the likelihood of carcinogenesis from I^{131} therapy in toxic nodular goiter than in toxic diffuse goiter.

DR. RAWSON: I don't think we know. From published statistics we know that the incidence of neoplasms is much greater in patients with nodular goiter with hyperthyroidism than in patients who have hyperthyroidism of the Graves' disease type. Therefore if carcinomas should be observed in patients after I^{131} therapy, the incidence would be higher in the toxic nodular type; but it is quite possible that the cancer really existed before therapy and was coexistent with the thyrotoxicosis.

DR. JAFFE: Dr. McCullagh, have you subjected any of those patients to surgery who still had palpable nodules after they became euthyroid? If so, did you find any evidence of carcinoma in that group?

DR. McCULLAGH: So far as I can remember, none of them has undergone surgery.

DR. CHAPMAN: We operated on one, that famous case of ours, that early one who had a multi nodular goiter. We biopsied the one on the right and it was benign. After treatment, the nodule on the left remained, and we operated and that one was an adenocarcinoma. As a result, our policy is to avoid treatment of nodular goiters with radioactive iodine; we do all we can to get them operated on.

DR. KEATING: I have to qualify our vote because we use radioiodine as a preoperative measure. We convert these people to euthyroids, and, if there are any palpable nodules, thyroidectomy is performed.

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CARCINOMA

Part I — Indications and Plans for Treatment

DR. CHAPMAN: The last part of this conference is concerned with carcinoma of the thyroid. Dr. Sonenberg will open with a presentation on the indications and plans for treatment with radioiodine.

DR. SONENBERG: I am just the spokesman for a group that includes Drs. Rawson, Berman, Rall, and Trunnell. In this presentation I should like to refer to certain aspects in treating patients with carcinoma of the thyroid which are not emphasized as much, or have not been published as much, I should say, as some of the others.

Early in the course of treating carcinoma of the thyroid, we were struck by several things. I will not go through the total management of a patient, but we do thyroidectomize all our patients either with surgery or radioiodine. In Figure 49 is plotted the 96-hour urinary excretion for one of our patients, Excretion is inversely related, we feel, to retention.

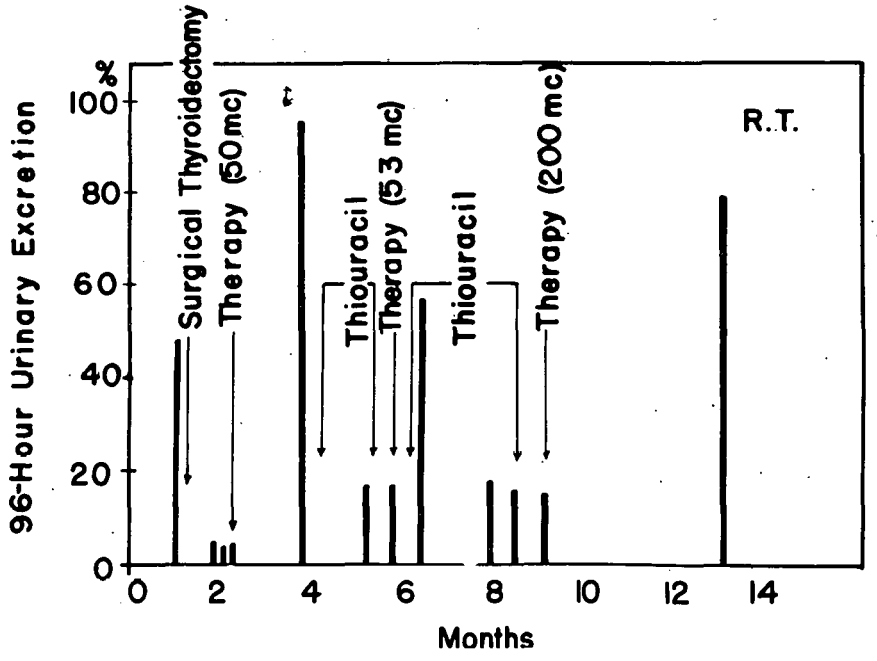


Figure 49. Ninety-six-hour urinary excretion of I^{131}.

When the patient had very little excretion, she was given a therapeutic dose of 50 mc. For all practical purposes, the patient retained no subsequent radioiodine, until she was put on thiouracil and again given another 3-mc dose. There is one thing about these 2 doses, something we see in other patients, that is that although these doses destroy the capacity of tu-

mors to take up radioiodine, the clinical course is in no way altered. This led us to a tentative decision that the patient should get as large a dose as possible, or something we would consider a carcinocidal dose. In line with other decisions about X-radiation therapy, we like to give as large a dose as the patient can tolerate. With this in mind, we have been represented as a group giving large doses, and I should like to discuss some of the consequences of this position.

One thing that has happened, and I won't go into a discussion of how we calculate these doses, is that there is an effect on the hematologic system. The hematocrit falls and there is a decrease in the total white count as well as in the number of lymphocytes and even the platelets, resulting in a pancytopenia with huge doses (Figure 50). The patient whose blood values are shown in Figure 50 received 842 rep. Although it was not our intended dose, it is a significant dose, being 254 mc.

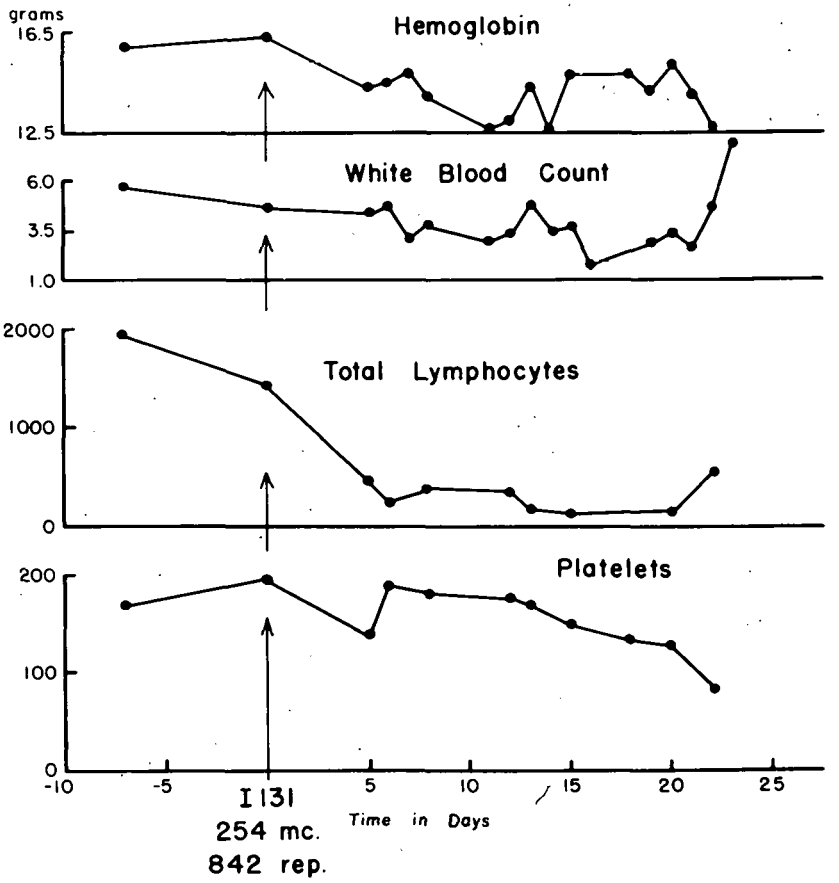


Figure 50. The effect of 254 mc of I^{131} on the hematopoietic values.

The hematologic effect is directly proportional to the dose (Figure 51). As we increase the dose, there is an increased fall. When the number of mc administered to the patient, or even mc retained in the tumor or elsewhere were plotted against the per cent fall from pre-

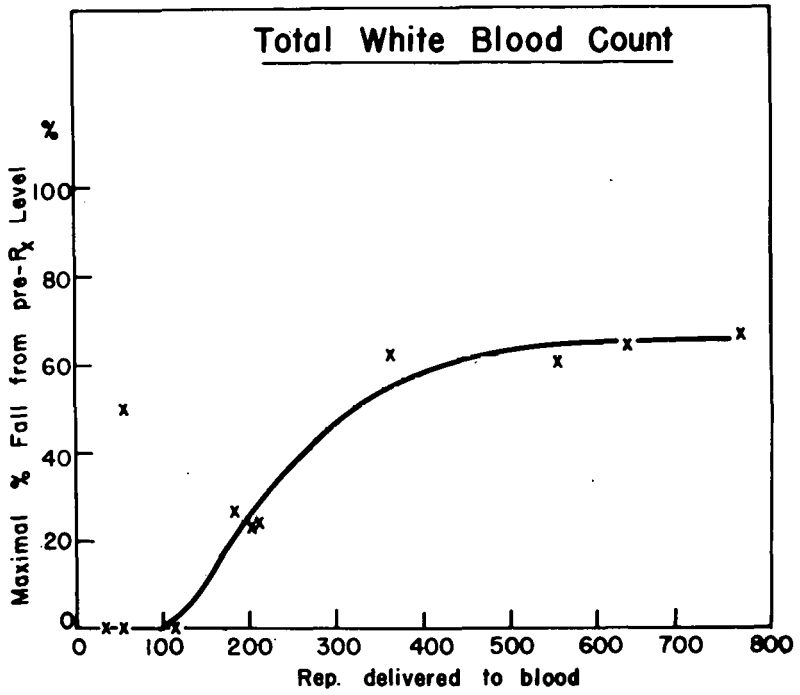


Figure 51. The per cent fall in the total white blood values from the pretreatment level plotted against dose.

treatment levels, there was actually no correlation and the points were distributed widely. The response is obviously related to the amount of radiation and not to the number of mc administered. The per cent fall of lymphocyte values is proportional in a good correlation, to the amount of radiation delivered (Figure 52). So large doses do have their limitations in terms of response of the hematologic system. This, in a sense, is a limiting factor and, in a way, almost the most important limiting factor, although it is hard to decide which factors are more important than others at times.

We have one patient that was referred to earlier, who developed acute myelogenous leukemia after receiving enormous doses of radiation. This was observed about 5 yrs. after the first dose. It represents perhaps a disadvantage of radioiodine, and perhaps the disadvantage of giving a large dose. It is hard to be certain whether the leukemia resulted from the I^{131}.

There are other organs or systems that might be affected by these enormous doses of radiation. Dr. Rawson referred to some women whose gonadal function has been studied. Although there has been some interruption of the menstrual pattern, the cycle was usually resumed. One man, who was presumed to be the father of a normal child before radioiodine therapy, had no spermatogenesis nor spermatozoa subsequent to therapy, although the tubules appeared normal.

In the chest, we have also seen dramatic results so far as eradicating metastases is concerned, but, in addition, we have seen some complications. One patient received radia-

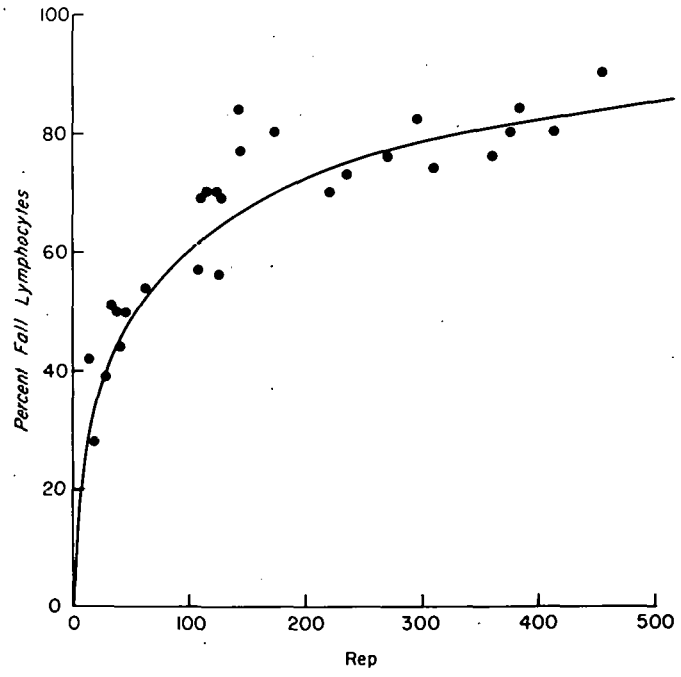


Figure 52. The effect of dose upon the lymphocyte values.

tion to the chest and subsequently developed moderate fibrosis in the lungs. At autopsy this was substantiated by the characteristic finding of thickening of the alveoli showing pulmonary fibrosis.

This was seen in still another patient who died, in which there was fibrosis bilaterally even though the parenchyma had been freed of metastases. So still another complication of this therapy is the induction, perhaps, of pulmonary fibrosis or pneumonitis.

We have taken 15 patients who had had pulmonary metastases and have tried to see if there is any pattern, in order to predict which patients might develop this type of complication. In Table 36 are shown the dose administered, the time, the interval between the first dose and the first notice of any change in the lung as well as the effect on the metastases. We have recorded the chest dose in terms of mc. The chest dose is merely the dose administered minus the cumulative urine dose, minus the amount that collected in the neck. We assumed that everything else that was retained was present in the chest. We have not referred to the uptake in pulmonary lesions because this involves a problem in geometry and this particular issue is being worked on now. There are about 7 patients that had changes in the lung that were revealed either by roentgenographs or by histologic examination at necropsy. Although many patients showed an improvement in their metastatic lesions, only about 7 patients developed pulmonary fibrosis.

Going back to the amount of radioactive iodine that we think may have been retained

Table 36

STUDY OF 15 PATIENTS WITH PULMONARY METASTASES AT THE TIME OF TREATMENT WITH RADIOIODINE

Case	Dose (mc)	Chest dose (mc)	Time*	Effect on metastases	Pulmonary damage
W.Mc(1)	112	106	8 yrs.	+1	0
(2)	107	85	5 yrs.	+2	++
G.F.	249	161	3 mos.(d)	+1	++++
O.D.	175	135	3 mos.(d)	0	++++
L.F.	300	210	2 yrs. 11 mos.	+1	+++
J.P.(1)	180	69	6 yrs.		
(2)	292	22	2 yrs. 3 mos.	-1	0
T.G.(1)	127	99	7 mos.	+1	+
(2)	241	125	5 yrs.	+2	+
A.G.	254	145	6 yrs.	+2	0
P.L.(1)	246	81	4 yrs. 5 mos.	0	0
(2)	302	46	3 yrs. 9 mos.	+1	+
G.G.	150.5	37	5 yrs. 3 mos.	+2	0
M.K.	198	36	4 mos.(d)	-2	0
L.L.	198	66	1 yr. 10 mos.	?	?
I.M.(1)	239	<121?	2 yrs. 8 mos.(d)	+1	0
(2)	209	<164?	2 yrs. 2 mos.(d)	+2	0
J.D.(1)	302	<133	3 yrs. 1 mo.(d)	+1	0
(2)	208	< 55	2 yrs. 9 mos.(d)	+2	0
S.F.	355	84	1 yr. 9 mos.(d)	+1— -2	0
D.K.(1)	129	110	5 yrs. 9 mos.	0	0
(2)	252	48	3 yrs.	+1	0

Chest dose-asymptotic urine-neck

Effect on metastases	Pulmonary reaction
-2 progress-death	0 none
-1 progression	+ minimal X ray
0 no change	++ moderate X ray
+1 improvement	+++ moderate X ray and symptoms
+2 disappearance	++++ death in pulmonary insufficiency

*Internal from dose until Dec. 1956 or until death.

in the chest, it seems that grossly the patients who had the largest doses were the ones that developed this complication. These patients who had marked pulmonary changes had 161 and 135 mc in their chest. Other patients had 210, 85, 46, 125, and 99 mc in the chest.

This is not to say, however, that every situation where a large amount of radioactivity localizes in the chest will result in pulmonary fibrosis. Grossly, if there is more than perhaps 85 or 80 mc in that region, I think we have to be concerned and may find this particular complication in patients who have diffuse as opposed to localized metastatic disease in the lungs. This is a serious complication and limits the size of the doses that we give.

Notwithstanding this complication, we have seen patients who have actually improved and not shown this complication. One patient, who in 1948 showed a diffuse pattern in his

chest, was treated with 2 large doses. Roentgenographs taken last year revealed a significant clearing in the chest. The issue has been raised that he might have a little bit of pulmonary fibrosis, but this man functionally is in rather good shape. He, too, had an amount of radioactivity in the chest that was significant, of the order of 100 mc.

In a way, I have presented this to show the disadvantages, but I would also like to point out that within this framework we have treated 45 cases and have obtained significant improvement in about 33 of them. To be sure, some of the patients subsequently had relapses and died, but I think this is still an impressive number which showed either sustained objective or temporary objective improvement. We have not included patients who have had subjective improvement.

DR. FRANTZ: What is your longest follow-up, Dr. Sonenberg?

DR. CHAPMAN: Were all these with metastases?

DR. SONENBERG: They all had metastases, but not all had lung metastases. I would say that only 10 to 25% of all thyroid cancer patients that come for treatment are presented to us for study. The longest follow-up is 9 years.

DR. STANBURY: In other words you have seen 400 or 500 patients with carcinoma of the thyroid and you have treated 10%. Is that correct?

DR. RAWSON: I think about 250 to 300 cases of carcinoma of the thyroid have come to the Center. We have accepted only those with metastatic disease for inclusion in our study. These observations were on patients in whom we were able to induce adequate function.

DR. McCULLAGH: What do you mean by sustained?

DR. SONENBERG: Patients like the one I told you about who had significant clearing for as long as 8 years and still has no signs of relapse. However, other patients who have shown clearing have subsequently had reappearance of the lesions.

DR. MILLER: We still ask the question how many patients did you have to see to get this 45?

DR. SONENBERG: I think we multiply that by about 7, that is about 15% of patients with metastatic disease who became available for treatment. As Dr. Rawson indicated, we had to see approximately 300 patients to treat these 45.

DR. MILLER: How many did you study that you could not induce uptake? Was that 85%?

DR. RAWSON: No, between about 50 and 60% have increased function induced.

DR. SONENBERG: Actually some of these patients originally were not suitable for treatment, and either after thiouracil or thyroidectomy satisfactory uptake was induced, so we were able to treat them. I think the larger group represents about 300 cases who presented themselves at the Center since 1947 or 1948. Of that 300, we were able to induce uptake and treat 45.

DR. WERNER: In how many did you fail to induce uptake? Was that another 45?

DR. SONENBERG: Actually uptakes were induced in about 2/3 of the ones we attempted.

DR. WERNER: So this 45 represent 2/3 of the ones attempted?

DR. SONENBERG: Yes. These 45 had induced uptakes. If we had to summarize about

indications for treatment and plans for treatment, we would start out in the following way and add certain qualifications: First, most of the patients we have treated were those that were considered to be inoperable by the surgeons. There are very few we have treated in a primary way who have not been treated previously surgically. A few were treated in a primary way because they were poor surgical risks or because they had such far-advanced disease that the surgeons thought they were inoperable. We have only gone ahead with radioactive iodine in cases in which we have been able to induce what we thought was sufficient uptake by the tumors. We have measured uptake inversely in the way I described. If the patient excreted 80 or 90% of a given tracer dose after thyroidectomy, the concentration of radioactive iodine in the tumor was considered to be inadequate. If, however, after treatment with thiouracil or after thyroidectomy the urinary excretion was down to 40%, so there was 60% retention, we would consider that adequate retention. After studying retention, we calculate the dose by giving the patient a tracer dose and checking blood levels over a period of from 10 to 21 days, integrating under the curve and converting the number of μc per g into rads. The dose selected is one that will deliver less than 500 rads to the blood. Now we add one or two other qualifications. One is that if a patient has diffuse pulmonary metastases, we try to localize less than 80 mc in the chest. This is very arbitrary and based solely on a few patients that were studied. In addition, we also deliver less than this amount of radiation in the second dose than in the primary dose. Our position is that we like to give large doses although we are presently qualifying this so that the doses are not quite as large but are within the framework of the limitations I mentioned.

DR. KEATING: How many large doses of this order will you administer to these patients?

DR. SONENBERG: I really cannot answer this question. The patient who developed leukemia is one for whom we did a lot of good so far as the metastases were concerned, but she developed this complication. She received almost 1000 rep. So when you ask how many doses, I think I am in no position to judge whether blood radiation is cumulative. We certainly would like to scale it down now because of those factors. We would make our limit 500 rads.

DR. JAFFE: Do you have any information on small doses rather than large ones? Can you prove large doses are better than smaller ones given over a longer period of time?

DR. SONENBERG: We gave small doses to several patients and noticed no change in the size of metastases in those who received them, but who subsequently retained less radioiodine.

DR. JAFFE: The roentgenograph shown in Figure 53 demonstrates the effect of small doses of I^{131} in a patient who had carcinoma of the thyroid gland. This little boy was 4 yrs. old when he was referred to us. He had evidence of a miliary type of metastasis distributed throughout both lungs. His surgeon did a partial thyroidectomy, and he was then referred to us for radioiodine treatment. He received about 6 mc of I^{131} every 2 weeks, and we watched his blood picture very carefully because, at that time, we did not know how much

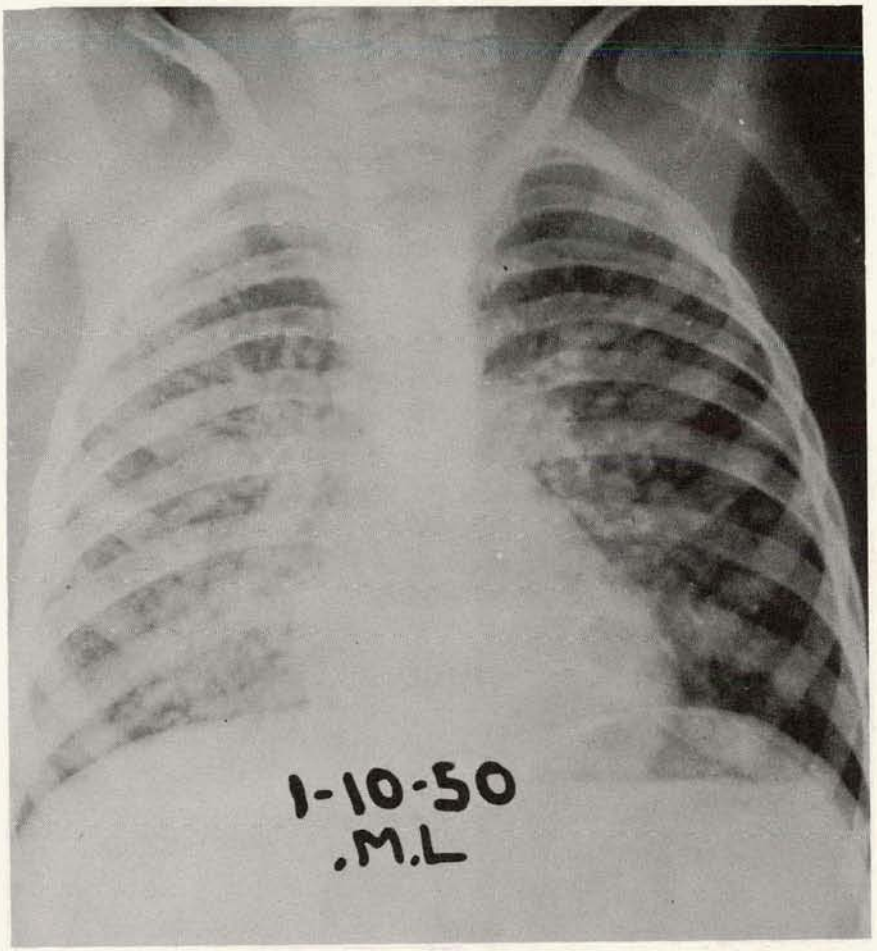


Figure 53. Roentgenograph of the chest of a 4-year-old boy showing extensive miliary type metastases throughout both lungs.

I^{131} this youngster could take. We continued to treat him until we no longer could demonstrate any evidence of uptake of a therapeutic dose in the chest. This treatment schedule continued for more than a year. He finally received a total of 175 mc of I^{131} orally and he became clinically myxedematous. Figure 54 is one of a series of roentgenographs that were made for follow-up, and it is the last one that was made recently. This is a 6-year follow-up of this child who is now clinically well and is maintained on substitution thyroid medication. There is no clinical nor roentgenographic evidence of residual or recurrent disease. We did not prescribe any thyroid medication until the child became myxedematous. By that time the metastases were no longer visible. Therefore, I do not believe that the thyroid medication had any influence in this case.

DR. SONENBERG: We have not seen them regress on thyroid. Regression has occurred only after we have given them a therapeutic dose of I^{131}. So I would not attribute any beneficial effect to exogenous thyroid administration.

DR. McCULLAGH: How long does it take radioactive iodine without thyroid to bring

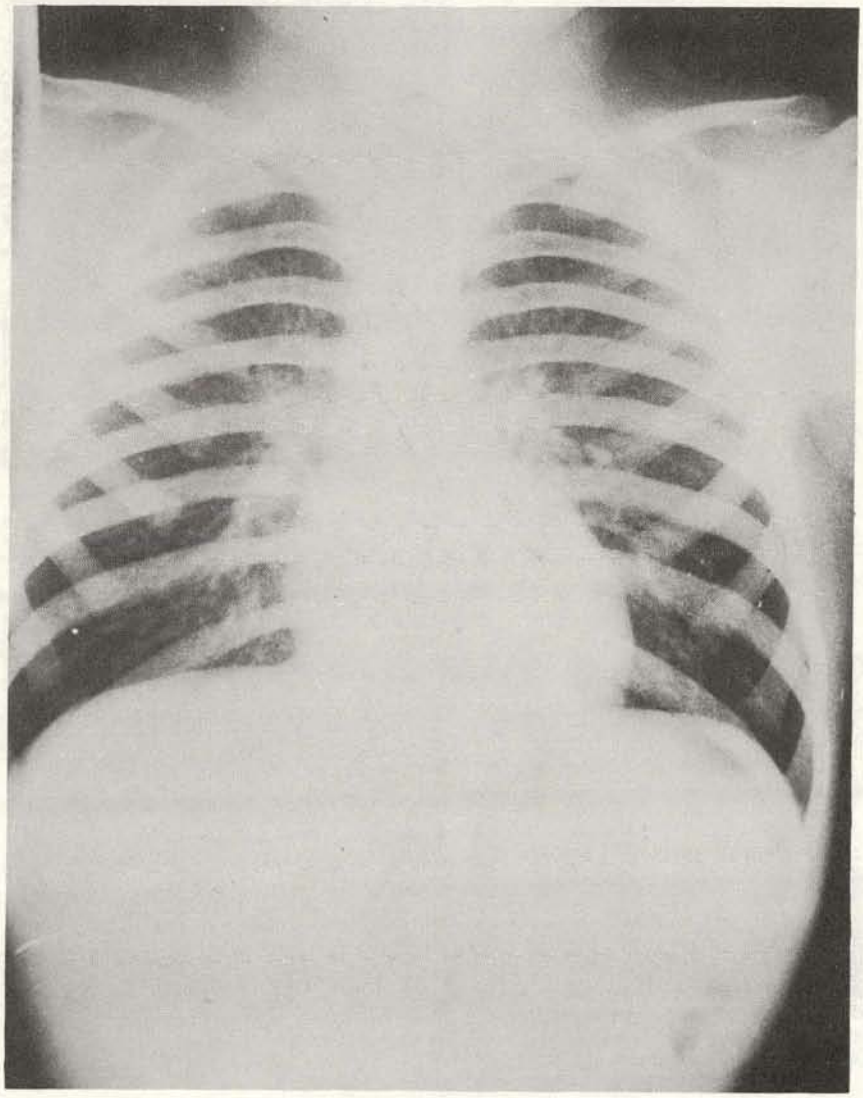


Figure 54. Roentgenograph of chest of same patient as is shown in Figure 53. Note complete clearing of the pulmonary metastases with I^{131}.

about noticeable improvement in metastases in the lung?

DR. SONENBERG: We have seen patients who had changes within a month. It is a difference that the radiologists pick up.

DR. McCULLAGH: Are there also some patients who require a much longer time to improve, and still apparently change as a result of radioactive iodine alone?

DR. RAWSON: I think that is well demonstrated by a 4-year-old boy whom we treated. Actually, serial chest roentgenographs taken about every 2 or 3 months were rather discouraging. It was not until a year and a half later that we became aware of the fact that it had disappeared. Then, going back, we could see how the disease had been regressing, but we had missed it. That was on I^{131} alone and without any thyroid during that time.

DR. CHAPMAN: May I ask Dr. Jaffe about this boy again? Did he have his thyroid removed?

DR. JAFFE: The nodule in his thyroid gland was removed surgically after a period of observation by the pediatrician who apparently thought that it was of no significance. It wasn't until the child developed a cough that a roentgenograph of the chest was ordered by his pediatrician that the metastases in both lungs were demonstrated. The nodule that was removed from the thyroid gland prior to I^{131} treatment showed definite evidence of thyroid malignancy.

DR. CHAPMAN: Total thyroidectomy was not done, and this is the result of continued therapy at the rate of 4 mc?

DR. JAFFE: No, at the rate of 6 mc every 2 weeks to a total of 175.

DR. FURTH: Do you know what the total-body radiation was?

DR. JAFFE: No, I do not.

DR. FURTH: With a cumulative dose of about 500 r, which is about the maximum tolerated dose, you would expect in man a maximum of about 1% leukemias. (Almost every dose of radiation confers upon the patient an increased likelihood to develop leukemia, the frequency diminishing with the dose.) This is no great risk if you consider the possibility of rescuing the patient with an existing malignant disease. There is the possibility of rescuing some patients by raising the dose of therapeutic irradiation. Bone marrow grafts may be protective in minimizing leukemia incidence and some other radiation effects. So one should think of taking bone marrow from the patient before treatment, preserving it in the frozen state, and repopulating the patient after massive therapeutic irradiation with his own bone marrow. This is a thought for your consideration.

DR. KEATING: Would you give a patient a dose that provides all the exposure you have indicated, all at one time?

DR. SONENBERG: No, we would scale it down. First of all, it is difficult to calculate blood doses on the basis of the tracer dose. As Dr. Rall mentioned, we have seen discrepancies between tracer and therapeutic doses where the latter delivered 7 times more than the predicted dose. We try to leave ourselves a little leeway on that ground, too. In effect, we are now giving doses that deliver only about 200 rads.

DR. JAFFE: Dr. Clark might like to know that the little boy received X-radiation therapy for an enlarged thymus at birth.

DR. FURTH: May I make another comment? Because of the difficulties of estimating the total-body dose, we should think of biologic dosimetry; e.g., lymphocyte depression (good if done meticulously) or sperm counts. We might think of physiologic effects; e.g., depression of some function.

DR. CHAPMAN: That is post hoc reasoning, however, and does not give us the estimate ahead of time. You said the difficulty lies in the fact that the tracer does not indicate what actually happens later with the therapeutic dose.

DR. CLARK: I would like to show a case of a 4-year-old girl, similar to Dr. Jaffe's, in which the diffuse miliary type of metastasis to both lungs (Figure 55) cleared with re-

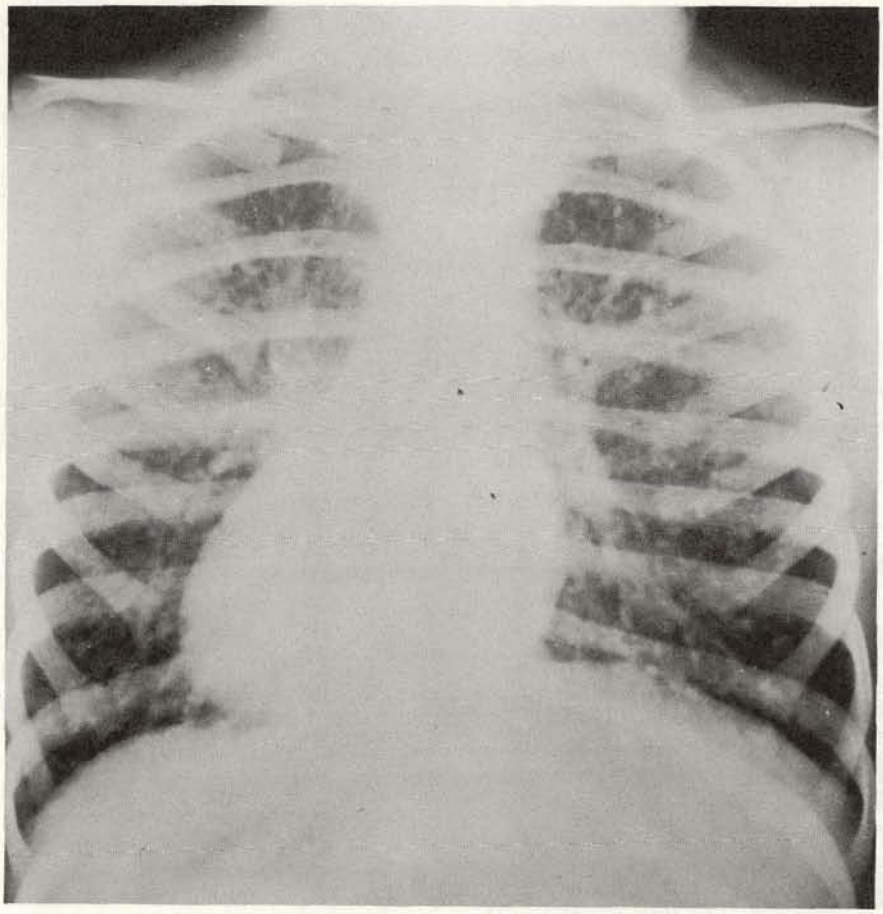


Figure 55. Roentgenograph of chest of 4-yr.-old girl showing diffuse miliary type spread of carcinoma of the thyroid.

peated small doses of I^{131}. We first saw her in March, 1952. In addition to the lung findings, she had evidence of bilateral involvement of the deep jugular lymph systems.

A photomicrograph of the tumor is shown in Figure 56. There are a few papillary elements in the tumor, but most of it was of the follicular type.

A radioautograph is shown in Figure 57. There was good, but spotty localization of I^{131}.

We treated her for 1-1/2 years with doses of 10 and 20 mc every 2 weeks. She received a total of about 400 mc.

Figure 58 shows her roentgenograph in October, 1953. It was reported by our radiologist as being essentially normal. The lungs have remained clear to date. We subsequently did bilateral radical neck dissections because residual pea-sized nodules persisted in both jugular lymphatic systems. Most of the lymph nodes were very sclerotic and contained numerous little islands of cells with pyknotic nuclei. These probably represent residual tumor cells. In view of this, it will be interesting to see what will be the future course in the lungs.

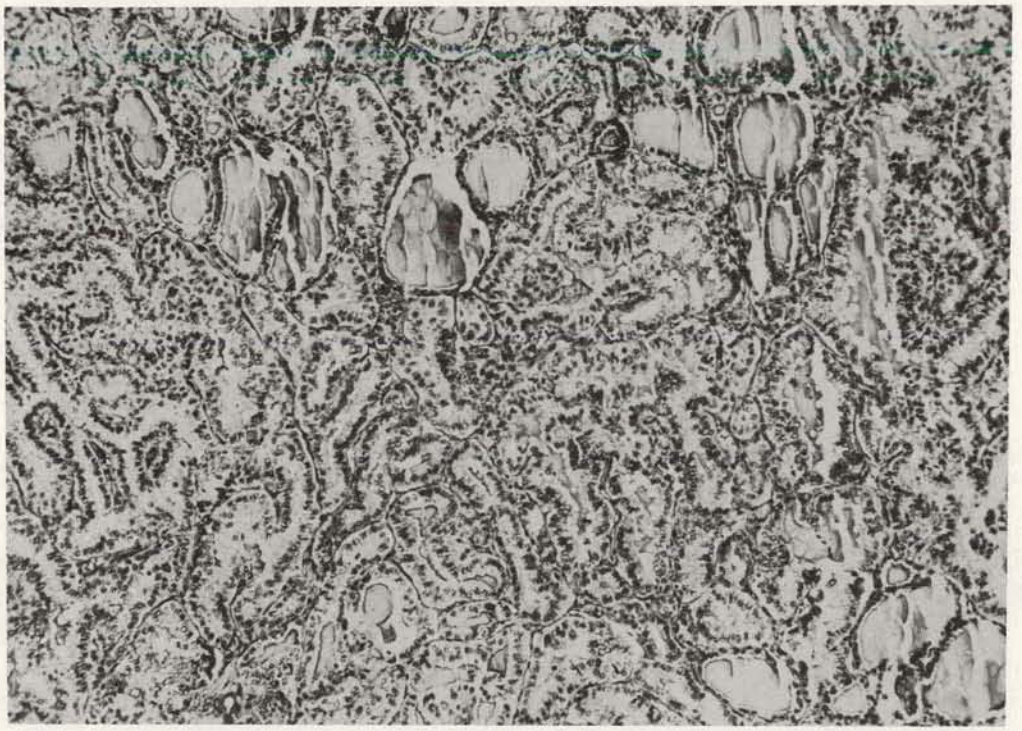


Figure 56. Photomicrograph. Most of tumor is of the follicular type with a few papillary elements.

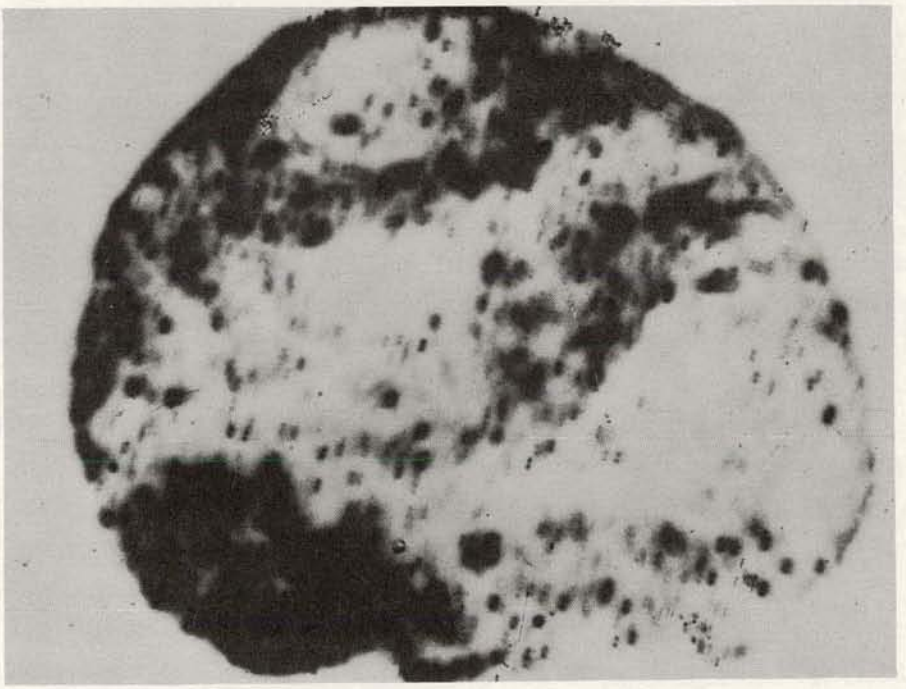


Figure 57. Radioautograph showing spotted localization of I^{131} in the tumor.

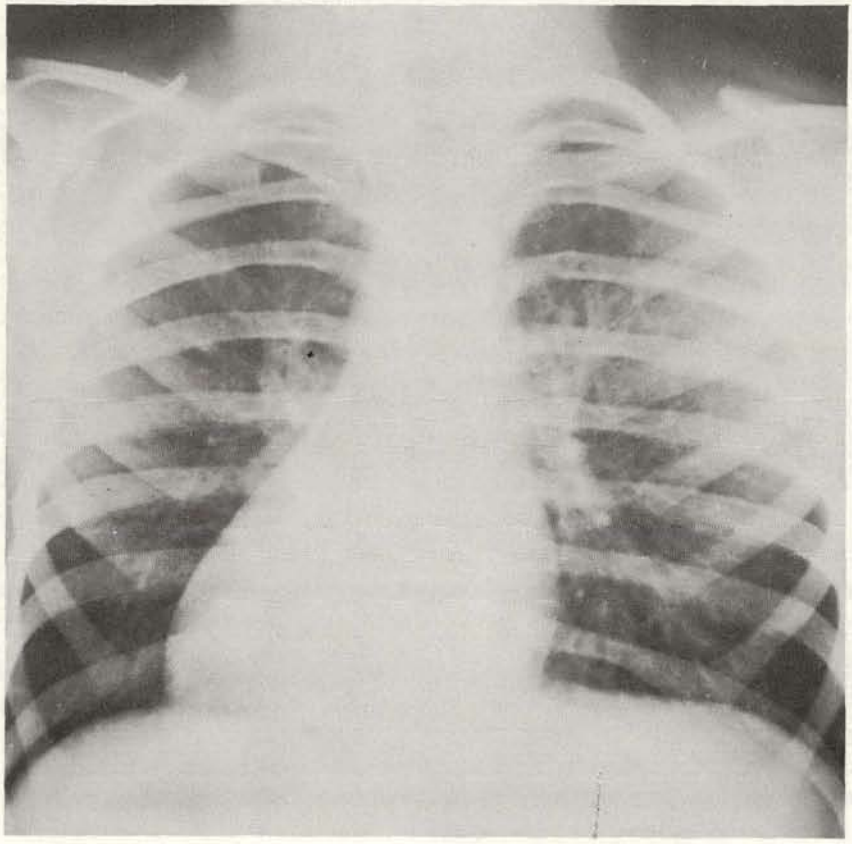


Figure 58. Roentgenograph of chest after treatment with I^{131}. All the lesions had cleared roentgenographically.

DR. RAWSON: Do you do major excretion studies on these patients?

DR. DOBYNS: I was going to say that that was one of the things I was going to talk about before. Namely, that after the initial dose of 10 mc, if you measure the urinary excretion, I think you would find that perhaps 90% was out in 3 days in the urine, in subsequent doses. I think that is based on findings in about 200 patients.

If one follows a first small treatment dose a short time later with a second, it will be found that much of the second dose is excreted in the urine. It therefore appears wisest to try to give the fully desired dosage the first time. It has seemed to us that there is a considerable difference between the dose that merely cripples the uptake mechanisms, and perhaps only temporarily, and the one that permanently damages or kills cells. Perhaps some of the groups have or soon will make very complete studies on urinary excretion, thyroid disappearance curves, and analysis of compounds in the blood of patients receiving a series of small therapeutic doses of I^{131} given at various intervals.

DR. CORRIGAN: I have some data in support of Dr. Jaffe's thesis that might be of some interest. I also have some typical cases.

Our philosophy was a little different from that which has been expressed by repre-

sentatives from some other institutions. I don't say it is better; I only say it is different. Since cancer cells have only a very poor uptake and, even more important, an extremely poor retention, we decided to try to treat one cell at a time. We would try to have a few radioiodine atoms available at the time each cell assumed any degree of function. We would take only those cases that were absolutely hopeless from all other points of view. If they could possibly be treated by surgery, X irradiation, or anything else anyone could think of, they would not get radioiodine. We had a 4-year-old, somewhat similar to the one Dr. Jaffe described, but unfortunately, we did not have a chance to treat her, and she died elsewhere. Our youngest patient was 17. She had local peritracheal metastases and is now alive and well and has two normal children.

Figure 59 gives the blood picture of one of our patients, age 22, whose treatment be-

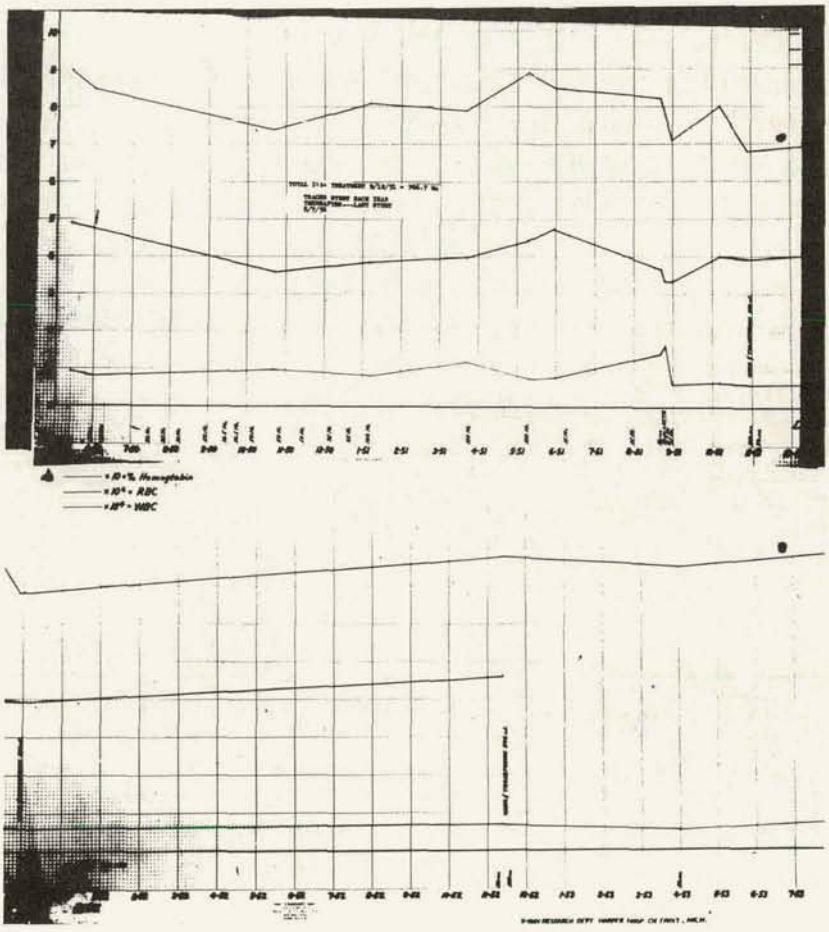


Figure 59. Graphic record of blood components in a patient who received 706 mc of I^{131} in small doses from May, 1950 through September, 1951. Eleven subsequent tracer studies on a semiannual and annual basis since that time have shown no signs of recurrence. Complete clinical and roentgenographic examinations were conducted each time. Clinical aspects of the case were under the direction of Drs. Wyman D. Barrett and E. C. Vonder Heide.

gan in May, 1950, and who now lives in perfectly good health and spirits and is perfectly normal so far as anybody knows.

Whenever her platelet count changed, treatment was stopped and also when we could not measure a retention at the end of one week,* it was stopped. This patient received 706 mc over the course of about 2 yrs. with perfectly satisfactory results.

We had a total of 219 cases, of whom 115 could have been considered treatable (Table 37). Thirteen of these refused treatment, 15 were treated by X irradiation and consequently were not treated with I^{131}. I would like to point out this chemical block business; almost without exception those were myelograms. Try to get your staff to do tracer studies before they do a myelogram in cases of anything that could be a thyroid lesion in the spine.

Table 37

TRACER STUDIES ON ALL CASES OF CARCINOMA OF THE THYROID BETWEEN JANUARY 1, 1947, AND OCTOBER 1, 1956. 23 OF THESE CASES WERE COMPLETELY UNSUSPECTED FROM THE POINT OF VIEW OF MALIGNANCY AT THE TIME THE TRACER STUDY WAS CONDUCTED. OTHERS WERE EITHER KNOWN OR SUSPECTED CLINICALLY.

Treatable metastases		115
Treatment given	52	
Treatment refused	13	
Treatment not given for other reason*	50	
Not treatable		10
Operated completely		60
Chemical block		14
Moribund		14
Quibble		3
Misses		3
Total		219

*"Other reason" means patient was treatable by other means, usually X-radiation therapy.

The data in Table 38 show how we came out in a period of a little under 10 yrs. We had a total of 55 possible treatable cases, 37 of whom were relatively successful. Of course, for the ones that died under 3 months, I think everyone will concede that therapy did not have a chance. The final score at the moment is 37 to 18. All of these were treated by a small dose technique, spaced usually at 1-week intervals over a period of years.

*This is a measure of a dynamic state. The concentration in the patient's metastases disappeared within 24 hrs. of clearance of the blood. Blockage was considered to have occurred if the metastases had no detectable count above blood and soft tissue background at the end of 1 week.

Table 38

RESULTS OF I^{131} THERAPY IN 55 PATIENTS WITH CARCINOMA

		Living	Died
Under 3 months	6		6
Under 1 year	16	6	10
1 - 2 years	3	2	1
2 - 3 years	5	5	
3 - 4 years	6 (2)*	6	
4 - 5 years	4	4	
5 years and over	14 (1)*	13	1
Untraced	1	1	
Total	55	37	18

*Followed by X-irradiation treatment.

Several had bilateral lung metastases.

DR. POCHIN: I believe my function in this program is to be controversial and this I will be. We think you can control treatments by making repeated γ counts of remaining uptake in the tumor. I want to talk about the indications for ablating the thyroid and those for starting treatment after you have ablated; and also about plans for the conduct of treatment and for stopping treatment. First of all, taking a few things for granted (Figure 60), I am assuming that all radically operable tumors will be treated surgically. And I am assuming that we are talking of differentiated tumors and that purely anaplastic tumors are treated otherwise, usually by external radiotherapy if appropriate. There are a few anaplastic tumors, or predominantly anaplastic tumors, in which we have found uptake or have gotten a response, but we are concerned mainly with differentiated tumors with evidence of uptake after thyroid ablation. In the differentiated group I would include papillary tumors or predominantly papillary tumors, provided surgery or repeated surgery had not appeared to be appropriate treatment in that particular patient. When I speak of papillary tumors or anaplastic tumors, I am talking about tumors in which the particular metastasis that you choose to biopsy happens to have that structure. There is great irregularity in histology from one metastasis to another.

Our intention then is to perform thyroid ablation surgically if there is a large mass in the neck that can largely be removed, or to ablate with radioiodine if one recurrent laryngeal nerve is already gone or if there is gross distortion of the structures in the neck. After ablation, we would review that patient in 6 or 7 weeks to see if there is any remaining uptake in what appears to be thyroid tissue, as there commonly is after what is regarded as a simple surgical thyroidectomy, or after the effects of one ablation dose, say of 80 mc. If there is any such remaining uptake, the patient will have a further dose at 6 or 7 weeks after the ablation. Patients will then come back 6 or 7 weeks later, and they will normally be fully myxedematous, unless there is a large mass of functioning tumor tissue.

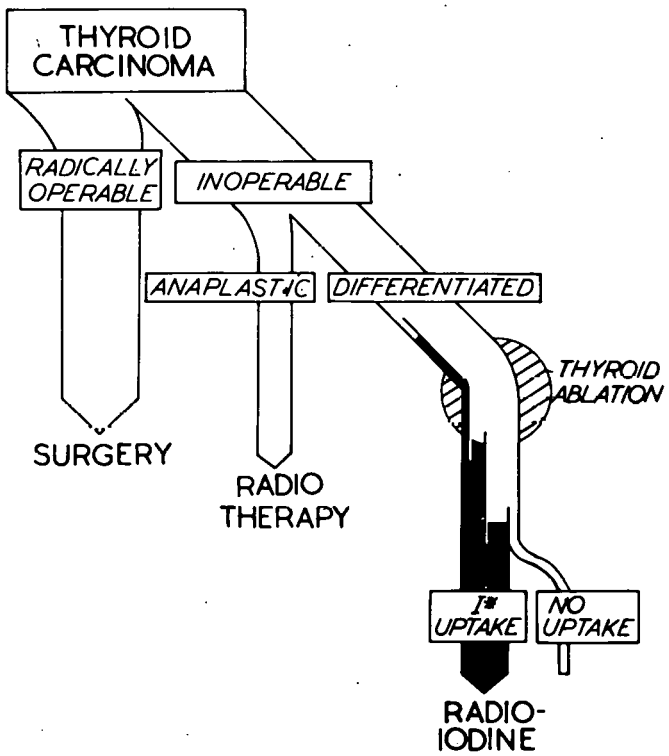


Figure 60. Diagram illustrating the basis used in selecting patients with thyroid carcinoma for radioiodine treatment. The black marking indicates the possible development of radioiodine uptake in tumor tissue before, immediately after, or late after, thyroid ablation.

The question then is, what amount of uptake in the tumor do you require before you are prepared to start treating. Here I would disagree with any set figure; for one thing it is very difficult usually to know what mass of tumor tissue you are dealing with, and after all, it is the tissue concentration of radioiodine that you are concerned with. Secondly, if you know the mass, you do not know what proportion of the mass is necrotic. Thirdly, if you do know what proportion is necrotic, you do not, in any case, know the radiosensitivity of the tumor. But once you have a patient in this stage, if you find any clearly definable uptake, we would feel that the right treatment would be to test the response of that tumor by a therapeutic dose. We would give a first therapeutic dose of say 150 mc and see what sort of response occurred. There is no exact agreement there; most people would want to treat if they had 0.1% of the dose concentrated per g of tumor; very few people would treat if they got only 0.001% per g of tumor. If it was between, I think that since the thyroid is ablated, and since presumably you are not afraid of irrevocable bone marrow changes from one 150-mc dose, then the right thing to do is to give such a dose. Whether 6 months of myxedema is better than 1 month of myxedema, or whether myxedema plus thiouracil, or myxedema plus TSH, is a better stimulus to tumor uptake of radioiodine than myxedema

alone, we don't regard as either proved or disproved; and, in fact, we regard myxedema as usually giving a maximal stimulus. If there was very little uptake, we would maintain the myxedema, but if there was clear uptake, we would give a dose at that stage. And I would repeat the point that came up earlier, that if you leave a patient completely myxedematous, you are presumably leaving her tumor under TSH stimulation and it is difficult to know whether that does have adverse effects or not. It might very reasonably have adverse effects.

Once you have started with a treatment dose, we believe that you should follow it with γ counts over the tumor rather than by excretion in the urine; and measure the actual uptake that you can detect in the tumor.

When you get a progressive fall in this figure with successive therapeutic doses, which you very commonly do under these circumstances, I admit that you don't know whether this is a reducing quantity of tumor, or a constant amount or increasing amount of tumor of decreasing efficiency of uptake. But the measurements we have made by test doses given soon after a therapeutic dose, in the few patients in whom we have been able to do this, have indicated that uptake returns relatively rapidly after a therapeutic dose. I know this is in conflict with some evidence from radiotherapy, but we have obtained full uptake again at about 4 weeks after a therapeutic dose; that is, where the uptake is high at the time of the dose, it is absent at 1 week or 10 days or a fortnight after it, and then rises to a constant level reached at about 4 weeks after the dose. So we would initially give doses at 6-week intervals and hope to obtain a progressive reduction in uptake figure on successive doses and a corresponding reduction in tumor mass.[1-3]

You may get a rather easier method of following the fall in tumor uptake if you follow the progressive fall in the amount of organic or protein-bound radioiodine in the plasma; the thyroid is now gone, the tumor is turning out hormone into the circulation and its concentration at 6 days or so after each dose may give evidence of the amount of functioning tumor tissue that remains.[1]

This will provide a basis for treatment in which you ablate the thyroid, test for uptake, and, on finding uptake, start giving 150-mc doses at intervals of about 2 months to begin with and, as the total uptake falls below about 1%, at 3- or 4-month intervals; and, when the uptake falls to 0.1% at 6- or 9-month intervals. Then you switch to annual test doses when you can no longer detect radioiodine uptake in tumor tissue. Admittedly, a lot of the radioiodine that you give is carried into the urine, but if your concentration per g of remaining tumor remains constant, as it often seems to do, you have an equally valuable therapeutic effect with each dose until you get down to very small dimensions of remaining tumor masses. It seems to me that there is no other form of radiotherapy in which you would stop treatment when you know there is remaining tumor tissue.

This method can only be adopted if you are not afraid of bone marrow changes, and that is a point I want to discuss in a moment. Figure 61 shows results in 83 patients, of whom 18 have failed to survive the first 3 months after thyroid ablation during which iodine uptake would be unlikely to develop. These patients were never started on therapeutic

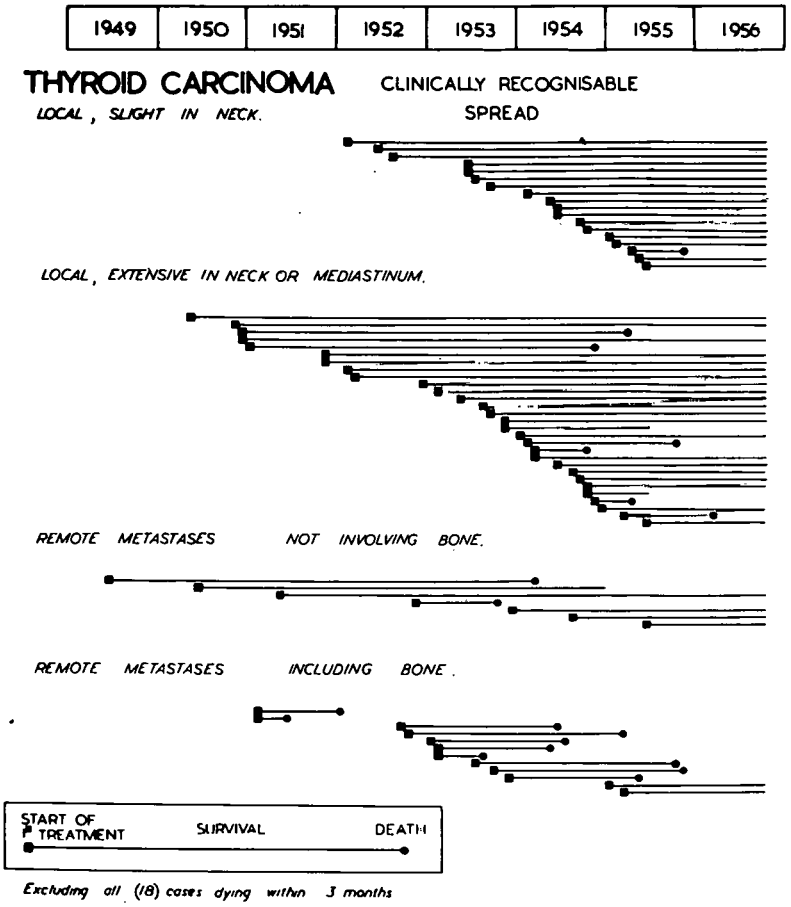


Figure 61. Length of survival of patients with thyroid carcinoma treated with radioiodine according to distribution of metastases at the start of treatment.

doses. In the remainder, a group of 10 had uptake which was initially demonstrated at sites of tumor tissue but which was reduced progressively by therapeutic doses until it was no longer detectable. This involves a duration of about 2 or 3 yrs. (Table 39). There are 10 other patients in whom this abolition of uptake is nearly reached, and 2 others in whom there is still a high remaining uptake associated with tumor tissue. We feel that prolonged dosage, if it is not prohibited by bone marrow changes or by other complications, is the right treatment, using a level of about 150 mc per dose. Once there is a fall in amount of functioning tumor tissue and the thyroxine elaboration is reduced, the dose from the thyroxine phase becomes negligible, and the plasma dose is about 0.33 rep per mc. So these are 50-rep doses, for all but the first few doses. The first few would have about 1 rep per mc for every 1% per liter of protein-bound thyroxine elaborated by the tumor.

I don't want to talk about results now, and I don't want to talk about results for 30 yrs. anyhow. The one main point that has emerged from our experience with these patients is that patients with bone metastases are the ones in whom we are afraid of bone marrow

Table 39

COURSES OF RADIOIODINE TREATMENT IN PATIENTS WITH FUNCTIONING THYROID CARCINOMA

	Millicuries (total)	No. of therapeutic doses excluding ablation	Duration (months)	Remaining uptake % of dose
Course completed	550	4	17	< 0.01
	830	5	11	< 0.02
	830	5	19	< 0.02
	980	6	22	< 0.01
	980	8	31	< 0.015
	1130	8	44	< 0.01
	1280	8	34	< 0.015
	1300	9	50	< 0.01
	1400	10	54	< 0.005
	1410	10	49	< 0.01
Average	1070	7.3	33	
Course continuing	1130	7	24	0.01
	830	5	20	0.02
	1710	13	65	0.02
	880	5	14	0.03
	1630	10	41	0.03
	1130	7	31	0.04
	830	5	12	0.05
	1700	11	37	0.05
	680	4	9	0.06
	1280	8	22	0.07
Average	1180	7.5	28	0.04
	1710	11	32	0.22
	1020	7	15	4.5

changes, and in other patients we are not. Only twice have we had bone marrow changes that forced us to feel alarm or interrupt our therapy in any patient who has not had bone metastases, whereas in the patients with bone metastases, in whom the treatment was continued for over a year, we have usually found bone marrow changes. There seems a very strong correlation there. There are possible explanations for it, but in patients with bone metastases, the survival period has been short, except in 2 patients who were started on treatment about a year and a half ago. There is a clear distinction between those and patients in whom there were large masses in the neck but no bone deposits; the group with non-bony remote metastases (Figure 61) is too small to make much distinction on, but it does appear that there is distinction between that group and those with bone metastases. So we feel that a patient should be given repeated doses unless there are blood changes, until the uptake at the tumor site ceases to be detectable, and that this result can be achieved quite commonly in patients without bony metastases.

DR. TRUNNELL: I would like to take issue with Dr. Pochin on two points. In arguing

the case for repeated administration of relatively small doses, he has omitted consideration of a possible decrease in tumor radiosensitivity with passage of time. Such a decrease in radiosensitivity (or increase in radioresistance) in other kinds of cancer subjected to other kinds of radiation over a period of time is well known. Take, for example, a lymphosarcoma that may respond very well the first time it is X-irradiated, poorly the second time, and not at all the third. Too, I would like to disagree with the idea that pouring radioactive iodine into a virtually tumorless patient constitutes little risk. To do so means that the kidneys, gastric mucosa, bone marrow, lining of the mouth, salivary glands, and the bladder and urethra are all being irradiated needlessly. It reminds me of firemen who go on chopping holes in the roof and pouring water into a house after the fire has been controlled reasonably well.

DR. POCHIN: It is the real point to answer, which are you most afraid of, persisting carcinomatous tissue or these possible effects on bladder and urethra; and I would rather have the fire out if it is possible. We had expected to find radioresistance developing, but it is rather surprising that it does not seem to do so, and that the points continue on a straight line for so long.

DR. RAWSON: I would like to ask a couple of questions and then make a comment. Both Drs. Clark and Jaffe have given us some rather remarkable results in young children. Our results in children have been rather disappointing. We have been unable to induce function in the metastases if they were in children under the age of about 12. We started this work in 1948. Leonidas Marinelli discussed the possibility of frequent small doses, and we chose a dose of 25 mc after we had induced good function in these cases. I think there are about 4 of those patients; all failed to pick up or retain radioactive iodine on the chest dose given after the therapeutic dose. This may represent a difference in the biology of tumors we have seen, or there may be some other unknown factor. I have discussed this with Dr. Pochin a number of times. I personally cannot accept the change in function of the tumor as representing decreasing growth of the tumor. It appears to me that growth and function of the tumor are not synonymous. As a matter of fact, I rather suspect they are widely separated.

DR. FURTH: After 2 weeks of treatment, I^{131} "killer" thyroid tissue may still be present, not yet absorbed.

DR. RAWSON: That is what we have found when we did wait longer, and in some cases we waited a long time. Two of the young girls acquired a marked retention of radioiodine with a short period of prior treatment with thiouracil. However, after a 25-mc dose, it took many months before they acquired function again.

DR. CLARK: We have 3 children with a diffuse miliary type of pulmonary metastasis who have had a good response to repeated small doses of I^{131}.

DR. RAWSON: Have you had any children that failed, as we have?

DR. SONENBERG: With these multiple small doses I wonder why, if we do not check the urine for retention as Dr. Pochin does, you say you give it for a year? Why not quit after the second dose?

DR. CLARK: We have not checked our patients by means of urinary excretion but most of the patients have been scanned from time to time, and as long as we think there is any pickup of I^{131} by the tumor, we will continue treatment. They are also checked roentgenographically at regular intervals.

DR. RAWSON: Our patients had a miliary type also.

DR. CLARK: We had one other little girl that had one small solitary lesion, and she has shown no response whatsoever. No pickup was demonstrated on scanning. This lesion could have had a fair localization of I^{131}, and I doubt if it would have made much difference in the urinary excretion. Surgical excision of such a lesion must certainly be considered.

DR. RAWSON: All ours that were miliary have spread.

Part II — Dosage Method and Results of Treatment

DR. CHAPMAN: We must now turn to the problem of dosage method and results of treatment.

DR. FRANTZ: This is the case, which was treated so successfully at Memorial Hospital, that Dr. Chapman would not let me present earlier. The patient was a woman of 49 who had had a slow-growing tumor in her thyroid for many years. In 1924, the tumor was enucleated by Dr. George Brewer, then Professor of Surgery, and was considered a benign adenoma. In 1934, she went to Memorial Hospital with bilateral pulmonary metastases and was treated there. A succession of chest roentgenographs (Figures 62-65) shows a diminution in the size of the nodules although there was considerable radiation fibrosis, so that by 1938, her chest was virtually clear. She remained free of symptoms subsequently and died suddenly in 1942 of a coronary. Her chest plates had been checked by her radiologist throughout this whole period at 6-month intervals. There never was any recurrence in the chest. She died, therefore, at least 29 years after the onset of the tumor, 19 years after the enucleation, and 8 years after the metastases were first demonstrated, at the age of 68. It is this type of case that makes it so difficult to compare different types of therapy. It is this case also that brought to our attention the radiosensitivity of follicular tumor metastases.

We have talked a great deal about our cases of thyroid cancers but our experience is really limited in numbers, only about 450 cases from 1915 to date. We feel, however, that we have something to say because of experience with cases with a very long follow-up like the one just cited. Figure 66 is a radioautograph of tissue from a paillary carcinoma. In our experience, and this is contrary to some reports, one cannot treat papillary tumors with radioiodine. We have never demonstrated I^{131} uptake in papillary tumors. The illustration shows the inactive papillary tumor surrounded by active thyroid gland.

It puzzled me in the past to hear about lung fields completely cleared by radioiodine therapy of metastases, presumably from papillary cancer. We have seldom seen any re-

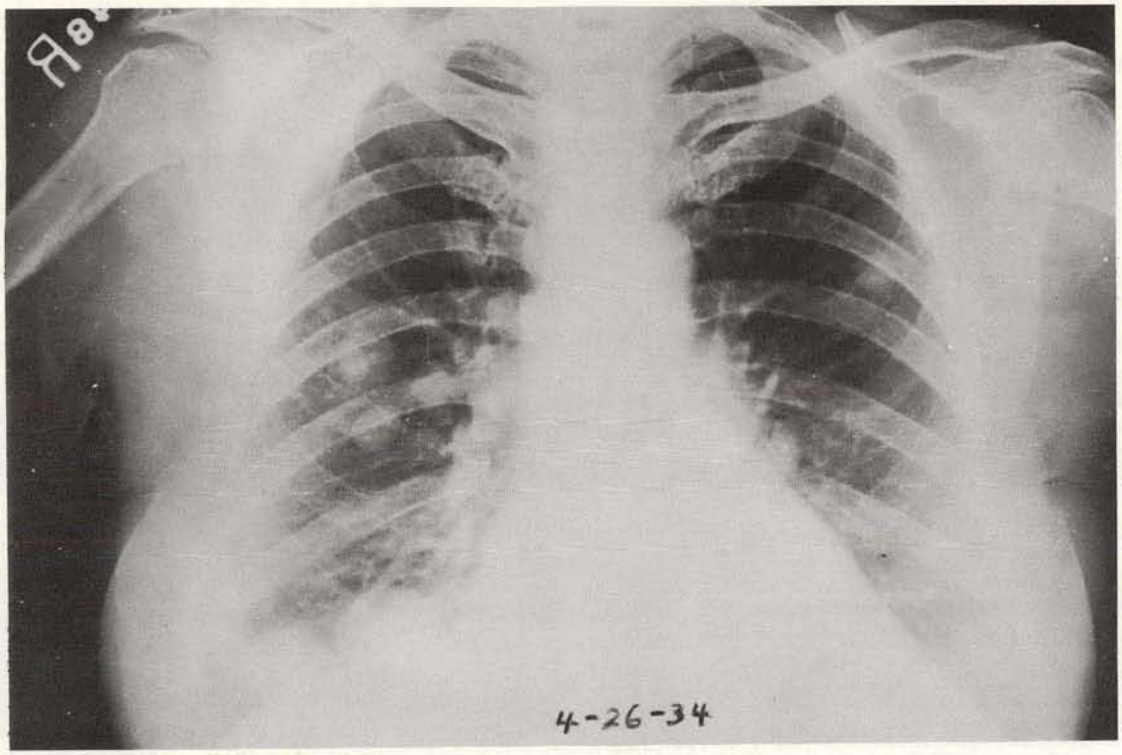


Figure 62.

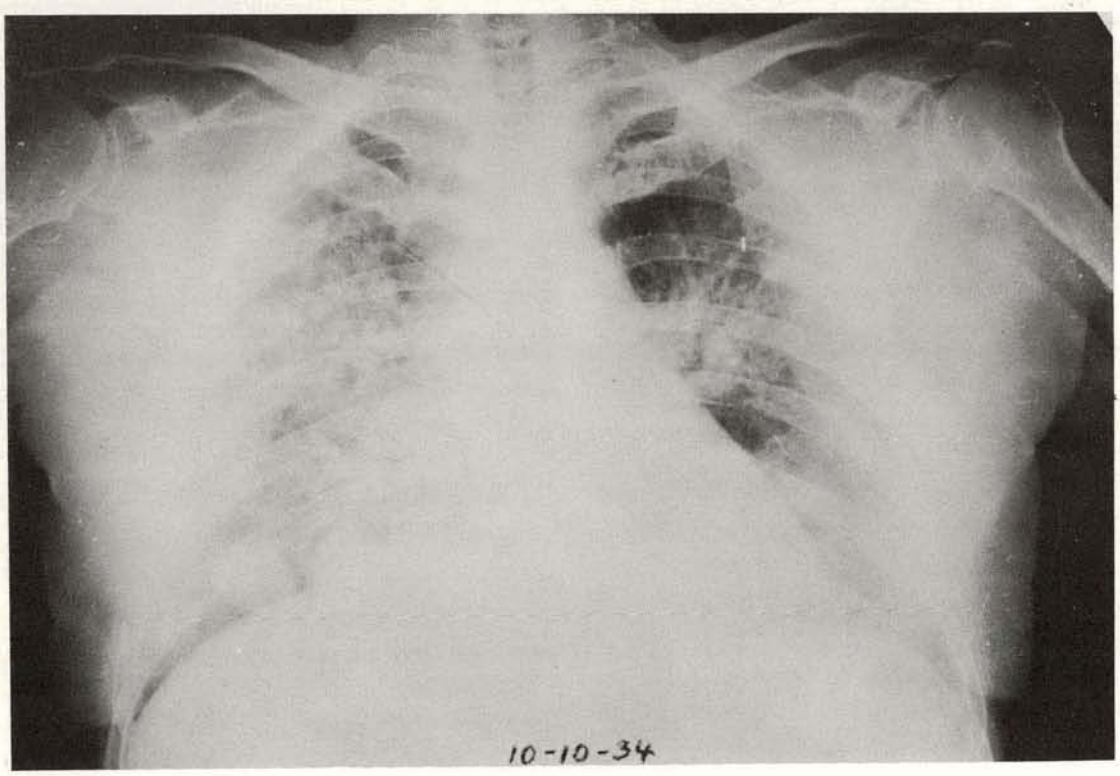


Figure 63.

Figures 62-65. Series of roentgenographs showing effects of irradiation upon pulmonary metastases.

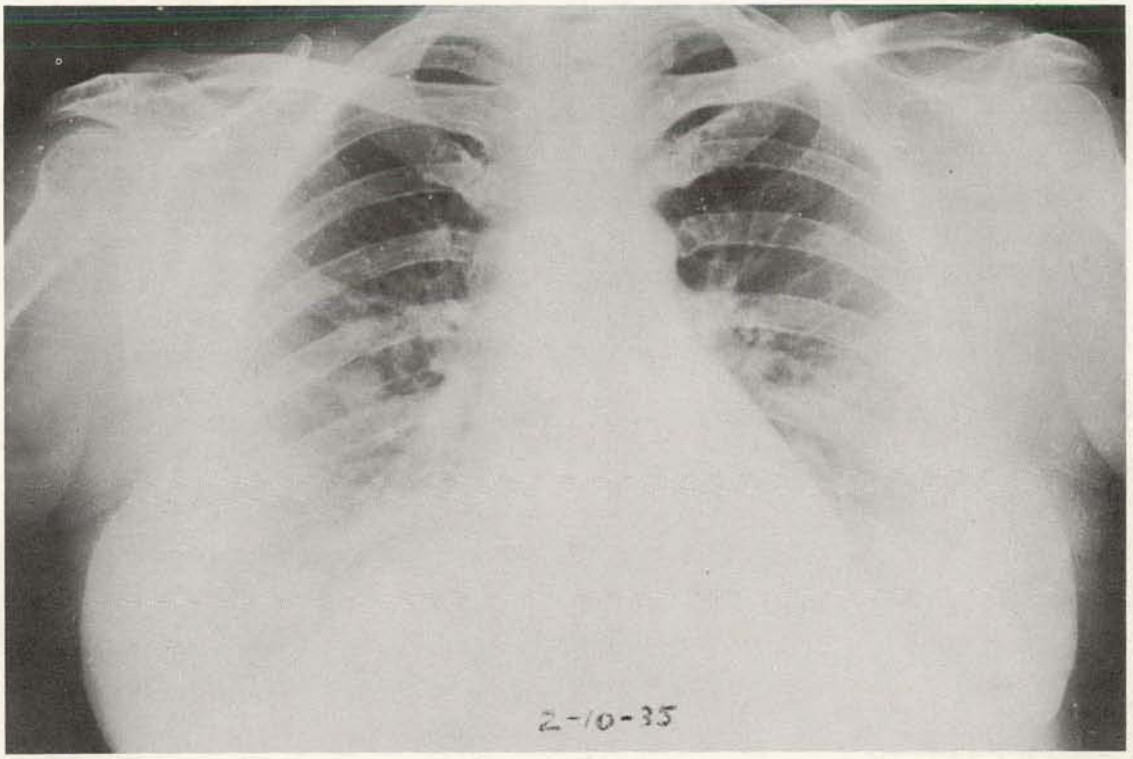


Figure 64.

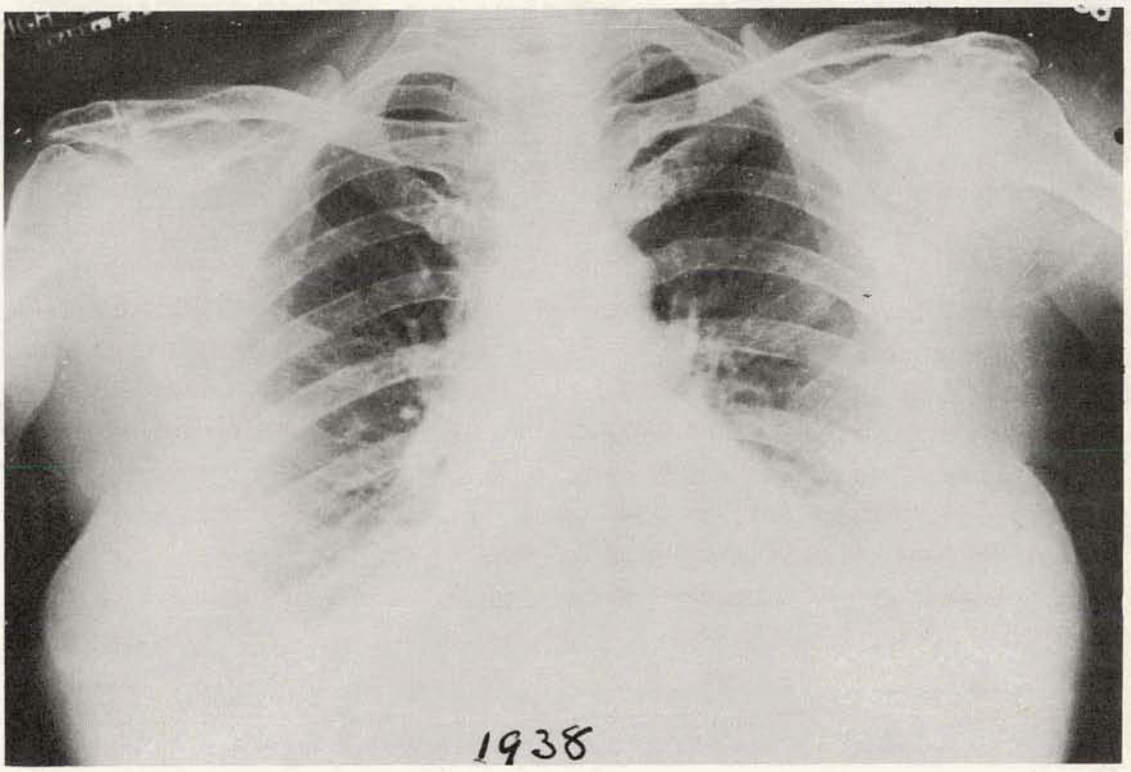


Figure 65.

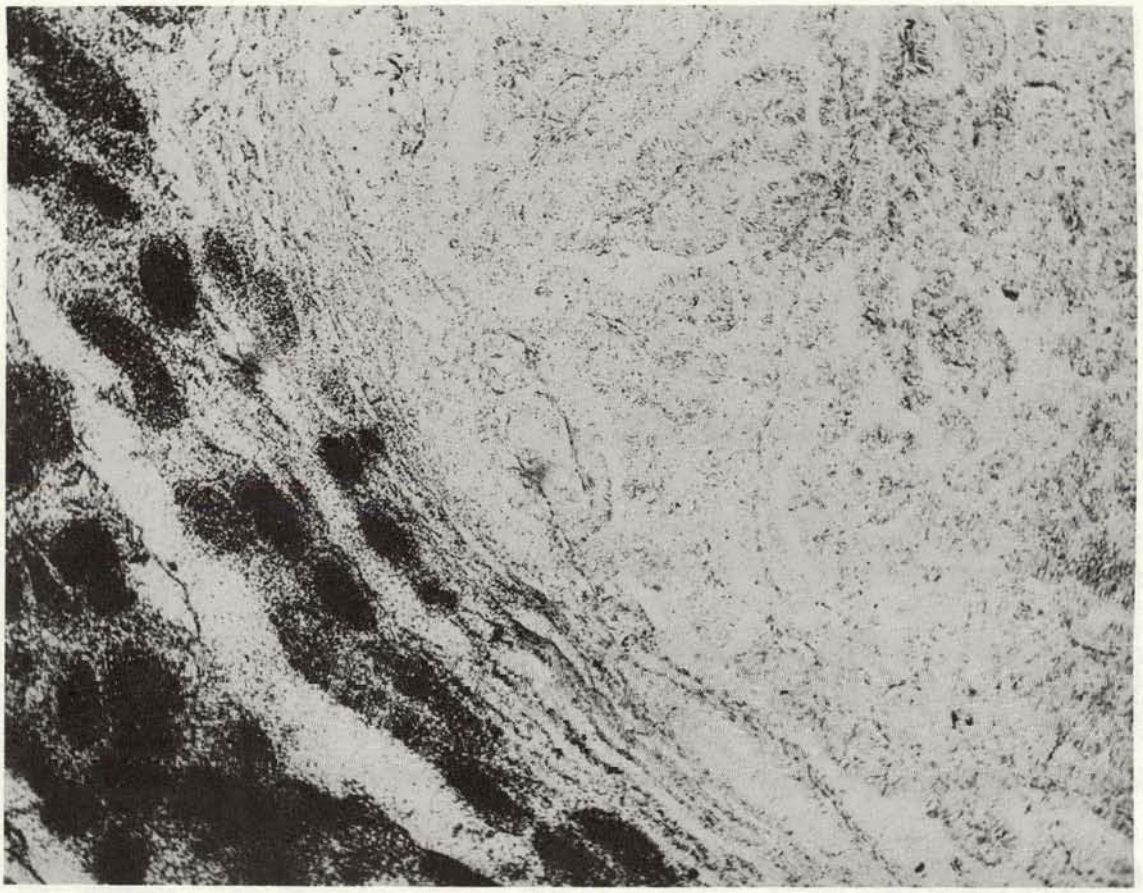


Figure 66. Radioautograph of tissue from a papillary carcinoma.

gression following X irradiation of papillary tumors. If they do not respond to X radiation, as the previous patient's follicular tumor did, I do not know why they should respond to radioiodine in the improbable event that they take it up.

We share with Memorial Hospital another case that seems to offer a solution to the problem. Sometimes one can learn a good deal from a single case. A girl named Dorothy came in August, 1934, at the age of 8, to Memorial Hospital, with a tumor of the thyroid and metastases and lymph nodes in the neck.[4] She had a right hemithyroidectomy and excision of a supraclavicular mass of metastatic nodes. Dr. Fred Stewart, who I think knows something about histopathology, said she had a papillary tumor with a follicular component.[5*] A month later, a chest plate showed multiple pulmonary metastases. These were not treated, but a right radical neck dissection was performed in November. In May, 1935,

*The case appears in the reference given with a diagnosis of "follicular and alveolar carcinoma of the thyroid." This is in contradiction with the report that Dr. Foote read me from the chart over the telephone. The case, however, remains essentially the same, and since I presented it at the meeting it seems wise to let it stand, controversial though it may be (another lesson!).

Dorothy, having reached a somewhat more mature age, began to have symptoms of increased intracranial pressure. She was referred to the Neurological Institute where Dr. Byron Stookey removed a solitary metastasis in her brain. That solitary metastasis in her brain was a pure follicular tumor. I therefore suggest that Dorothy could have had just exactly what Fred Stewart said she had in her neck, a predominantly papillary tumor, which behaved like one in local metastases. I know she had a follicular tumor in the brain. What the spontaneously disappearing lung lesions were, remains a mystery. She was known to be well 17 years after onset, 15 years after operation. She is married and the mother of 1 or 2 children.

This has all come together as part of a picture that I simply could not understand previously, having taught generations of third-year students that characteristically, papillary tumors are multiple, often bilateral, in the gland, that they metastasize to the regional nodes, recur locally, and appear in the lungs in the terminal stages of disease. On the other hand, I taught that follicular tumors are characteristically single, seldom return when enucleated, never go to the regional nodes, and go to the bones often before the primary lesion is appreciated. I should not really describe their biologic characteristics with such emphasis any more, yet I wish I could because I think it is the right teaching in general. Usually these two different types of carcinoma remain true to type and metastasize differently.

In this connection, the photomicrograph shown in Figure 67 was made from tissue from one of Dr. Sloan's favorite patients. She must be very fond of him because he has operated on ther 11 times, I think, and she asks for more. That is the kind of man Dr. Sloan is and that is why we have such an amazing follow-up. In the first fifteen years of intermittent surgery, her tumor was purely papillary. Then Dr. Sloan felt some very tiny lymph nodes, so small that we laughed at him for finding them. They were so superficial that we suggested they were probably bits of suture material. But he went after these nodes. One was 3 mm in diameter and one was 2 mm. In the 3-mm node (Figure 67), there was a metastasis in the marginal portion of the node which I considered papillary. It has a psammomatous body near it. I also thought it was papillary because, according to the radioautograph, there was no uptake. In the 2-mm node that was adjacent to this node, but not part of it (Figure 68), there was also a minute metastasis in which there were follicles. These were very well-differentiated follicles, and they had function (Figure 69). So in these two immediately adjacent lymph nodes there were two types of metastases. Then Dr. Sloan's finger "fell behind the patient's esophagus." (How it could fall anywhere is difficult to understand, after the number of operations and the amount of scar tissue that must have been present.) He encountered a lump he had not appreciated at all on physical examination. He took it out. It was about 5 cm in diameter and it was a pure follicular malignant adenoma. So—I am not quite sure now which kind of tumor is which. We speak of these tumors as mixed papillary and follicular type, but expect them in general to follow the pattern of growth and spread considered typical of the "pure" papillary carcinomas.

Before I forget it, I want to say one thing also in connection with Dr. Dobyns' magnif-

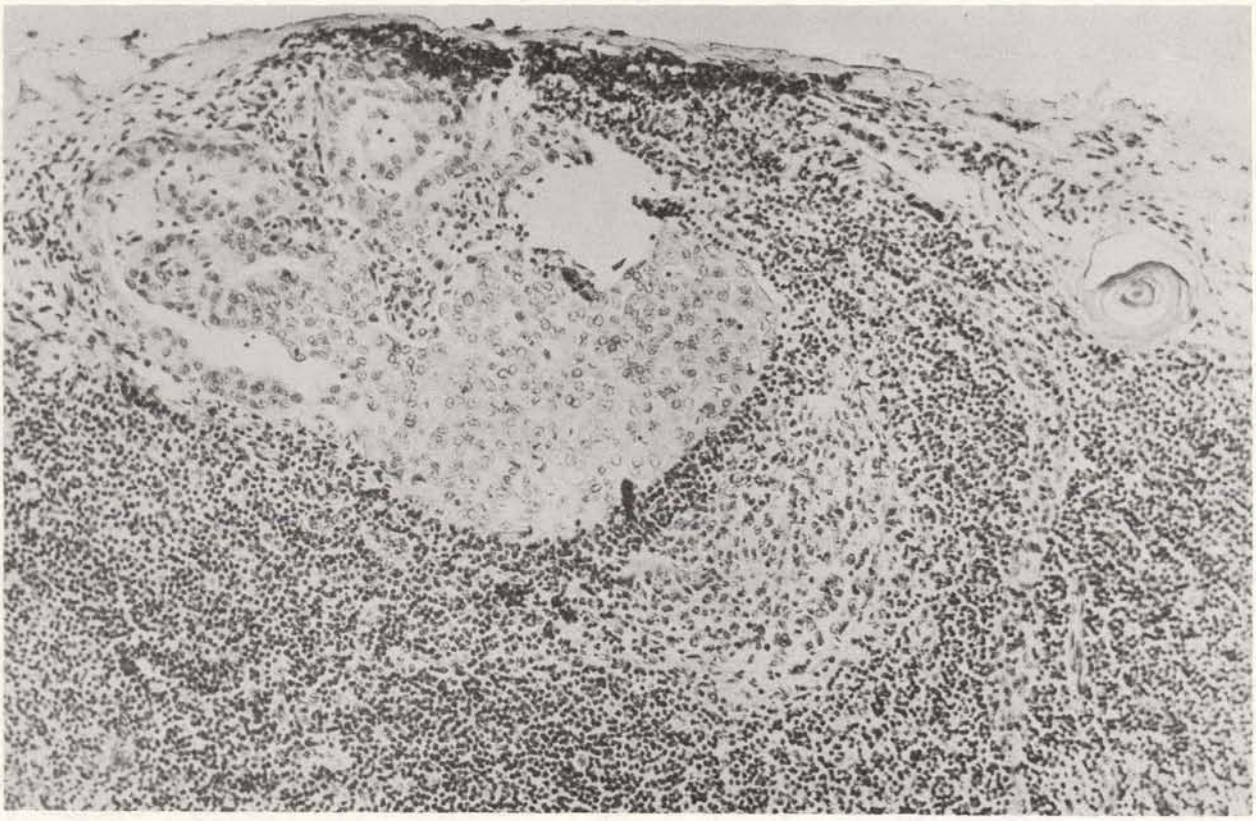


Figure 67. Photomicrograph of lymph node showing papillary metastasis.

icent work I wish I had done myself in the last 10 yrs., and which remains to be done in our hospital. That is, the preoperative determination of the nature of the adenoma as to its function and as to its potential malignancy by radioautographic studies. I think Dr. Dobyns doesn't do the frozen sections, do you?

DR. DOBYNS: I do the surgery. We always ask that frozen sections be prepared. I prefer to go out and read the sections as the time of the operation.

Since early in 1947 we have been advocating the following sequence of steps in the care of a patient with an adenomatous goiter:

1. Give a tracer of I^{131} to determine by directional counting whether the tumor is hot or cold and thus prepare the surgeon for the likelihood of a malignant nodule.

2. Operate only when I^{131} is present in that thyroid.

3. Always remove the mass in thc thyroid by keeping outside the capsule of that mass; this means removing a pad of normal tissue with the capsule.

4. Prepare a frozen section and if there is any uncertainty as to the possibility of malignancy,

5. Immediately count the radioactivity in samples (of equal weight) of the tumor and normal thyroid tissue.

6. If the tumor is decidedly cold compared with the normal thyroid, the remnants of

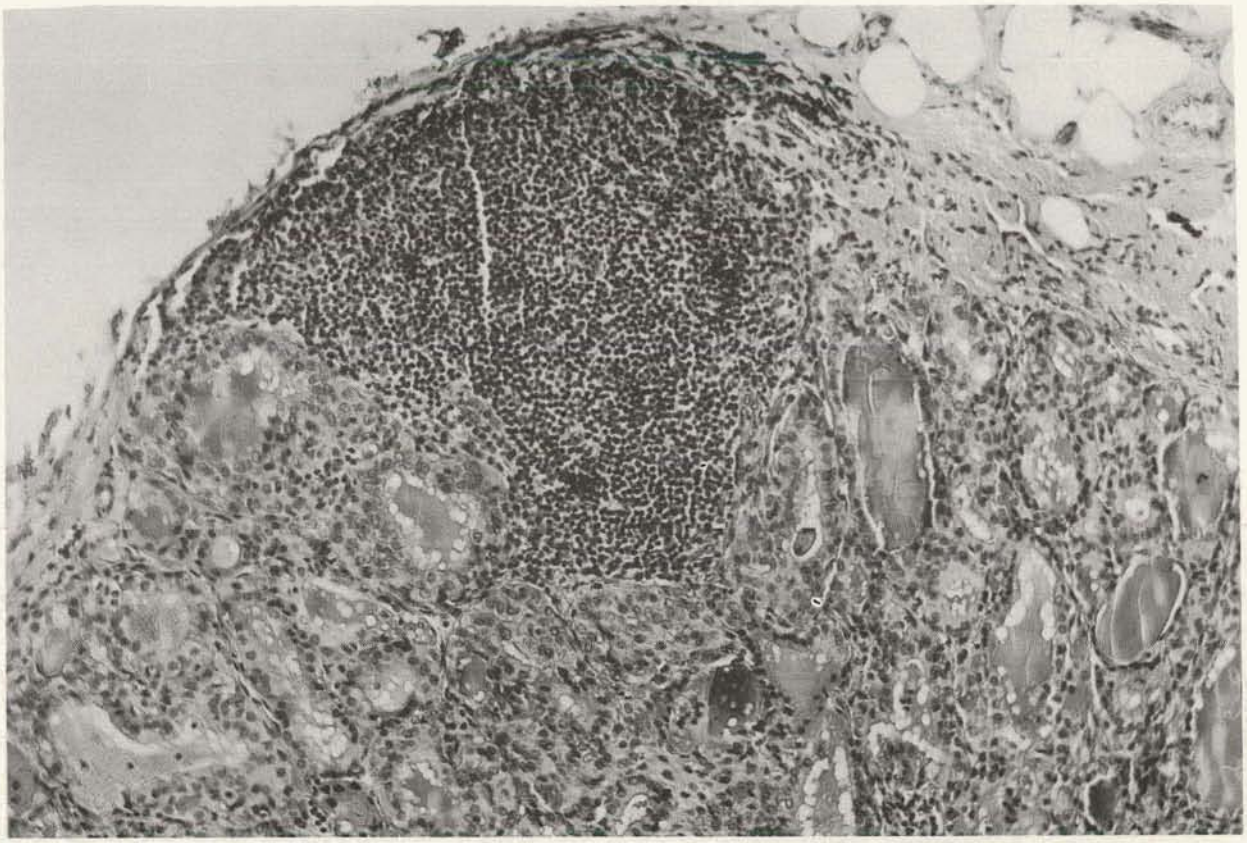


Figure 68. Photomicrograph of 2-mm node adjacent to the one shown in Figure 67. Note well differentiated follicles.

that lobe and isthmus are clearly and completely removed, or if total thyroidectomy is called for, the completeness of the removal is checked by counting radioactivity before the incision is closed.

It seems to us that this is the best way to avoid uncertainties that arise all too often in thyroid surgery.

DR. FRANTZ: And if the tumor is functional, do you say it is benign or malignant?

DR. DOBYNS: If it is less than about 5% of the normal, you had better remove it widely because it is among this group that malignancy is found.

DR. FRANTZ: By enucleation or by lobectomy?

DR. DOBYNS: By lobectomy; I would never remove any neoplasm by enucleation if I could help it.

DR. FRANTZ: But you wouldn't then go on to remove the opposite lobe?

DR. DOBYNS: I always look on the other side. Only under certain circumstances do I resect the other side.

DR. FRANTZ: That is something I will try to get, a Geiger counter in the operating room. . . .

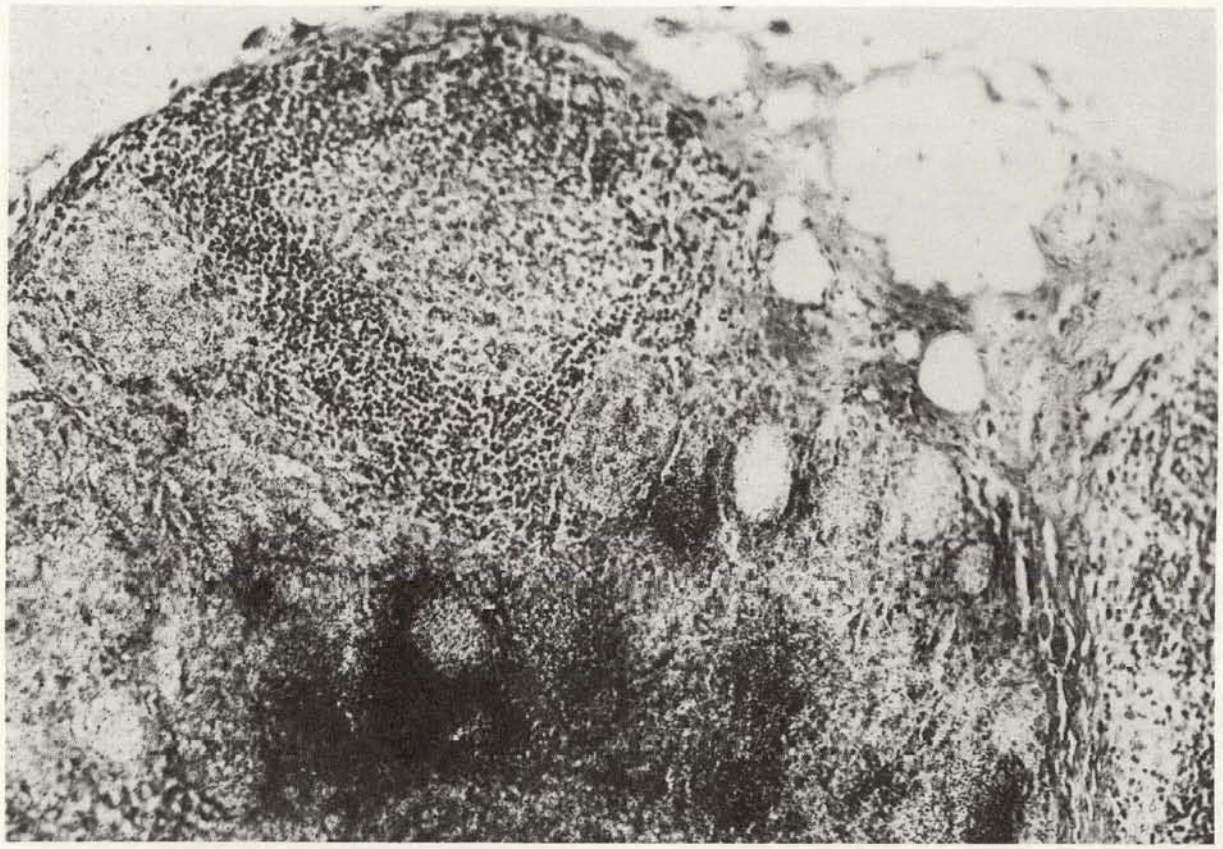


Figure 69. Radioautograph of same node as that shown in Figure 68. Note evidence of follicular function.

We have now a total of about 450 cases with tumors that I have called carcinomas. In how many of these the diagnosis will be confirmed by metastases and how many have been or will be cured of cancer is another matter. One must remember that when the surgeon approaches a tumor in the thyroid gland, he may remove it by lobectomy, or, on occasion, by enucleation. It is perfectly possible that, in a certain number of instances, he removes a cancer that has not yet metastasized and hence he has "cured the patient." However, as years go on and as I review the cases of long survivors, I have become more and more uneasy about the diagnosis of malignant follicular tumors and malignant papillary tumors. I am encouraged (and I am ashamed to be encouraged, because it is to the patient's detriment) by a case in which my original diagnosis was confirmed a few months ago. Twenty-one years ago I had made a diagnosis of papillary cancer. The patient had had what we think of now as inadequate surgery. I offered further study with radioiodine some 10 yrs. ago, and she refused it on the advice of her uncle, now deceased, who was a physician. She now has lung metastases after 21 yrs. So I subscribe to everything Dr. Dobyns said about not wishing to publish any series until I have a 20-year follow-up. Dr. Dobyns, you will achieve that and I will not because of our age differences.

We do have 177 cases with a possible 10-yr. follow-up. The breakdown in Table 40 might interest you. The figures show almost the same proportions that I reported 10 yrs. ago when I said that approximately 75% of our thyroid cancers were in the relatively benigh, slow-growing group, i.e., were either the papillary type or the malignant adenoma

Table 40

THYROID CANCER
POSSIBLE 10-YEAR FOLLOW-UP
(177 Cases)

Papillary		81	45.8%
Adenoma malignum			
Follicular	48		
Hürthle cell	9	57	32.2%
Grade II		20	11.3%
Grade III		19	10.7%
			100.0%

type. As a subdivision of malignant adenoma, I have segregated the Hürthle cell carcinomas because, so far, they have shown no function in our experience although they behave otherwise like malignant adenomas.

The data in Table 41 show those who are dead with disease. The percentage of deaths in papillary tumors seems to contradict the opinion held by some that these are not really lethal cancers but just papillary tumors with regional node involvement. Of the 23.5% dead

Table 41

THYROID CANCER
POSSIBLE 10-YEAR FOLLOW-UP
(177 Cases)
DEAD WITH DISEASE

	No. cases	Dead	
Papillary	81	19	23.5%
Follicular	57	23	40.3%
Grade II* (2 p-op)	20	16	80.0%
Grade III* (2 p-op)	19	17	89.5%
Total	117	75	42.4%
(Lost 10)			

*2 long survivors.

with tumor, i.e., 19 cases, distant metastases were present in 10 cases, and lymph node metastases were documented in 5 of the 9 who died with disease apparently limited to the neck (Table 42).

Table 42

THYROID CANCER
GRADE II. PAPILLARY (81 CASES)

32 Dead:	
	9 with local disease (5 with lymph node metastases)
	10 with distant metastases
	13 without evident disease
40 Living:	
	3 with local disease
	1 with metastases
	36 without evident disease
(Lost 9)	

The death rate from follicular carcinomas is higher (Table 43). There are 23, or 40.3%, who had died, of which 14, or 60.9%, had distant metastases. Three of the patients with follicular tumors who died with disease had Hürthle cell carcinomas and all had distant metastases. There were 9 cases of Hürthle cell tumors in all, 5 of whom are living without evidence of disease. The 6th living was one who failed to return for follow-up for many years, but we knew the patient was alive. This made me uneasy about the diagnosis made in 1934. She is now dying,* with massive local and mediastinal involvement with tu-

Table 43

THYROID CANCER
GRADE I. FOLLICULAR (57 CASES)

31 Dead:	
	8 with local disease
	14 with metastases
	8 without evident disease
	1 post-operative
25 Living:	
	3 with local disease
	1 with metastases
	21 without evident disease
(Lost 1)	

*Died May 12th, 1957, of pneumonia, with massive cervical and mediastinal tumor, but with no metastases.

mor, true, by biopsy, to histologic type. The duration of her disease from onset is 33 yrs.

In Grade II there are tumors that I have always called the "I-don't-know-what-they-are" type (Table 44). Most of them eventually prove themselves to have been Grade II, i.e., the highly malignant, rapidly fatal type. A very few patients live a long, long time, and it is then that there is a great temptation to reclassify them, and put them back into Grade I, but it seems hardly fair. Grade II is a small group, as you see, and of such varied histologic appearance that no one surgical pathologist has had enough experience to be sure of the classifications of any given variant.

Table 44

THYROID CANCER
GRADE II. (20 CASES)

18 Dead: 4 with local disease 10 with metastases 2 without disease: One at 17-1/2 years; One at 22 years* 2 post-operative
2 Living without disease:** One 20 years after 1st definitive operation at age 4. One 15 years after lymph node removal at age 15, and 3 years after total thyroidectomy.

*Similar case dead at 16 years post-operatively with recurrence first at 9 years post-operatively.

**Children: Would probably now be classified Grade I.

There were two Grade II carcinomas that were histologically similar, both spindle cell types. Both were in women in the early fifties. Both patients had partial thyroidectomy with what was thought to be complete removal of tumor. Both had postoperative radium pack. Both were free from evidence of disease for 8 yrs. Then the second case, who had had a larger radiation dose, 33,600 mg-hours, bilateral, had local recurrence of regional node involvement and died at home, 110 months post-operatively. The other lived 22 yrs. after operation and died without evidence of return of disease. The only significant difference between these 2 cases is, then, the long survivor had a tumor for 12 yrs. before operation with gradual slow growth, more rapid in the 12th yr. In the case which succumbed to disease, the tumor was of only 10 months' duration and had grown rapidly.

In Grade III, there is one surprise (Table 45)—a 14-yr. survival. I produce this for every visiting pathologist and once every 6 months at surgical pathology conferences for the resident turnover. I have never had a vote for this as anything but a Grade III. No one has called it a reticulum cell sarcoma, which is, of course, the other thing to think of, and which we know to be radiosensitive.

To return to tumors possibly suitable for I^{131} therapy, our first case, in which we found pick-up in a metastases was studied at the time of Pearl Harbor. For some years

Table 45

THYROID CANCER
GRADE III. (19 CASES)

17 Dead: 2 post-operatively 10 with local and metastatic disease 5 with only local disease known
2 Living without disease: One 11 years (now age 88). Op. lobectomy. No X radiation. One 14 years (now age 63). Op. right lobectomy. Tumor shaved off trachea. Post-operative X radiation.

thereafter, however, we did not have a sufficient supply of material for adequate isotope dosage.

In the past 10 yrs., on the basis of figures shown previously, I made a rough calculation and found that we might have expected 20 or 25 cases of the adenoma malignum type with distant metastases to show up which might be suitable for therapy (Table 46). We have had, however, in the last 10 yrs. only about 14 cases in which we attempted therapy, even with TSH as an adjuvant. Only these 14 had uptake in the metastases which was, in our estimation, sufficient to warrant therapy. Of these, 9 are dead of disease and 5 are living.

Table 46

THYROID CANCER

Total cases to date	450
Expected adenoma malignum cases with metastases	20-25
Cases suitable for I^{131} treatment of metastases	14
Dead of disease 9	Living 5

Having listened again to Dr. Pochin's approach to this disease, in which he continues therapy even with very little uptake, I think perhaps we could have treated some of the others intensively. Some of these are living, however, and have been made comfortable at least, with other therapeutic measures. Also, in the case of the 9 dead with disease, we probably did not treat these patients as intensively as Dr. Pochin would have. They all were very uncomfortable when we took them off thyroid and allowed them to become myxedematous before treatment, and we were discouraged by uptake in a metastasis of only 1% or less. We also did urinary excretion studies, and we usually did not treat those with an excretion in 48 hrs. of as much as 90% of the administered dose. We kept quite a number of these patients going with other therapy, X radiation treatment, for instance. Two of

them rose from their beds and walked, for no reason that I can understand, with the administration of testosterone. Sometimes we gave testosterone for a while and went back to radioiodine therapy, which would again be effective.

Let's see what the dosage was in those patients who were failures of therapy, and what was the length of their survival (Table 47). These are the 9 dead. The first one, R.B., a woman aged 52, was maintained for 2-1/2 yrs. She came to us with very extensive disease, the total dosage was 1475 mc. Her original uptakes were encouraging. She had lesions in the skull and later in more distant bones, but we did not succeed in arresting the disease. She developed a transverse myelitis on another basis, and this did not help us in our therapy. She did not at any time give us trouble with leucopenia or low platelet counts.

Table 47

THYROID CANCER – I^{131}-TREATED CASES
DEAD OF DISEASE

	Total mc	Yrs. after I^{131}		Total mc	Yrs. after I^{131}
R.B.	1475*	2-1/2	L.K.	453††	2-1/2
G.D.	1239*	4	H.K.	375*	5
A.K.	1117**	3	J.M.	365‡	4-1/2
E.B.	840*	5	M.S.	300*	1
S.S.	700†	4			

N.B. All had bone metastases except J.M.
*Disseminated disease.
**Leucopenia, low platelets.
†Metastases not functional.
††Single lesion. Death auto. accident.
‡Lung metastases.

The next case, G.D., a woman aged 58, was one in which a scapular and a sacral lesion had been treated previously by means of X radiation. We gave her 1239 mc of I^{131} dosage for the skeletal lesions. She had had, previous to our administration of I^{131}, 5200 r X radiation to the sacrum, a dose beyond her skin tolerance. She had developed a huge decubitus ulcer over the sacrum and was in considerable pain. We were able to relieve the pain. (All these cases, by the way, except H.K., had elective thyroidectomies before I^{131} therapy.) This patient became well enough to go back to her work in a factory, and well enough so that I was able to persuade one of the plastic surgeons to throw a flap into the hole in her back, after excising the ulcer which was foul and suppurating. She also had a great deal of symptomatic relief over a period of about 4 yrs.

Patient A.K., a woman aged 56, had only one clinical lesion which was in the sternum when we first saw her. We were able to measure this and observe the change in size and also to obtain a biopsy after therapy. Her initial uptake in the sternal metastases was 21% after total thyroidectomy, in another hospital. There was, however, 2% uptake over T2, 3 and 4, which were found to be diseased when she began to have cord symptoms a month

after operation. Therapy was pushed up to a total of 1117 mc, but always with caution because of low platelet values and leucopenia. I^{131} finally had to be discontinued. She developed further osseous and cerebral metastases and died 3 years after beginning I^{131} treatment, in a terminal care home, so that no autopsy was performed.

The skin over the sternal lesion in this case, by the way, showed marked radiation changes after therapy, and the pulsating tumor became stony hard. The biopsy specimen from this lesion, after therapy, was an almost solid mass of fibrous tissue. If I chose the fields for photomicrographs I could publish them and they would look very much like some from another case (from another hospital) published in Life Magazine as evidence of obliteration of the cancer. Other fields in our case, however, showed altered, but possibly viable cancer cells. True, these were, encouragingly, apparently locked up in scar tissue. It might take a long time for such cells to become active again, and this particular bone focus may well have been controlled.

E.B., a woman aged 52, had a much lower dosage because of her personal prejudices and those of her physician, which made it impossible to treat her exactly as we might want. She was a gypsy and her decisions were directed by powers beyond our control. She had extensive disease, left ilium and femur, C3, C4, and C5. She also was subject to very severe radiation sickness. She hallucinated a number of times during therapy, which made things difficult in the hospital. She was one of the ones in whose treatment we alternated I^{131} with testosterone. On two occasions on testosterone she got up and walked on a nonexistent femur; on the basis of roentgenographic evidence, it was gone from the head right down the shaft beyond the greater trochanter. However, it had been subjected to heavy radiation, and I presume there was a good deal of strong fibrous tissue there. She drove her car regularly from New York to Asbury Park, New Jersey, to go swimming. We gave her a good deal of palliative relief over a period of 5 yrs. with this inadequate dosage alternating with testosterone. She received a total of 840 mc.

S.S., a woman aged 50, was also a failure of I^{131} therapy, and this was somewhat of a surprise until her demise at Delafield Hospital a year after beginning therapy. Then we found out that she had a widely disseminated non-functional papillary tumor. The histologic type had not been determined earlier.

L.K., a man aged 52, was a physician. We learned a great deal from his case, because he did not do what we told him to do! He had a single metastasis, in the skull. It could be measured, and a moulage was made of it, a little plaster cap that fitted it. We could put it on to see whether the tumor was larger or smaller. After an elective thyroidectomy, we used to ask him to stop taking thyroid so that we could get more uptake in his skull lesion. We did get uptake several times. These uptakes were not terribly high, in fact they impress me now, as I look at them, as somewhere in Dr. Pochin's range, 2.8 to 0.85% of the administered dose. When we treated him, there would be some regression in 2 or 3 weeks. Then the regression occurred when we had not treated him, or did not expect it because of very little uptake. I asked him one day why he thought we were not getting more uptake, and he said, "I must confess to you, Dr. Frantz, I have never entirely given up my thyroid.

I had tried to do so just before coming in for the dose because I wanted to please you. But let me say to you that I would rather die of thyroid cancer than live with hypothyroidism, and I have been taking quite large doses of thyroid." Thereafter, we let him manage his own therapy, only asking him to tell us how much thyroid he was taking. He used to overdose himself, and whenever he did, his tumor would become concave instead of convex, and would stop pulsating. So we have known, ever since 1948, that there is an inhibiting effect of thyroid on a functional thyroid tumor. This patient was decapitated in an automobile accident and our collaborative physiologic studies came to an end, 2-1/2 yrs. after beginning of therapy in a favorable case. No postmortem examination was performed.

Case H.K., a male aged 61, could not have a total thyroidectomy because of the extreme vascularity and fixation of the tumor. He had a severe local reaction to I^{131}, but the uptake after that was never high. His disease progressed locally, and in the terminal stage there were also lung metastases. We achieved palliation for a short time in the first few months. The patient lived 5 yrs. after the first time I^{131} was given, having received a total of 375 mc. He finally succumbed to massive local disease.

These cases all had bone metastases. J.M., a man aged 43, was hyperthyroid on the basis of lung metastases. A total thyroidectomy and laryngectomy had been done in two stages—the first in Italy. He had no thyroid tissue in the neck at all, but he did have symptoms of real hyperthyroidism on the basis of his known lung metastases. He was finally a failure of I^{131} therapy as far as control of his cancer was concerned, but his hyperthyroidism was checked effectively. He left us to go to Delafield Hospital. The therapy was continued there also with failure. Postmortem examination showed metastases in the lungs, tracheobronchial lymph nodes, liver, brain, vertebrae, periadrenal fat adrenals, and pancreas. There was some papillary component in this carcinoma.

M.S., a female aged 64, came to us for therapy in the terminal stage of disease. Her downhill course was rapid, and we achieved no palliation in a year of treatment. She had developed a chondrosarcoma also in a heavily irradiated clavicular metastasis.

Now let us look at a few good results; we have only 5 possible good results (Table 48).

A.G., a woman aged 65, had a single nodule originally in the skull, now has other foci that developed later in the ilium, pubis, and ribs. She also has hypertensive cardiovascular disease. The skull lesion responded favorably, treatment having been started 5 yrs. ago. We are not sure now whether she is having repeated small strokes or if the intracranial pressure increases because of the skull tumor. She may have died over last weekend because she has had another cerebral accident.*

E.K., a woman aged 55, is in status quo, with a single metastasis in the ilium, She has received only 699 mc, but has also had external irradiation. We had to give it to her because she had so little uptake and so much pain. She is a 5-yr. stationary case.

A.H., a woman aged 47, is interesting because of the life history. It is comparable in prognosis with the case illustrated by the roentgenographs in Figures 62-65, which show

*Still living, May, 1957.

Table 48

THYROID CANCER – I^{131} TREATED CASES

LIVING

	Total mc	Status	
A.G.*	505	Poor	5 yrs.
E.K.*	699	Status quo	5 yrs.
A.H.**	646	Status quo	6 yrs.
R.N.†	250	Arrested	6 yrs.
M.T.†	1085	Arrested	9 yrs.

*Disseminated disease in bone.

**Lung metastases controlled.

†Single lesion in bone.

lesions in the lungs that disappeared following X-radiation therapy. This patient had had a lump in her neck for 10 yrs. At the age of 17, she gave it to someone in Washington, D. C. It was a single lymph node and had metastasis in it. In that same year, 1941, she had a subtotal thyroidectomy on the right side. Following that, she had recurrences in 1942, and three times lymph nodes were locally excised, also in Washington. From 1942 to 1951 she was well. She had grown up, married, and applied for a job at Macy's department store. A routine employee chest film was made, and she was found to have a huge mass in the mediastinum and many densities in both lung fields. She came to us, and we did an elective total thyroidectomy. Upon the removal of the thyroid, we found no tumor in the gland. Her radioiodine uptake was 20% over the pretracheal mass, and we then, therefore, started I^{131} treatment in June, 1951. The total dosage was 646 mc. She developed a leucopenia which stayed our hand a little. She now has considerable uptake again. She is one of the cases who is difficult to make return for further therapy because of her personal problems and because of the physician who is in attendance. We have to put out bait both for physicians and for patients to get some cases back for therapy. This patient has had the tumor since 1931. It is obviously only held in abeyance and it might conceivably have been still in abeyance had she had no therapy at all while in our hands.

R.N., a woman of 66, had a perfectly colossal nontoxic nodular goiter removed in 1947 at the age of 63, at another hospital; something she had carried for 30 yrs. It was considered by the pathologist to be an entirely nontoxic nodular goiter. Three years later, while combing her hair one day, she felt a click and was found to have a metastasis in her skull. The remnant of the gland itself was ablated by I^{131}, and she is now completely athyrotic. The skull lesion has largely recessed and has become fibrotic following this therapy, to which X radiation was added, because she has had no uptake for 6 yrs.

M.T., a woman aged 53, is our one good result (Figure 70). This is a patient in which a single lesion has been arrested for 9 yrs. She came into the Neurological Institute with

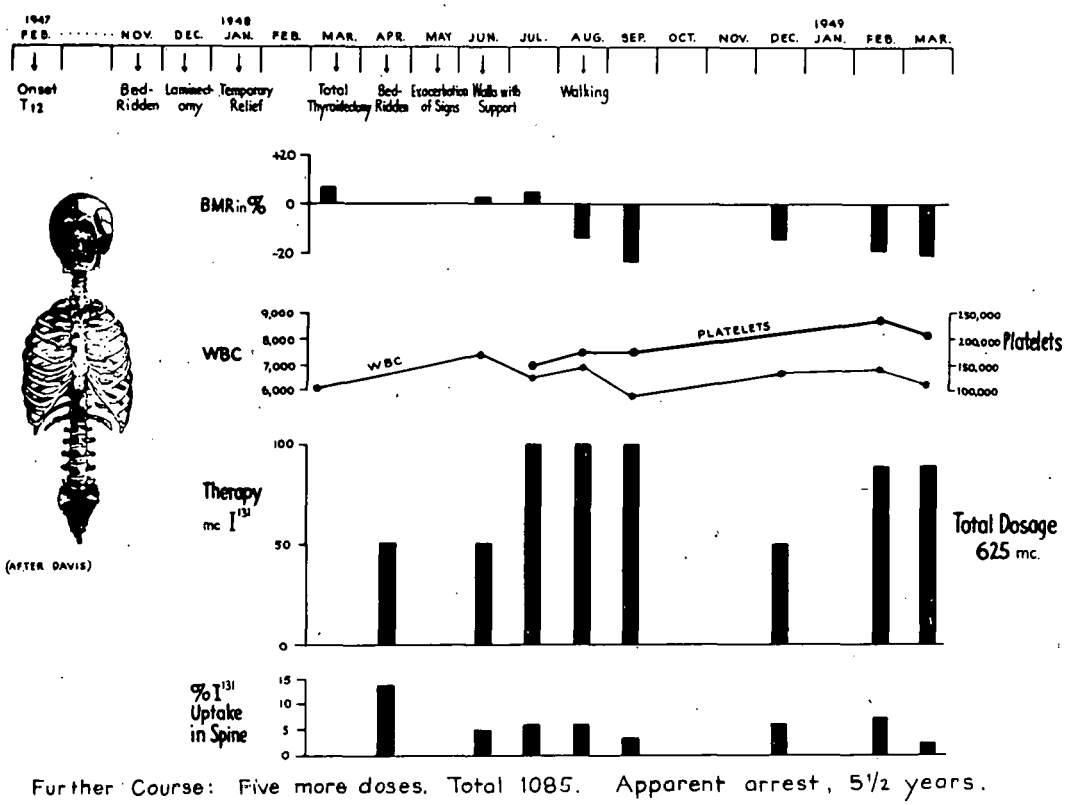


Figure 70. Effect of I^{131} upon a patient with cancer of the thyroid. The disease has been arrested for 9 yrs.

a tumor at T-12 which had given her cord symptoms. She was in severe pain and had difficulty in moving her legs and difficulty with her bladder. These symptoms had been present from February, 1947, until December, 1947, when she had a decompression laminectomy which gave temporary relief. Following this, radiotherapy was also given which was thought to have helped her. However, she began to have pain again and difficulty with her legs. Biopsy revealed a "benign metastasizing colloid goiter." We then received the patient at Presbyterian Hospital and did a total thyroidectomy. Only 1 of 5 people who examined her thyroid preoperatively could feel the primary tumor. It was a tiny little calcified adenoma in the lower pole of the right lobe. Postoperatively, in her 4th week, we started therapy. We were terrified about the size of the first dose, but we bravely gave her 50 mc, and her cord symptoms returned about 10 days after the dose. It took me a little time to remember that I did not need to be too frightened because she had had a decompression. I was afraid we had done her immense harm. The radiation reaction, however, subsided. Then we gave continued doses, as you see from the chart in Figure 70, with decreasing uptake. There was no particularly deleterious effect on platelets or white count. Her total dose is now 1085 mc, and she is in apparent arrest, totally athyrotic 9 yrs. after total thyroidectomy. We have given the dose, as you see, while she was off thyroid, but we have not

let her get too myxedematous. We used to give a tracer dose and then a therapy dose. Now we do not give a tracer dose. We just give a therapy dose, and determine the uptake on that. We have followed some patients with bone marrow studies, but most of them just with platelet and white counts.

DR. CHAPMAN: Someone asked about Dr. Pochin's work and his administration of thyroid. Would you like to say a word on that?

DR. POCHIN: I should have made that clear. Once myxedema has developed and once radioiodine therapy has been started, all our patients are continuously on thyroxine except for the 4 weeks before each dose and for the 2 days after each dose.

DR. FRANTZ: Our maximum single dose is 100 whereas yours is 150.

DR. POCHIN: We have done some measurements on the speed of return. It looks as though the uptake is pretty well back at 3 weeks after coming off thyroxine; the return of the uptake in the tumor is restored.

DR. CHAPMAN: The figure we have come to use is 3 weeks. That is a happy balance, perhaps, between the desire attained and the physiologic effect. We seldom find we can keep the patients off for 5 or 6 weeks, so I think it has shrunk down to about 3. Maybe the patient's own wisdom decides this, I don't know.

DR. McCULLAGH: The question of the advisability and possible value of thyroid treatment in metastatic carcinoma of the thyroid has been mentioned more than once at this meeting. It was only a short time ago that we found that Dr. Frantz made the observation she spoke about, a good many years ago. Since then I have been interested, too, and realized that such changes added up to an opinion of some improvement—either lack of progression of the disease or actual regression in some cases—as a result of giving sufficient thyroid therapy. Dr. Crile has been very much impressed by this and has gone into the matter with his typical enthusiasm. I am impressed myself, but I want to show roentgenographs of two patients because I think that you will be interested in seeing them, and I would like to know what you may think. Is it your opinion that the evidence shown here really indicates that these patients are helped by thyroid, or that as much improvement might have been expected because they had radioactive iodine therapy? There are other patients on whom we have records and who, we believe, are relatively improved by taking large doses of thyroid. The dose was the equivalent of 2 grains or more per day of desiccated thyroid. So far as I am aware, only one showed regression of metastases according to roentgenographic evidence, and in others, the metastases were judged not to be advancing at the speed at which they had been originally advancing or they remained stationary where previously they had been advancing.

I have a series of roentgenographs of a young girl, aged 17, who had papillary carcinoma. I am not sure how papillary or how follicular this cancer was. It was diagnosed in August, 1950, by biopsy of the nodule in the right lobe of the thyroid and right cervical lymph node. She was known to have a nodule in the thyroid some years previously. In December, 1950, she had an I^{131} uptake of 60% in 24 hrs. The uptake, however, was chiefly in the neck, and there is evidence of metastases in the chest (Figure 71).

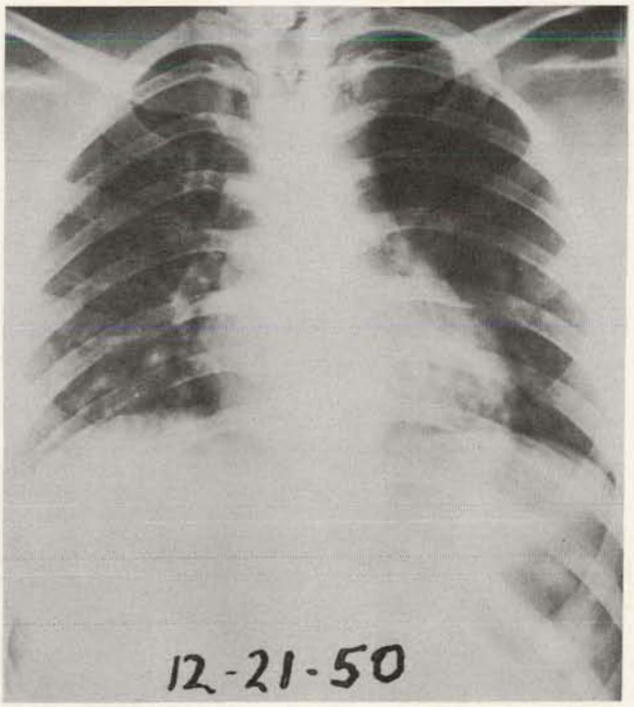


Figure 71. Roentgenograph of chest, December 21, 1950. Patient, 17-year-old girl, had papillary carcinoma diagnosed by biopsy of nodule in right lobe of thyroid and right cervical lymph node. Nodule in thyroid first noted in 1946. I^{131} uptake in December, 1950, was 60% in 24 hrs.

The roentgenograph in January, 1951 (Figure 72), was made 1 month after thyroidectomy; she was taking no thyroid. Her uptake was 35%, chiefly in the neck, whereas it appeared that there might be some increase in metastatic involvement in the chest in this

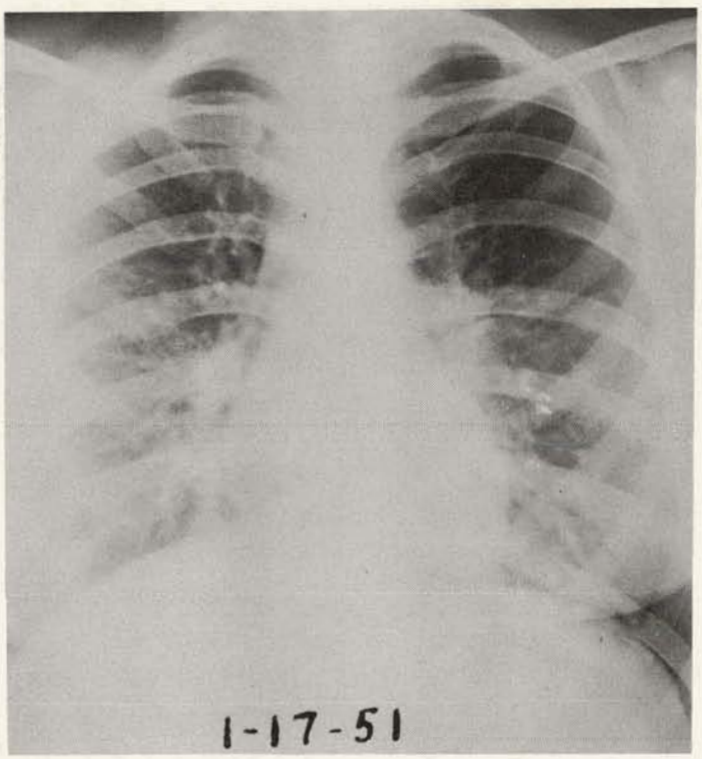


Figure 72. Same patient as shown in Figure 71. Roentgenograph of chest, January 17, 1951, 1 month after total thyroidectomy. I^{131} uptake was 35% in 24 hrs., chiefly in neck. I^{131} treatment, 30 mc.

short time. She was given 30 mc of radioactive iodine.

In May, 1951, her condition had worsened, I think, to a degree (Figure 73). This is 6 months postoperatively; her uptake was 16% again, chiefly in the neck, whereas the lesion was chiefly in the chest. She was then given 50 mc of I^{131}, and at this time desiccated thyroid was begun, 2 grains per day.

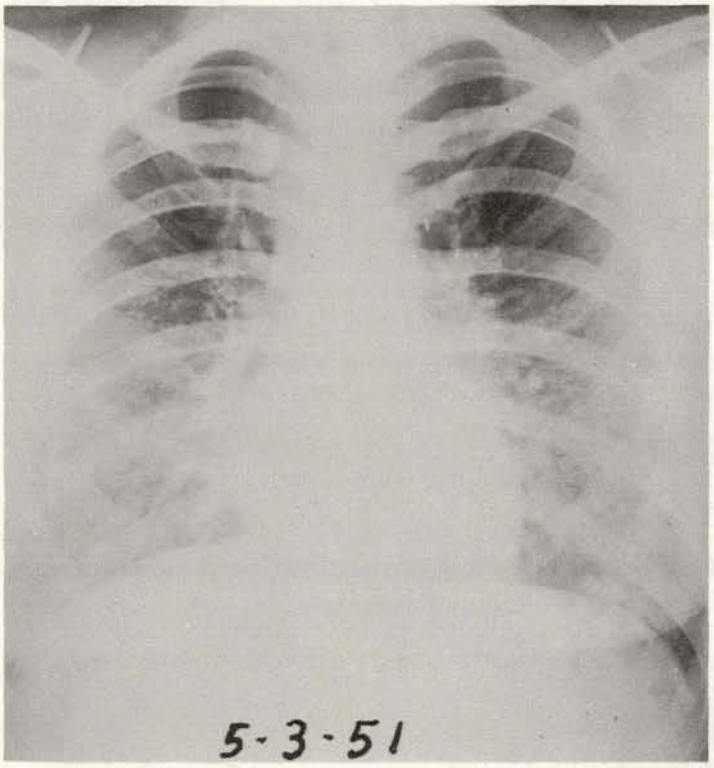


Figure 73. Same patient as shown in Figures 71 and 72. Roentgenograph of chest, May 3, 1951, 6 months after total thyroidectomy. I^{131} uptake was 16% in 24 hrs., chiefly in neck. I^{131} treatment, 50 mc. Desiccated thyroid, 2 grains daily begun.

Figure 74 shows her condition in September, 1951, 10 months postoperatively. She had had radioactive iodine on 2 occasions, the last in May. The uptake now was low, and she now was given 50 mc of radioactive iodine; thyroid was continued. There was still plenty of evidence of disease present.

On October 5, 1951, 11 months postoperatively, the dose of thyroid was increased to 3 grains a day.

In January, 1956, her chest looked much clearer than it had previously (Figure 75). We are inclined to ascribe a good deal of this improvement to the thyroid which was given. It is true that there was improvement following her last radioactive iodine dose. This was after thyroid had been started. It appears to us there was little improvement prior to the beginning of treatment with desiccated thyroid and rather marked improvement thereafter.

The second patient I wish to discuss was seen 7 years after a total thyroidectomy for what was classed as papillary carcinoma. In June, 1955, a month before the first picture was taken, she had an I^{131} uptake of 40% in 24 hours, chiefly in the neck, and was given 30

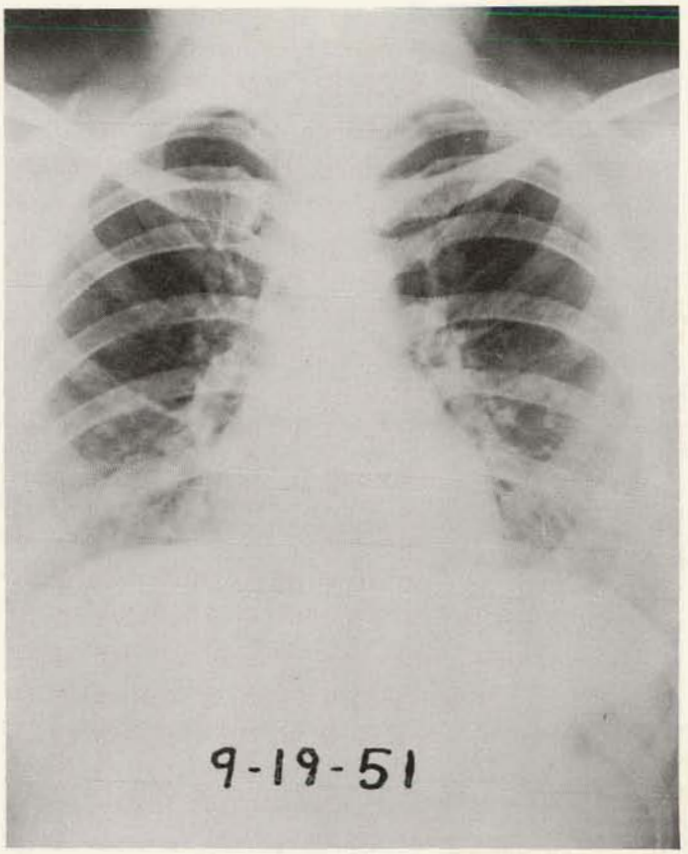


Figure 74. Same patient as shown in Figures 71 to 73. Roentgenograph of chest, September 19, 1951, 10 months after total thyroidectomy. I^{131} uptake was 9.5% in 24 hrs., chiefly in neck. I^{131} treatment, 50 mc. Daily administration of 2 grains of desiccated thyroid had been stopped on August 18, 1951; on October 15, 1951, daily administration of 3 grains was begun.

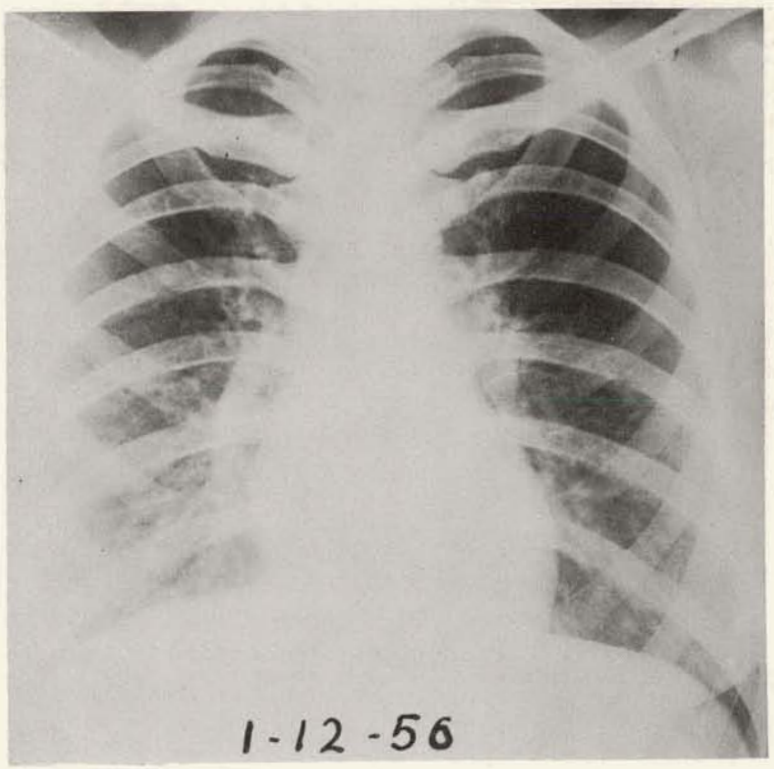


Figure 75. Same patient as shown in Figures 71 to 74. Roentgenograph of chest, January 12, 1956. She had been taking 3 grains of desiccated thyroid daily, since October 5, 1951.

mc of I^{131}. On July 20, 1955, the date of the chest roentgenograph shown in Figure 76, she was again given 30 mc of I^{131}.

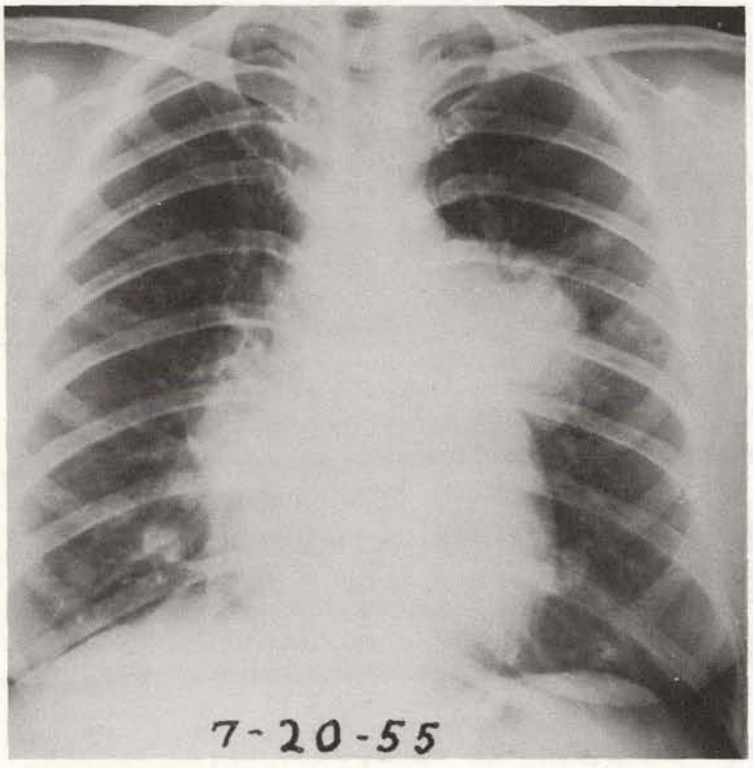


Figure 76. Roentgenograph of chest, July 20, 1955, 7 years after total thyroidectomy for papillary carcinoma, of a 48-year-old woman. On June 21, 1955, I^{131} uptake was 40% in 24 hrs., chiefly in neck; I^{131} treatment, 30 mc. On July 20, 1955, I^{131} treatment, 30 mc.

In September, 1955, we expected, if an I^{131} effect was to be obtained, to see some shrinkage of the mass by that time (Figure 77). The uptake at this time was 25% in 6 hrs., chiefly in the neck, and she was then started on desiccated thyroid.

In December, 1955, there was a very striking change (Figure 78). The improvement that did occur had been much more rapid after starting the use of large doses of thyroid.

The point is that the improvement followed both I^{131} and desiccated thyroid, though there was no improvement for several months after the first dose of I^{131}. Is it reasonable or not to ascribe any of this improvement to the desiccated thyroid?

DR. KEATING: I suspect that many of us have some reservations about the thesis that desiccated thyroid alone may have a curative effect upon hormonally dependent metastatic cancer of the thyroid gland. Dr. McCullagh's cases are extraordinarily interesting, but I am disturbed by the fact that both patients received some radioiodine (although not very much, by modern standards). We saw 2 patients in the early days of I^{131} therapy whose course might be relevant to this discussion. The first was a 27-year-old woman who, in 1947, underwent removal of an immense tumor from the right side of the mediastinum. It proved to be a Grade 1 papillary and follicular adenocarcinoma of the thyroid gland, arising from the tenth rib, measuring 8 x 6 x 6 cm. Elsewhere, in 1946, the patient had undergone subtotal thyroidectomy for what was said to have been a nonfunctioning nodular

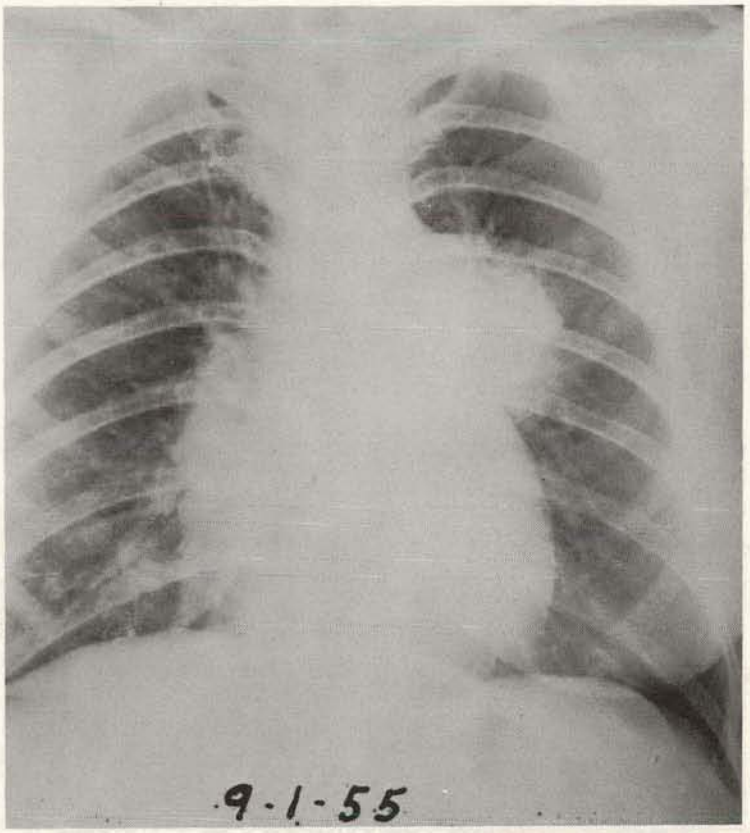


Figure 77. Same patient as shown in Figure 76. Roentgenograph of chest, September 1, 1955. I^{131} uptake was 25% in 6 hrs., chiefly in neck. Desiccated thyroid, 4 grains daily, was begun.

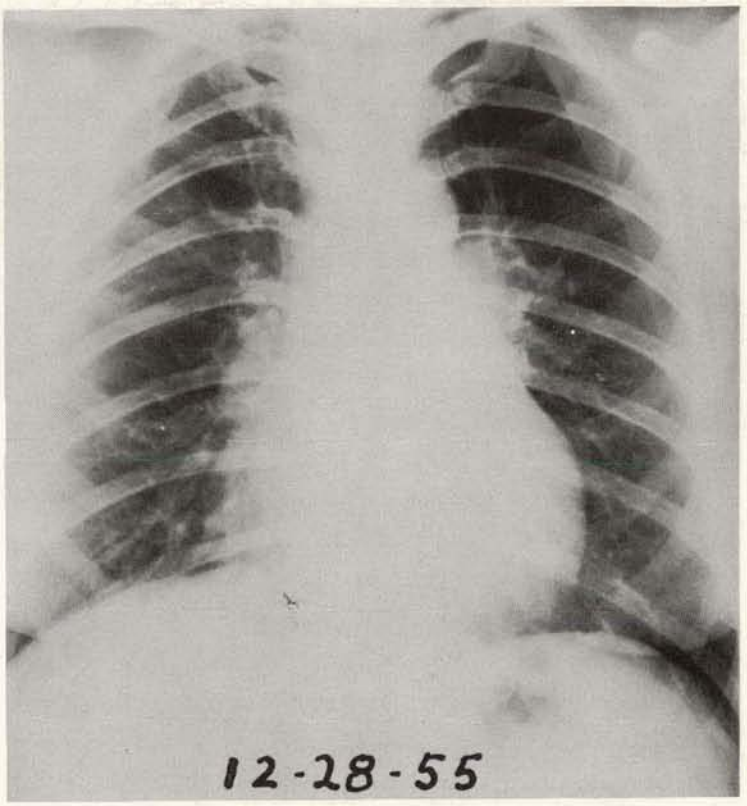


Figure 78. Same patient as shown in Figures 76 and 77. Roentgenograph of chest, December 28, 1955. Patient had been taking desiccated thyroid, 4 grains daily, since September 1, 1955.

goiter. There was no residual thyroid tissue palpable in the neck. A review of the roentgenographs of the thorax disclosed, to our dismay, that there had been visible in both initial and later roentgenographs of the thorax a large destructive lesion in the left second rib. Review of the specimen showed degenerating thyroid adenomas but no malignant process. Tracer studies made in June, 1947, after mediastinal surgery, showed that 53% of the radioiodine administered was excreted in the urine within 48 hrs., 40% was in the region of the thyroid gland, and 3% in the tumor of the left rib. The patient was given 50 mc on June 20, after which the uptake pattern was similar. On July 31, she received a second dose of 50 mc. The estimated uptake by the tumor on the first occasion was 500 μc per g; on the second, 350 μc per g. Tracer studies in September showed essentially no collection over the ribs, and only a detectable trace over the neck; nevertheless, a third dose of 100 mc was administered September 18. It was found that 95% of this dose had been excreted within 96 hrs. The patient began to receive desiccated thyroid substance on September 26. In February, 1947, examination disclosed frank myxedema and no uptake of radioiodine anywhere. The roentgenologic appearance of the rib was not changed. The rib was excised on March 13, 1948. No cancer cells could be found in it, the sections consisting of necrotic debris and a few cells with pyknotic nuclei. The patient has remained well without evidence of further recurrence from that time to this.

DR. FRANTZ: Have you ever gotten roentgenographic evidence of the disappearance of disease in a bone?

DR. KEATING: Not disappearance, but regression. I am not making such a rash statement. The second patient whom I should like to mention briefly was an attractive 20-year-old nurse, who had pulmonary metastases from a grade 1 mixed papillary and solid adenocarcinoma. She had received 50 mc of I^{131} in October, 1949, and 150 mc on January 27, 1950. The symptoms of myxedema were present from January until May, 1950, when, because of their severity, she was given desiccated thyroid substance. At the time the use of desiccated thyroid substance was begun, the nodules in the right side of the thorax were already disappearing, and roentgenographs made subsequent to that date to the present have not shown them. The patient was married in the summer of 1950, and is now the mother of 3 children. Despite the 3 pregnancies, she remains without evidence of disease. Yet, even though the pulmonary lesions did not disappear completely until after desiccated thyroid therapy had been begun, I should be most reluctant to say that the disappearance of the lesions was the result of the desiccated thyroid substance rather than of the radioiodine she received, and I find it equally difficult to accept the view that the thyroid therapy, rather than the radioiodine, was responsible for the result in Dr. McCullagh's case.

DR. FRANTZ: May I say one thing I meant to say in summary. As these cases have shown, there was no surgical ablation of the thyroid done in either one of these patients, so we don't know how much might have been gotten into the lung lesions with I^{131} had there been a total thyroidectomy. That is the first comment I would make. The second comment is that no one has biopsied the lung lesions they are treating. We know that these Grade I tumors can sometimes metastasize as one or another type. The reason I hesitate about

this thyroid therapy in my own mind is this: If you offer them regression with thyroid therapy, you may be content with regression instead of making an effort at real control of the disease, as is evidenced by the rib section; that is a small lesion and you have actually eliminated the tumor.

DR. KEATING: Of course, we have not published any data about this patient because 9 years have passed since treatment was instituted. In view of the biology of thyroid cancer, it is still possible that she may have further recurrence and conceivably might even die of the disease, despite our hopes on her behalf.

DR. FRANTZ: Indeed, she may have an osseous metastasis that will flare up later on. But I think with I^{131} given a tumor that has a pickup, you are offering something in the way of real therapy. With thyroid administration you are offering arrest, perhaps, of function but not destruction of the neoplastic tissue.

DR. TUBIANA: When we began to study the treatment of thyroid cancer with radioactive iodine, we thought that it was of primary importance to know, in each case, the concentration of radioactive iodine in the tumor. We were convinced rapidly that external counting was not a dependable technique.

The surgeon is not always willing to perform a biopsy on all patients, especially when the tumor is inoperable, so we devised a technique based on drill biopsy. We use a drill with a needle that turns 15,000 times per minute. The specimens weigh between 10 and 30 mg. They are weighed and their radioactivity is measured. They are then embedded in paraffin for radioautography. The results obtained since 1952 by means of this technique are shown in Table 49. The histologic and radioautographic studies show, as has been found elsewhere, that normal and cancerous tissues are intricately mixed. This explains the uncertainty of the results obtained by external counting.

This technique has enabled us to do some studies on the metabolism of iodine in neoplastic tissue. The results shown in Table 50 indicate that: 1) the iodine content of cancer-

Table 49

DRILL BIOPSY OF THYROID

Number of trials	Specimens	Good histologic information	% success	% failures
210 patients	191 patients	158	75	25

Complications	8	Hematoma	5
		Bleeding	2
		Hemoptysis	1

Results : Malignant lesions	53	Clinically malignancy probable	35
		Clinically benignity probable	18
Benign lesions	105		

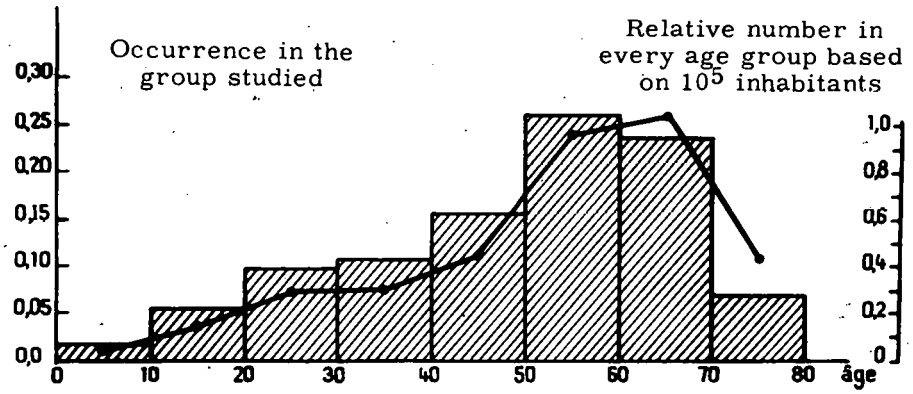
Table 50

RESULTS OF A STUDY OF THE METABOLISM OF RADIOIODINE IN CANCER PATIENTS

No.	Time after I^{131} ingestion (days)	I^{131} dose per g (%)	I^{127}				I^{131} total %				Pathology
			Total $\mu g/g$	Iodide (%)	Hormonal (%)	Specific act. (% of the dose of I^{131} per μg of I^{127})	Iodide	Mono I.T.	Di-I.T.	Hormonal I	
1	1	0.02	8.6	15	38	2.5	4	35	38	0	Vesicular
2	4	0.002	9.4	8	45	0.5	9	30	35	0	
5	18	0.94	103.7	6	9	10		30	60	trace	
6	18	0.27	97.3	8	10	2.7		30	59	trace	
7	18	0.16	128.2	7	9	1.5		35	55	0	
13	2	0.05					4	45	45	0	Papillary
14	2	0.2					3	40	50	0	
15	2	0.2					3	43	50	0	
16	2	0.2					5	45	45	0	
17	1	0.4	30	10	23	13					
18	1	0.07	2.4		8	30	5			2	Ves. meta. node K.
Eu-T.	2	1	1000 (600 - 1200)	6	43	1.5	6	38	35	12	
	5						5	52	19	20	

ous tissue is always very low; 2) the specific activity of iodine is generally higher than it is in normal tissue; and 3) most of the iodine is protein-bound but nonhormonal and that the synthesis of thyroxine is very slow although the turnover of iodine is fast. This suggests that it is possible that iodine could leave the thyroid in a nonhormonal chemical form.

Since 1950, we studied 171 cases of thyroid cancer. The age distribution (Figure 79) shows a maximum frequency between 50 and 70 yrs. In 3 of our 11 cases of less than 14 years of age, and in 3 out of 160 cases of more than 14 years, there was a previous history of neck irradiation (Table 51).



Age Distribution

Figure 79. Age distribution of 171 patients with cancer of the thyroid.

Of 169 cases, 77 were treated (35 were nonmetastatic, 42 were metastatic), 92 were not treated (79 were nonmetastatic and 12 were metastatic).

Figure 80 shows the results of the tests. A detectable uptake was found in about 1/4 of the metastatic cases previously untreated.

In 21 metastatic cases, in which there was no detectable uptake, a total destruction of the thyroid was brought about by surgery or I^{131}. Further tests showed an uptake in about 1/3 of the cases. In about 1/4 of the cases, this uptake was sufficient to make treatment with radioactive iodine possible (Table 52).

Among the 35 cases without metastases who were treated, 8 were treated before surgery, a radical thyroidectomy was then performed in 7 cases. The last patient refused surgery. In this last instance, the cancer that had been proved by drill biopsy was of the size of a small orange and disappeared after the treatment. The patient has been well for more than 3-1/2 yrs.; she still refuses surgery.

Radioiodine was administered in 20 cases after surgery. In 12 of these cases, the surgeon had not been able to remove the whole tumor (6 cases) or there had been a local recurrence (6 cases). Among these 12 cases, 2 are still alive after more than 5 yrs., 2 are

Table 51

PATIENTS WITH CANCER OF THE THYROID WHO HAD HAD IRRADIATION OF THE NECK PRIOR TO THE ONSET OF DISEASE

	Number of cases	Previous irradiation of the neck
Children (0 - 14 yrs.)	11	3
Adults	160	3

	Age at irradiation (yrs.)	Lesion irradiated	Sequelae	Age at onset of cancer (yrs.)
Mass.	7	Neck angioma	None	14
Vit.	1/2	Otitis	None	9
Noir.	4	Adenoids	None	13
Delet.	15	Tachycardia	Severe skin teleangiectasis	59
Pic	5	Larynx papillomatosis	Tracheotomy necessary	26
Dur.	7	Idem.	Skin lesion	36

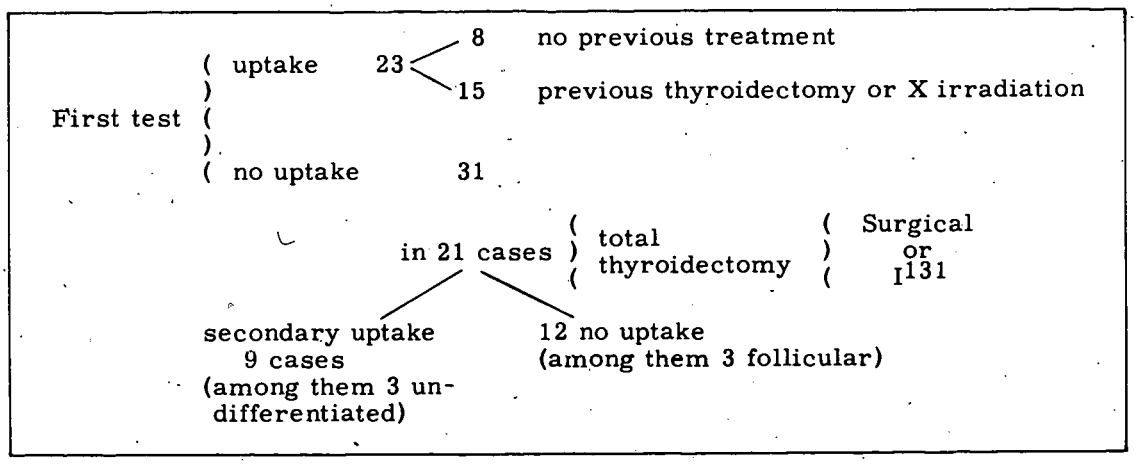


Figure 80. Uptake of I^{131} in metastases of 54 patients.

alive after more than 4 yrs., and 1 is alive after more than 2 yrs. Four are dead.

In 4 cases, treatment was given to patients in which the tumor was so big that it was inoperable. Two are still alive 2-1/2 yrs. after treatment. One died 5 yrs. after treatment.

Forty-two patients with metastases were treated. Twenty-seven received only 1 dose of 60 to 120 mc. In these cases, a second dose had not been administered either because, in spite of the destruction of the normal tissues, no uptake appeared in the metastases (18 cases) or because of the rapid growth of the tumor or the state of health of the patient did not permit a second dose. There were only 3 cases in which an uptake that was evident be-

Table 52

UPTAKE OF I^{131} IN METASTASES IN PATIENTS WITH CANCER OF THE THYROID

	Important (14)	Barely detectable (19)	No uptake (21)
Follicular	6	4	6
Papillary	1	3	2
Undifferentiated or anaplastic	3	6	10
Others or not classified	4	6	3

fore treatment disappeared, making further treatment impossible. Figure 81 shows the length of survival of these patients.

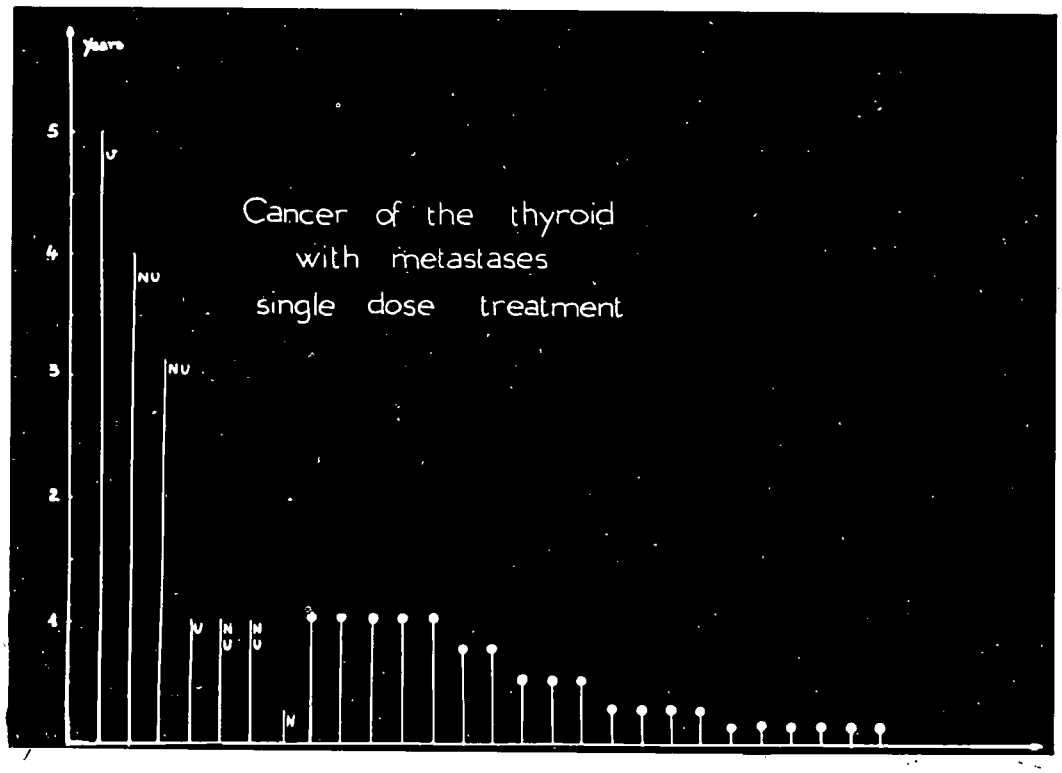


Figure 81. Length of survival of metastatic cases treated with a single dose of radioiodine (a point at the end of the line indicates death of patient).

Fifteen patients received from 2 to 5 doses (Figure 82). In 4 cases, the results were extremely good (among them 1 vesicular, 1 papillary, 1 anaplastic, and 1 not classified), and in 4 cases the results were good. Three of these patients are still living without any sign of recurrence more than 5 yrs. after first treatment. Lung metastases were completely cleared in 3 cases. Although the proportion of good results is relatively small, these results **are very encouraging.**[6]

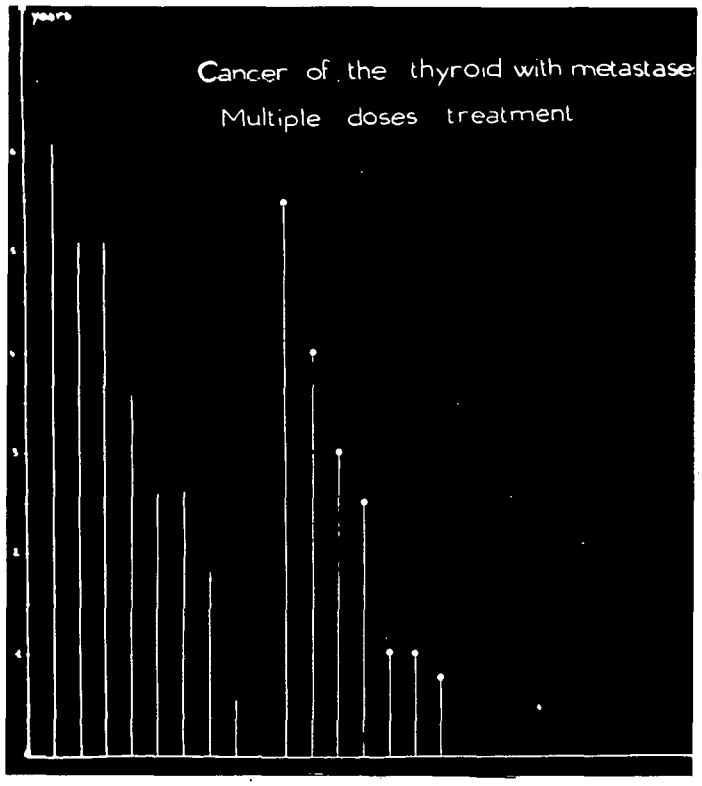


Figure 82. Length of survival of metastatic cases treated with several doses of radioiodine.

DR. SONENBERG: What size are the doses that you give?

DR. TUBIANA: In this one it was about 400 mc.

DR. CHAPMAN: I am sure my illustrations do not add anything but they emphasize two or three of the points raised. I must say that this work was done in our clinic, largely by Dr. Maloof who has been most interested in recent years in the problem, and the surgical review of the problem was done by McDermott and Cope. I have some of their illustrative material and would like to show briefly the experience in our thyroid clinic.

We were able to collect about 200 cases since 1931, and classified them into these three groups; papillary, follicular, and undifferentiated. The total number of cases is shown in white and the deaths in black in Figure 83. The data substantiate what has been said before, i.e., the slow growth, the late deaths of those with papillary carcinoma, and the middle

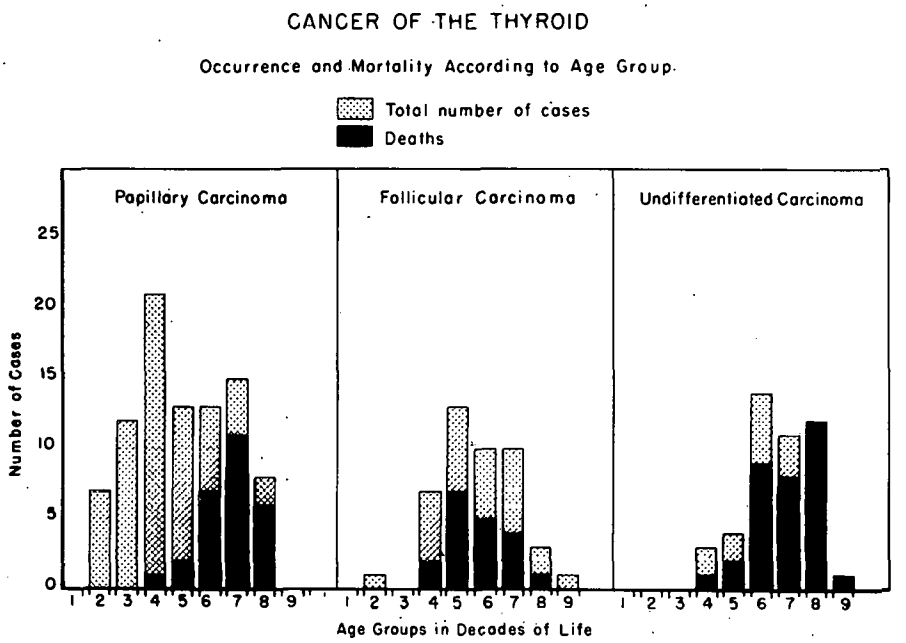


Figure 83. The incidence of the 3 main types of thyroid cancer, according to decades of life. Deaths from cancer are treated similarly according to the age at which the diagnosis was established.

position of those with follicular. The individuals with undifferentiated tumors seem to get the disease at later ages and then die rather soon of the disease. It was because of this, particularly in the long survival, that the surgeons took the attitude that radical neck dissection in a young girl in the second or third decade, was really not warranted. In other words, they would avoid mutilating surgery in a person with papillary carcinoma. Sure, remove as much of the primary disease as you can, hoping you get all of it. But don't just say, on the basis of statistics, that you would do a mutilating or widespread radical neck dissection.

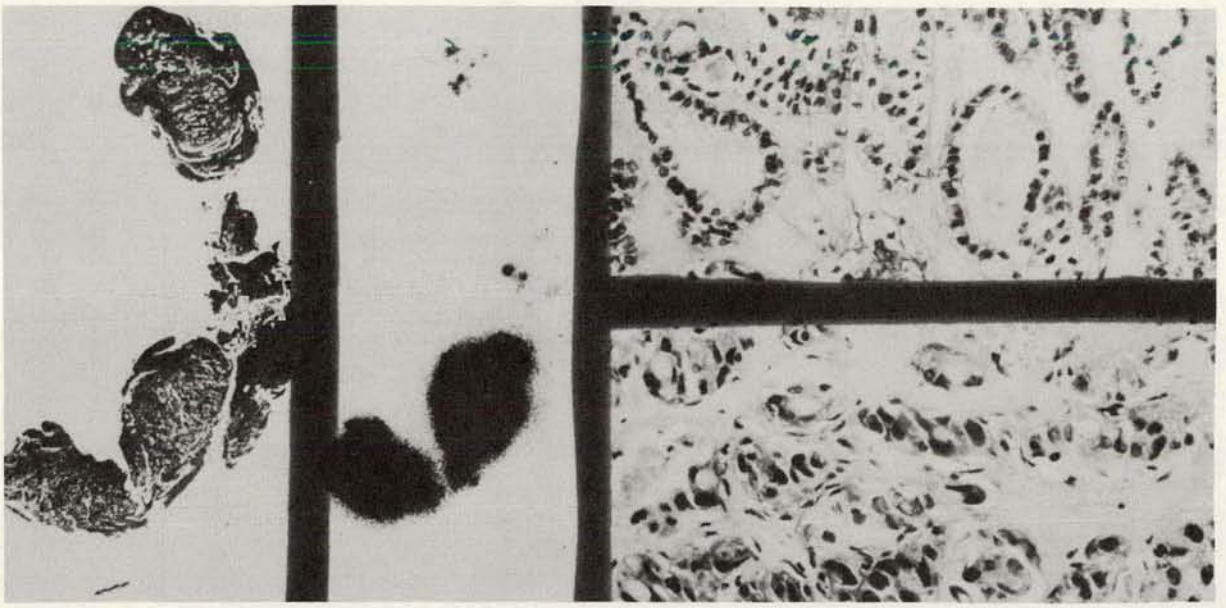
In breaking down these cases we found another interesting point, well known before, but now I think it is statistically borne out. That is, that in 32% of the papillary group, preexisting goiters were present over 3 years. This was rather a surprise to us. A knowledge of thyroid disease had been present for many years before surgery was finally undertaken that revealed the true disease. We are seeing this constantly in our clinic. We are following people (Table 53) with lumps in their neck and we say, the condition seems benign, and see them again in 6 months. By this time the patient already has metastases in the neck, and belongs in the papillary group. This recently happened to a nurse on our hospital staff. The same thing is true with private patients. I think we must not lose sight of the fact that known disease had been present for so long.

Dr. Tubiana showed the way he studied the pattern of tumors with biopsies. Figure 84 shows a metastasis with great variation in histologic appearance. Maloof arranged this one

Table 53

CLASSIFICATION OF THYROID CANCERS IN PATIENTS ADMITTED TO THE MASSACHUSETTS GENERAL HOSPITAL BETWEEN 1931 AND 1951

Type of cancer	Total number	Pre-existing goiter (more than 3 years)		Number of cases with metastases at first admission		Resectability		Hospital mortality	
		No.	%	Reg.	Dis.	No.	%	No.	%
Papillary carcinoma	89	28	32	54	7	79	88	1	1
Follicular carcinoma	45	27	60	8	20	34	75	1	2
Undifferentiated carcinoma	45	10	22	18	12	12	27	5	11



A B

Figure 84. Needle biopsy specimen from solitary sternal metastasis taken 10 days after administration of 200 mc of I^{131}. Radioautograph shows retention largely in lower segment. Note disarray of architecture, attributable to radiation damage in lower section; good follicular differentation in upper or less irradiated section.

and it really is quite revealing in that such morphologic variation occurs within a single metastasis. The patient is a 50-year-old man with carcinoma of the thyroid. He had a total thyroidectomy, and then developed metastases in the sternum. He was given 200 mc of I^{131} and 10 days later the biopsy of this tissue was done. Figure 84B shows the photograph of the needle biopsy specimen as a whole. Beside it (Figure 84A) is its radioautograph. You can see that the radioactivity seems concentrated at one end of the tumor. When you section this end of the tumor it looks like the lower half. You see the radiation effect, with its variation in nuclei, with obvious radiation effect. Then on section of the other end of the tumor, it seems very little has happened to it. This is all in just one metastasis.

DR. FRANTZ: How long previously was the radiation given?

DR. CHAPMAN: Ten days, 200 mc.

On the matter of feeding thyroid, I think it is interesting that Dr. Frantz was seeing her patient in 1948, then other people began to see patients during the early '50's. All seemed to come to the same idea together that thyroid seemed to have a suppressive effect on cancer. I think that is about as far as we can go. One of our patients, a woman, had a mass in her chest and then had a total thyroidectomy. Under the stimulation of the absence of the hormone and stimulation of TSH, this mass grew very rapidly. She was fed tapazole for a while, with the hope of further increasing its uptake. This was done

when we were following just a dogmatic line, shall we say, but putting in 300 mc discouraged it somewhat. Then we went along for 8 months when it was slow growing, and we gave 2 more doses to a total of 816 mc. We then put her on 4 grains of thyroid a day, and since then, 1953, this mass is still suppressed (Figure 85).

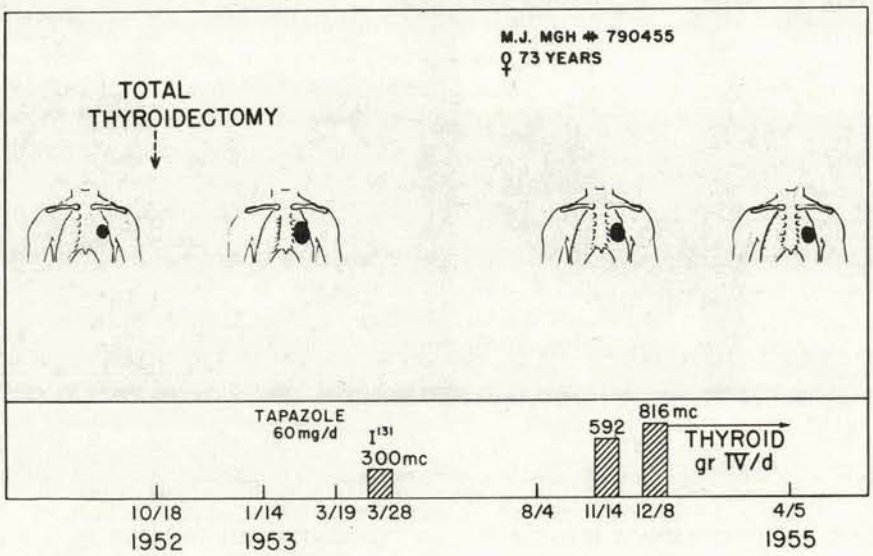


Figure 85. Suppression of the growth of a rib metastasis for 2 yrs. during the administration of desiccated thyroid, 4 grains daily.

We have one other illustration on the same point (Figure 86) which goes back to '49. The cumulative doses of I^{131} are shown. We put the patient on thyroid, and the mass in the pelvis continued about the same. She came to the clinic 2 weeks ago, and she is still living with disease which is suppressed. You can see that our dosage ranges are somewhat similar to others. We do not have any fixed program. These are repeated doses of a smaller order than we previously gave our patients. Now we view with alarm going above a total dosage of 500 mc and are on the lookout for deleterious effects on the hemopoietic system.

DR. JAFFE: Were there any patients that you treated with thyroid alone?

DR. CHAPMAN: Frankly, I chose these two cases at random. We have 6 in all. To be sure, they are confused with other forms of therapy. We have had others who have had only radioactive iodine, and they went on and died. Our total experience, out of these 200 patients, is that we have 20 patients with metastases whom we have treated. Of the total number of patients with cancer of the thyroid, 10 or 15% are suitable for treatment. Of the 20 we have treated with radioactive iodine, only 10 are living. Of these 10, 6 are on thyroid and seem to live longer and to do better than 10 nonsurvivors who did not receive thyroid. It is difficult to say what factor is operating; whether it is the radioactive iodine or whether it is the thyroid depressive effect, but physiologically, the latter makes sense.

DR. JAFFE: Does anyone have records of cases treated by thyroid alone? Without

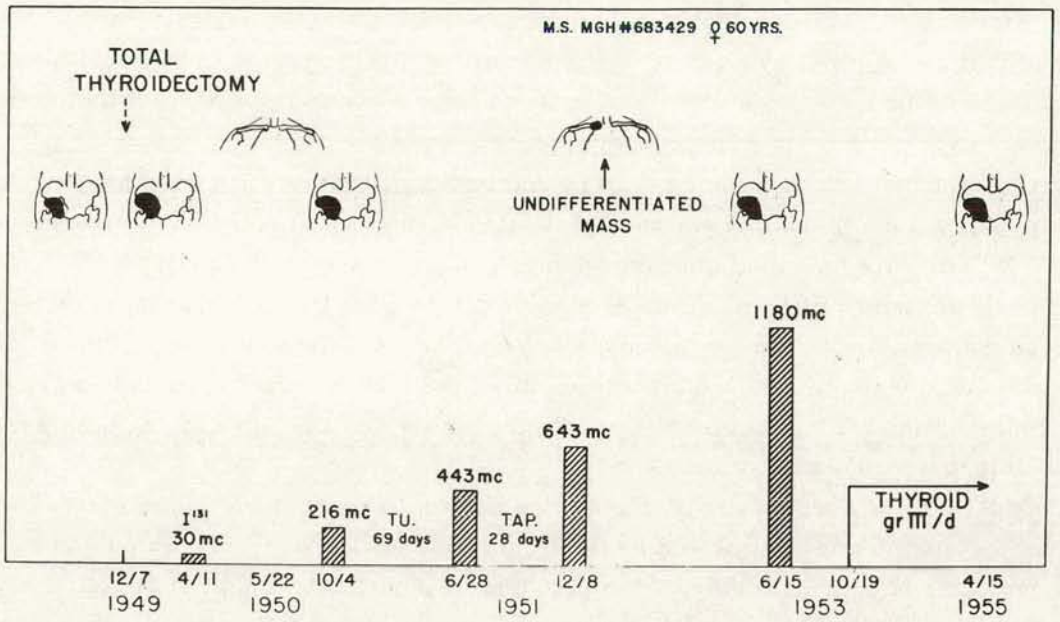


Figure 86. The sudden growth of metastasis after total thyroidectomy. For 2 yrs. on desiccated thyroid, the tumor has not significantly progressed.

radiation.

DR. VANDER LAAN: We have had such an experience, but I would not call it a record. I mentioned the patient earlier. It appears to me that there is a good deal of attention being paid to making the tumor avid for radioiodine. This is all done through the thyroid-pituitary mechanism, and tumors are made more avid with the hope that one can get a cancercidal dose of radiation into the tumor. If one accepts that, I think it implies acceptance of another type of approach; one can accomplish some good and possibly more good by simply suppressing the pituitary.

I have already referred to the relief from pain obtained with thyroid. The patient remains well 2 yrs. afterward. We could not induce radioiodine uptake by thyrotropin, but it caused prompt recurrence of pain. We did not give radioiodine. We continued thyroid, 3 grains a day, and that has been enough to keep the uptake in the range of 5%. She is still well.

DR. CHAPMAN: She was euthyroid to start with, was she not?

DR. VANDER LAAN: Yes she was.

DR. JAFFE: Dr. Rawson told me that several patients at the Memorial Hospital who had carcinoma of the thyroid gland with metastases were treated by surgical hypophysectomy, and no significant regression of the metastases was observed. Therefore, if the reported value of thyroid medication acts through depression of the pituitary gland, one would certainly expect a favorable response following surgical hypophysectomy. All of the patients who have had reported benefit from thyroid medication also had radioiodine treatment within 2 months of the onset of the use of thyroid medication. Therefore, I believe that we

should be extremely cautious about observing and reporting the benefits of thyroid medication, and that the critical evaluation of the benefit of thyroid medication would be especially valuable in those patients who previously had not received radioactive iodine therapy.

DR. CHAPMAN: I think your case is probably one of the very few that have not had any therapy other than thyroid. I am sure that more of them will come along in time.

DR. POCHIN: We have had at least 4 cases whose bone metastases have been responding well, as judged clinically, while on radioiodine plus thyroxine dosage,[1] and in whom blood changes prevented further radioiodine therapy. When they were then continued on thyroxine dosage alone, without radioiodine, their bone lesions started to grow again. It looks as though it was clearly not the thyroxine but the radioiodine that caused the initial improvement in these cases.

DR. DOBYNS: While she was giving her paper, Dr. Frantz made some remarks that prompt me to summarize the way I believe the surgeon should approach a nodular goiter and thus avoid, as nearly as possible, the problem of inadequate surgical attack. First of all, give the patient radioiodine and find out as nearly as possible by directional counting whether the nodule, by comparison with the normal thyroid tissue, is cold or cool. If a cold mass is detected, then one is prepared to go after it with considerably more concern than if this information is not available. I personally never explore a thyroid mass without first doing directional counting. Later, when the lobe is exposed, one's suspicions either are increased or allayed, depending on the appearance of the nodule. One should never enucleate a neoplasm of the thyroid because that may be inviting trouble. Remove it so that there is some normal tissue adjacent to it. When it is out, have a frozen section made promptly. If the pathologist is not able to give a firm answer, look at it yourself and discuss the evidence such as it is. Then have samples of the tumor put in a counter and find out whether it is hotter or colder than a sample of the normal thyroid (being careful not to contaminate either). I can assure you, on the basis of information learned from the radioautographs of thyroid tumors in general, that the difference is enough to give you an added sense of security regarding the possibility of malignancy. The colder the mass, the wider the removal should be. The final comment is the matter of looking at the other lobe—of course one always looks at the other lobe and always looks behind that lobe where the lymphatic drainage is most likely to be involved, i.e., tiny lobes in the region of the recurrent laryngeal nerve and along the trachea. I think if these steps are followed, at least I feel I have the greatest possible mental security in having done the best I can in trying to settle the issue at this first operation.

DR. FRANTZ: You said cases, Dr. Dobyns, in which there are no known distant metases. In the case of our 1 really good result, who has survived 8-1/2 yrs. and is completely athyrotic on the bases of her total thyroidectomy and treatment to her T-11 lesion, we had a postoperative uptake study and it showed the elective thyroidectomy was complete. I use the photograph of the gross specimen to show students what the gland looks like when it is nicely dissected. There was practically no uptake in the primary lesion. It was a cold

nodule calcified.

DR. DOBYNS: If you find the nodule significantly cold at the time of the operation, then I think the surgeon should remove the rest of that lobe, even if he had initially removed it with a pad of normal tissue around it.

DR. WERNER: I do not know much about thyroid cancer, but Dr. Sloan knows a great deal about it and he has pointed out that cancer of the thyroid has a very typical life history and that unless we correlate the disease in the individual patient with the time in the life history of the cancer, it is very hard to know exactly what kind of result you have. As Dr. Frantz brought out with her patient, the very first one was a very long life history without inadequate treatment. And I wondered whether in this whole discussion it can be said that, even with I^{131} therapy, that one is doing any better than the life history of the patient would have permitted had you analyzed the patient from the time of onset to the time treatment was conducted, to the time of death, or whatever was going on. Did I make that clear?

DR. CHAPMAN: I think it is perfectly clear. We do not know when we are changing or altering events that would have occurred anyway.

Part III — Biological Effects of Radiation and Complications

DR. CHAPMAN: We must leave this interesting discussion and go on to the problem of the biologic effects of radiation and complications.

DR. TRUNNELL: I am reminded of Hemingway's vastly over-rated Old Man and the Sea, in which, after the protagonist caught a big fish, the sharks kept taking bites out of it on the way back to shore until finally, when he got there, all that remained was the skeleton. I feel about my presentation as the old man must have felt about his fish. I have a whole set of illustrations, and in these 2 days, first one speaker and then another, perfectly legitimately, covered my subject. Consequently, rather than bore you, especially at this late hour, I have selected only the 4 or 5 illustrations that might still be worth showing.

I shall attempt to say a word or two about some of the normal tissues that have not been mentioned during the time we have been meeting. Those listed in Table 54 were selected from bits of postmortem tissue taken from 9 patients and represent normalized average figures for concentration. They were then converted to estimated doses of radiation. The left hand column in the table shows a typical dose for hyperthyroidism, although somewhat larger than most of you use, and the other shows a typical dose for thyroid cancer. About the only comments I need to make are that both of these figures are low. These people had all kinds of alterations and damage to their thyroid tissue and thyroid cancers so that by the time they finally succumbed, the uptake in these tissues was atypical.

I suspect that we have to make the same comments and qualifications about all the others; certainly these 9 people do not represent the average for the population. They aren't homogeneous as to sex or age; they have had long debilitating diseases, and, in numerous instance, have had adrenal disturbances. However, they represent the best mate-

Table 54

THE DISTRIBUTION OF RADIOACTIVE IODINE IN HUMAN TISSUES. A NECROPSY STUDY IN NINE PATIENTS.[7]

Tissue	Estimated total tissue dose (equivalent roentgens)*	
	Arbitrarily chosen doses	
	10 mc	100 mc
Thyroid cancer metastases	830.00	8300.00
Thyroid	378.00	3780.00
Bile	11.80	118.00
Gall bladder	1.06	10.60
Blood	9.25	92.50
Adrenal	7.90	79.00
Stomach	8.10	81.00
Urinary bladder	7.67	76.70
Ovary	6.47	64.70
Kidney	4.32	43.20
Liver	4.32	43.20
Uterus	4.30	43.00
Spleen	3.50	35.00
Testes	3.30	33.00
Red marrow	2.87	28.70
Muscle	2.09	20.90
Post. pituitary	1.47	14.70
Anterior pituitary	0.34	3.40

*The data that are listed are estimates of doses that would be delivered to the various organs if quantities of 10 or 100 mc of I^{131} were administered. Calculations are based on data obtained during a post mortem study of 9 patients.

rial we had available for this kind of exhaustive study. In addition to the measurements shown here, we made radioautographs and some fairly detailed studies of the usual histopathologic type.

I would like to add that the central nervous cells of these patients seemed to contain conspicuously small amounts of radioactivity. Some of our recent studies indicate, though, that the samples shown here are not representative. The only radioautograph that was positive for uptake except for thyroid or thyroid cancer, in any of the several hundred tissues taken from these 9 individuals is given in Figure 87. It is a section of prostatic tissue from a 60-year-old man showing some uptake in the corpora amylacea. Even this is not a new discovery because it was discussed by Wells in his Textbook on Pathology in 1920. Of course, he did chemical analysis instead of having the help of isotopes.

We thought we might say a word about the place of the scintigram or gammagram, as it is variously known, in looking for certain of these nodules in thyroid tissue that perhaps deserve to be removed. Dr. Dobyns' technique, particularly in his hands, certainly serves him well, but the scintigram is done automatically with somewhat less labor, and in a few situations has found thyroid cancers for us. More often it has helped us to decide whether

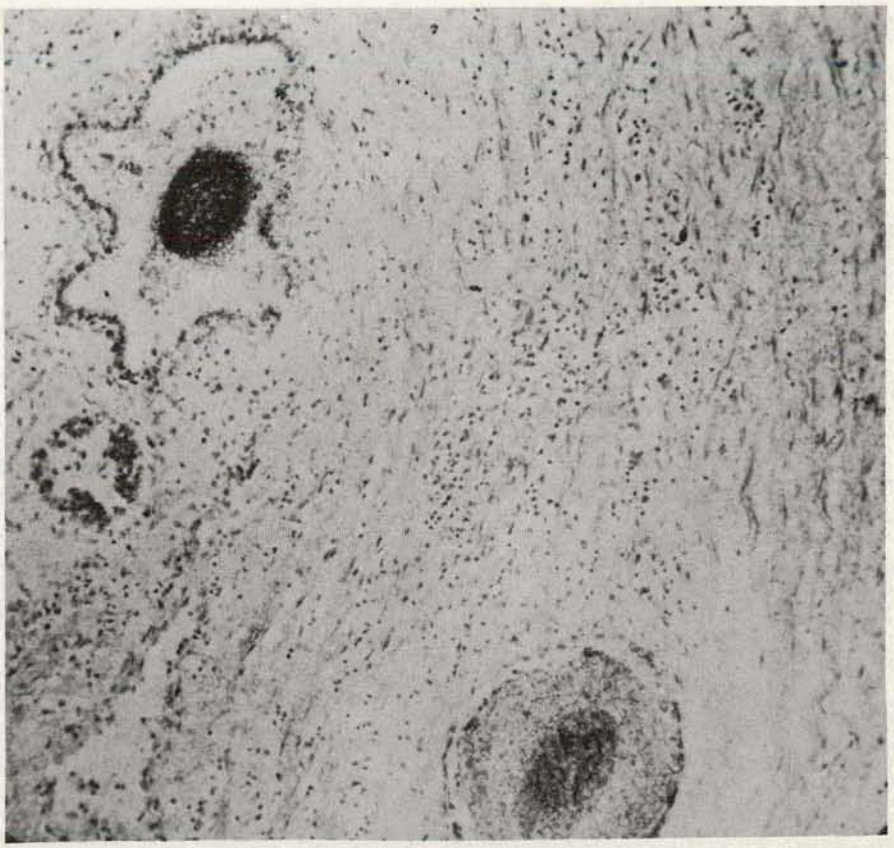


Figure 87. Radioautograph showing uptake of I^{131} in corpora amylacea of prostate gland.

or not conspicuous nodules ought to be removed. Occasionally it has even called our attention to nodules that we failed to palpate but which were, in Dr. Dobyns' terminaology, cold.

A somewhat typical scintigram is shown in Figure 88. This patient refused surgery.

DR. CHAPMAN: We see myxedema appear very late, after what appears to be a reasonable dose of radioactive iodine—to what mechanism would you ascribe this late appearance of myxedema, 8, 9, and 10 yrs. after?

DR. TRUNNELL: Do you mean in thyroid cancer?

DR. CHAPMAN: No, I mean after hyperthyroidism. I am not talking about cancer at the moment; I am talking about the long range effects.

DR. TRUNNELL: It may be a naive approach but I suppose that with certain of the thyroid cells having been destroyed, the burden on the rest of them uses them up sooner if there is a sort of fixed life span. I like to think that the healthy thyroid has some sort of shift work arrangement built in so that all the cells are not working all the time.

DR. CHAPMAN: Like the kidney, perhaps; the glomerulus opens and closes for a while and is followed by others in function.

DR. TRUNNELL: There is clear evidence for this, and I know there is some to the contrary.

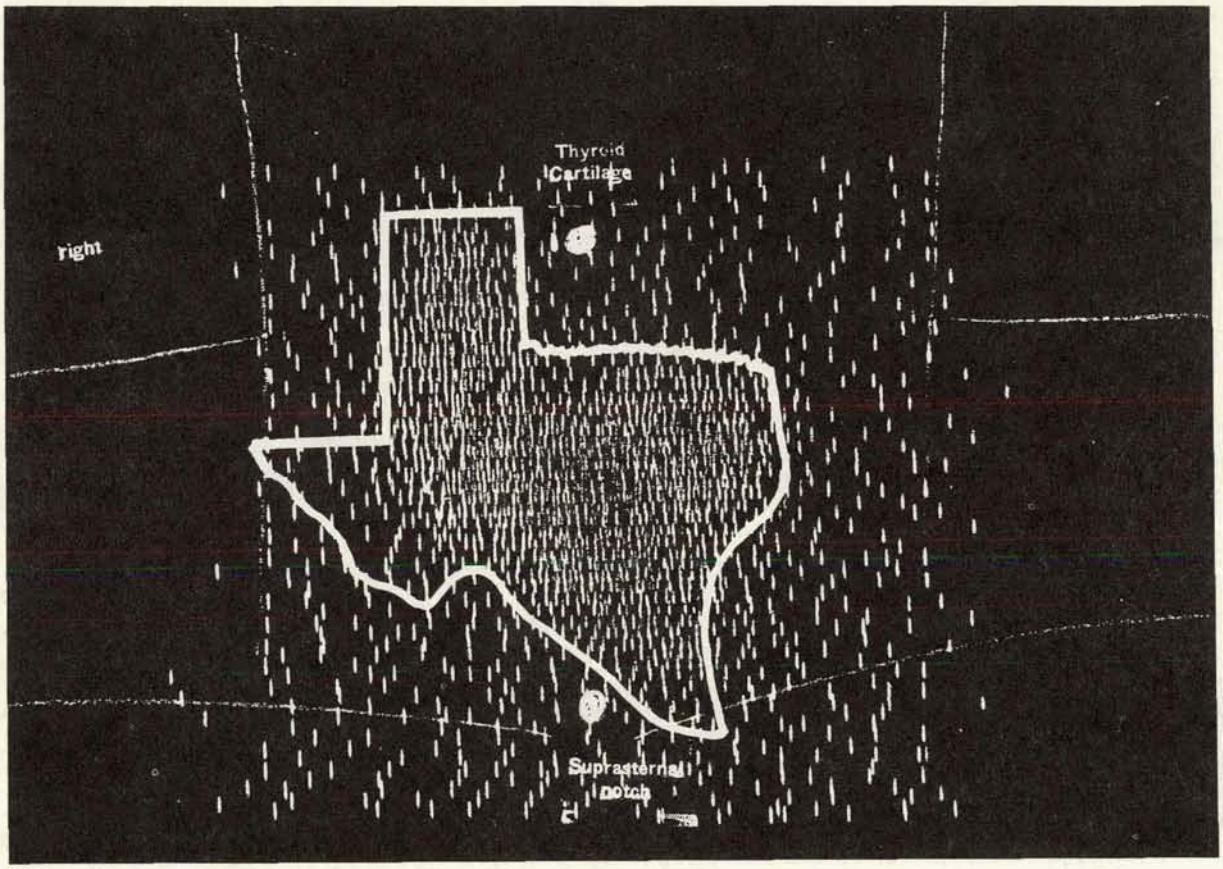


Figure 88. Scintigram from a patient with a very large thyroid gland.

DR. FREEDBERG: I think I have an opinion on the late development of myxedema. Perhaps it is an effect produced on the vasculature of the thyroid by the I^{131}. Figures 89 and 90 show respectively an early (2 weeks) and a late effect of I^{131} on the normal thyroid gland.

DR. CHAPMAN: You mean a sclerosing thyroiditis that finally leads to cell death from lack of nutrition?

DR. FREEDBERG: If you look at a thyroid gland several years after I^{131} irradiation, you see a significant change in the vasculature. The vessels are thickened; the lumina are narrowed and they may be obliterated (Figure 90). Perhaps the thyroid gland which normally gets a rather large blood supply needs that to survive and if you reduce the blood supply, the thyroid atrophies.

DR. CHAPMAN: That was not what I was talking about. This is very timely, though, and you came up with the right illustration at the right moment.

DR. VANDER LAAN: Twelve years ago in Cambridge, at the Macy conference on the thyroid gland, Dr. Marine advanced the opinion that iodine acted in Graves' disease by causing a sclerosing endarteritis in the thyroid. It would be my guess that the endarteritis follows the effect of iodine on the gland.

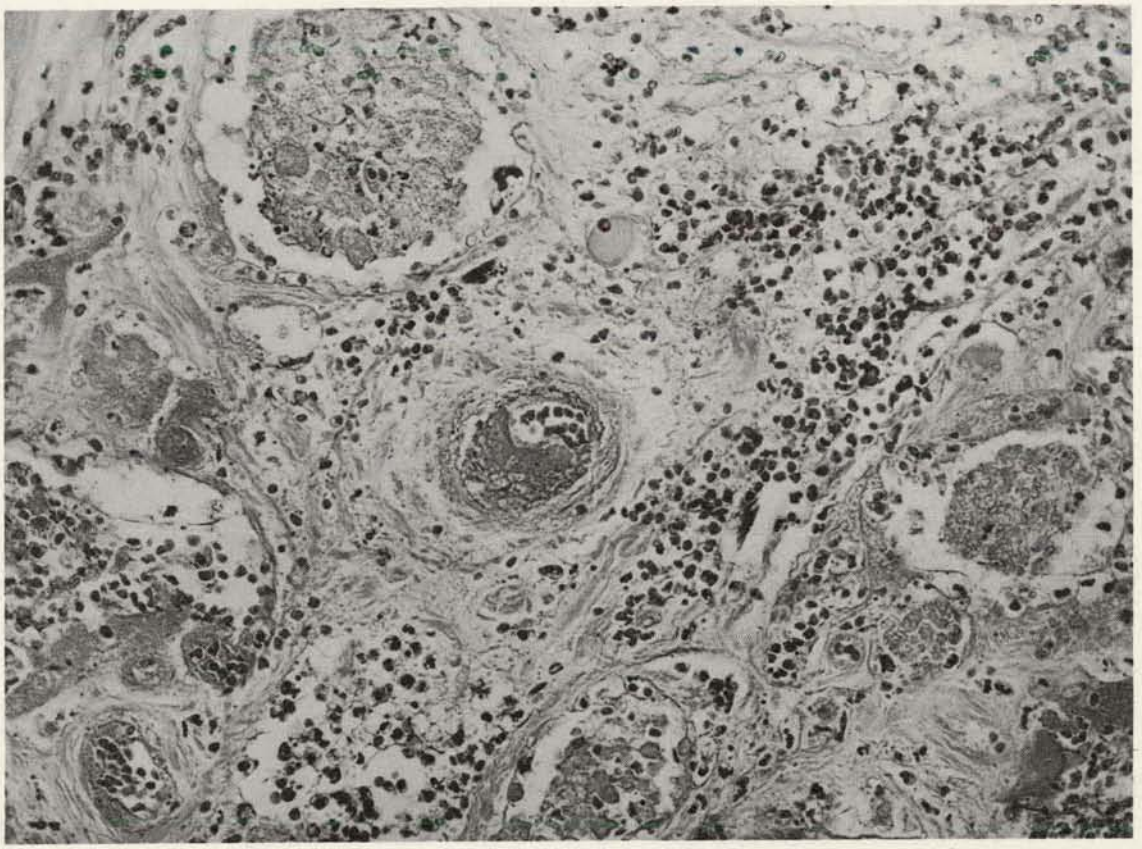


Figure 89. Acute effects of a therapeutic dose of I^{131} on the normal thyroid gland.

DR. FREEDBERG: The thyroid dose was 10 mc. Similar changes have been observed in the thyroid gland of patients given 3 doses of 10 to 15 mc at weekly intervals with 24-hr. thyroid gland uptakes after the first dose of 30 to 40%; the uptakes after the second and subsequent doses are far smaller.

Since we heard yesterday that radioactive iodine is not deposited uniformly in the thyroid gland, it is possible that some areas get more intensive irradiation than others. Yet, with the dosages mentioned, the thyroid gland is found at autopsy to weigh approximately 2 g and to be largely fibrotic. With the irregular distribution mentioned, one would expect some areas to remain relatively intact. That one may obtain a significant degree of vasculitis in the I^{131} irradiated gland is also supported by observations that hemorrhage occurs in such glands. There has been one report of severe thyroid gland hemorrhage following the use of dicumarol in euthyroid cardiac patients who received doses of radioiodine in the range mentioned above.

DR. CHAPMAN: Dr. Trunnell, you had something to say on that.

DR. TRUNNELL: I have one other idea, which is pretty unlikely, but it occurred to me that there ought to be some little center somewhere in the feedback circuit that actually

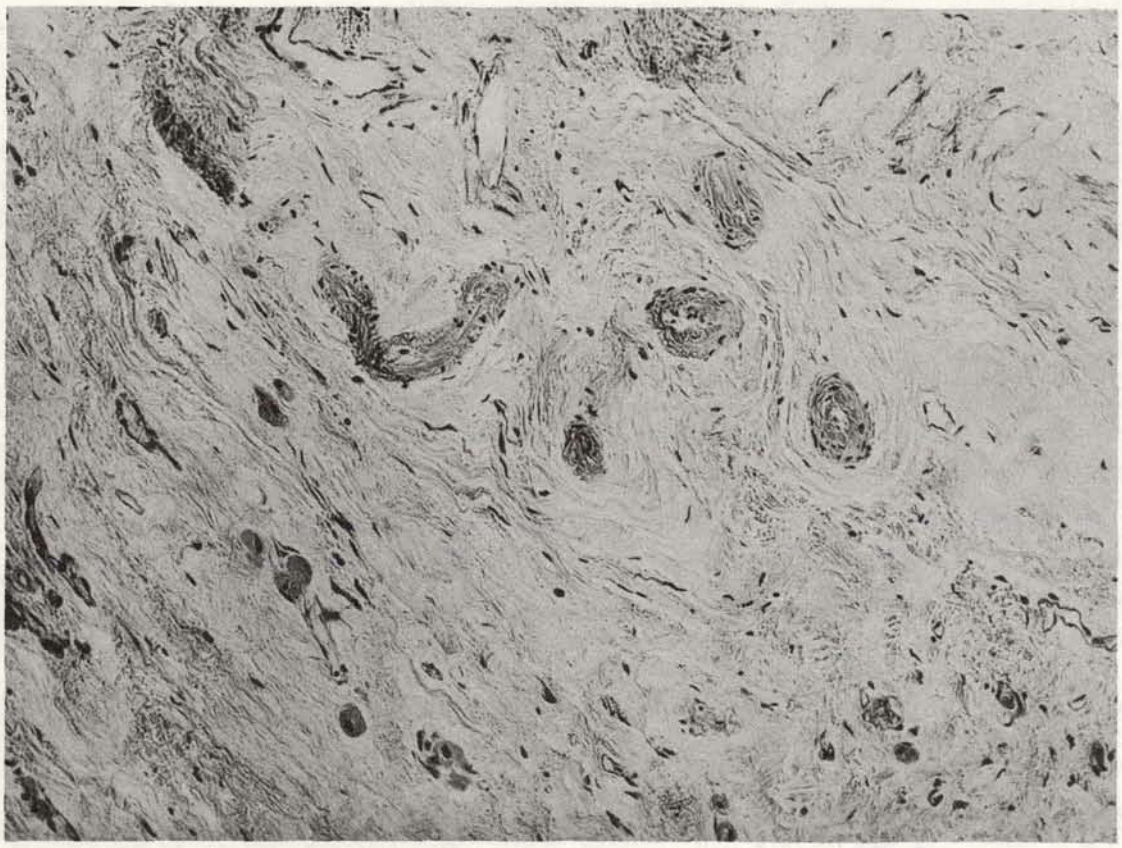


Figure 90. The late effects of I^{131} on the normal thyroid gland.

does PBI's every minute or so, perhaps continuously, and feeds the results of its assays to the pituitary. If perhaps it is a radiosensitive spot, it may begin to degenerate during the time the radioiodinated thyroxine is being sampled. With the passing years, it may cease to function so that the proper signal does not go to the pituitary.

DR. CHILDS: I would like to emphasize what Dr. Freedberg said regarding the changes in the thyroid following radiation. Many late radiation effects are thought to be due to obliteration of the blood vessels due to endarteritis. Not infrequently the skin will break down 10 to 15 yrs. after a heavy dose of radiation.

DR. SINCLAIR: Perhaps some of the radiologists can tell us what the results of doses on the order of 3000 or 4000 r are to the thyroid when it is not diseased and is irradiated incidentally in the treatment of head and neck cancer. There must be a lot of information of this kind. I think perhaps Dr. Childs can answer that.

DR. CHILDS: I would like Dr. Keating to answer it and tell you what causes myxedema.

DR. KEATING: I shall have to join Dr. Vander Laan on this side of the argument. I have been interested in this subject ever since the time one of our colleagues, a radiologist, took exception to our statement that myxedema may develop in a patient with carci-

noma of the breat treated with roentgen rays as a result of the passage of ionizing radiation through the edge of the intended field and, accordingly, through the thyroid gland. We were stimulated by the controversy to keep a record of this possibility for several years. We thus acquired a series of perhaps 15 or 20 cases of genuine myxedema that had occurred in chronologic sequence among patients who previously had undergone irradiation for carcinoma of the breast, the irradiation involving multiple ports, including the lower part of the neck. I shall have to ask Dr. Childs what the dose probably was in this series of patients. It was not too large; my guess is that it was of the order of 2000 r.

DR. SINCLAIR: You said there were 20 cases like that. What sort of incidence is that?

DR. KEATING: I am sorry that I have no way of knowing what the incidence of myxedema was in the foregoing series of cases. The series was never subjected to formal study, so that we have no follow-up or other data.

DR. CARPENDER: I can answer part of this, 4000 r over the neck will produce myxedema. I have one case.

DR. CHAPMAN: Are there any other contributions to this rather controversial subject?

THYROID ABLATION FOR CARDIAC DISEASE

DR. CHAPMAN: If not, we are going to conclude the program with a discussion of thyroid ablation for cardiac disease.

DR. FREEDBERG: Our clinic has been concerned, since 1946, with the treatment of euthyroid patients with intractable angina pectoris and congestive failure by the induction of hypothyroidism with radioactive iodine. The theoretical basis for this treatment has not been completely validated. However, the working concept has been that with reduction of the total metabolism of the body, the systemic circulatory requirements are reduced and are within the limits of the cardiac reserve.

We have recently reviewed our experience[8,9] with I^{131} in 118 euthyroid cardiac patients, 84 with intractable angina pectoris and 34 with chronic congestive heart failure. These patients have been treated from 6 months to 10 yrs. ago and have now been followed on an average of over 3 years after the induction of hypothyroidism. The method of selection and evaluation of the therapeutic result has been reported previously. Of the 84 patients with angina pectoris, 56 or 67% were benefited by I^{131}. Thirty-six of the 84, or 43%, had an excellent result with virtual freedom from angina pectoris and 20 of the 84, or 24%, were classified as a good result. The remaining 28, or 33%, were not benefited by I^{131}. The results in chronic congestive failure, however, have not been as striking. Eighteen of the 34 patients, or 54%, showed an excellent or good result while the remaining 16, or 46%, showed no change in cardiac symptoms after I^{131} induction of hypothyroidism.

The results in this group of patients are entirely comparable to those that have been reported several years ago[10] in a much larger series made up of 1300 patients observed

in 49 other clinics. Of 835 patients with angina pectoris, approximately 200 of whom had some evidence of congestive failure, 78% showed worthwhile improvement after I^{131} induced hypothyroidism. Roughly half of these showed an excellent result and the remaining half showed a good result. In 450 patients with congestive heart failure, worthwhile improvement was obtained in 68%; an excellent result was seen in about 27% of the patients. The remaining 41% had a good result.

It should also be mentioned that a smaller experience in patients with paroxysmal atrial arrhythmias or chronic pulmonary insufficiency suggests that worthwhile results may accompany hypothyroidism.

I would like to limit the remainder of my remarks to some preliminary observations that may bear on the "susceptibility" of the normal thyroid gland to I^{131}. From what we heard yesterday, quantitation of the radiation to the thyroid gland by I^{131} has not been achieved. We have been able to examine at various time intervals after I^{131} administration the thyroid glands of our euthyroid cardiac patients who have, because of the severity of their heart disease, expired. This has permitted, in a very gross way, the correlation of the radiation that has been delivered and permits some speculation on the amount required to ablate the normal thyroid gland and produce myxedema. A description of methods used in our laboratory to measure I^{131} uptake by the thyroid has been published previously. Our studies would indicate that the equipment used (4-channel system scintillation crystal counters connected in parallel or 4 Geiger-Mueller tubes connected in parallel surrounding the patient's neck with a tube circle of approximately 45 cm) measures rather quantitatively the thyroid I^{131} content in euthyroid and hyperthyroid patients. In patients with hypothyroidism and those with a high body content of I^{131}, the 24-hr. thyroid gland measurements are estimated to be approximately 5% too high. We measure routinely the 24-hr. thyroid I^{131} uptake and the effective half-life in practically all our patients, utilizing urinary I^{131} excretion as a check. We have done no thyroid scanning in any of these patients. The actual dose we have administered to more than 150 euthyroid cardiac patients has been of the order of perhaps 50 to 150 mc of I^{131} in divided doses.

Figure 91[11] shows the results of an experiment that bear on some of the data that were presented here yesterday, when Dr. Werner asked Dr. Sinclair whether the effect of giving a single dose of 5 mc would be the same as giving 5 doses of 1 mc each.

This figure shows the thyroid gland uptake, the thyroid gland net counts per minute, the cumulative urine excretion, and the stool excretion in per cent of the administered dose. The urine was collected at 6-hr. intervals. The patient had rheumatic heart disease with multiple valvular involvement and was in chronic congestive failure. No ascites, hydrothorax or peripheral edema could be demonstrated. After the first oral dose of 20 mc, the 24-hr. thyroid I^{131} uptake was 32%. The thyroid gland counts fell exponentially with an effective half-life of 6.6 days. Sixty-seven per cent of the administered dose was excreted in the urine in 3 days, and 75% in 7 days and, during this period, only 1.2% in the feces. A second dose of 15.3 mc was administered orally, and the thyroid gland counts did not increase very much. The 24-hr. thyroid uptake is only 8%. Correcting for the counts result-

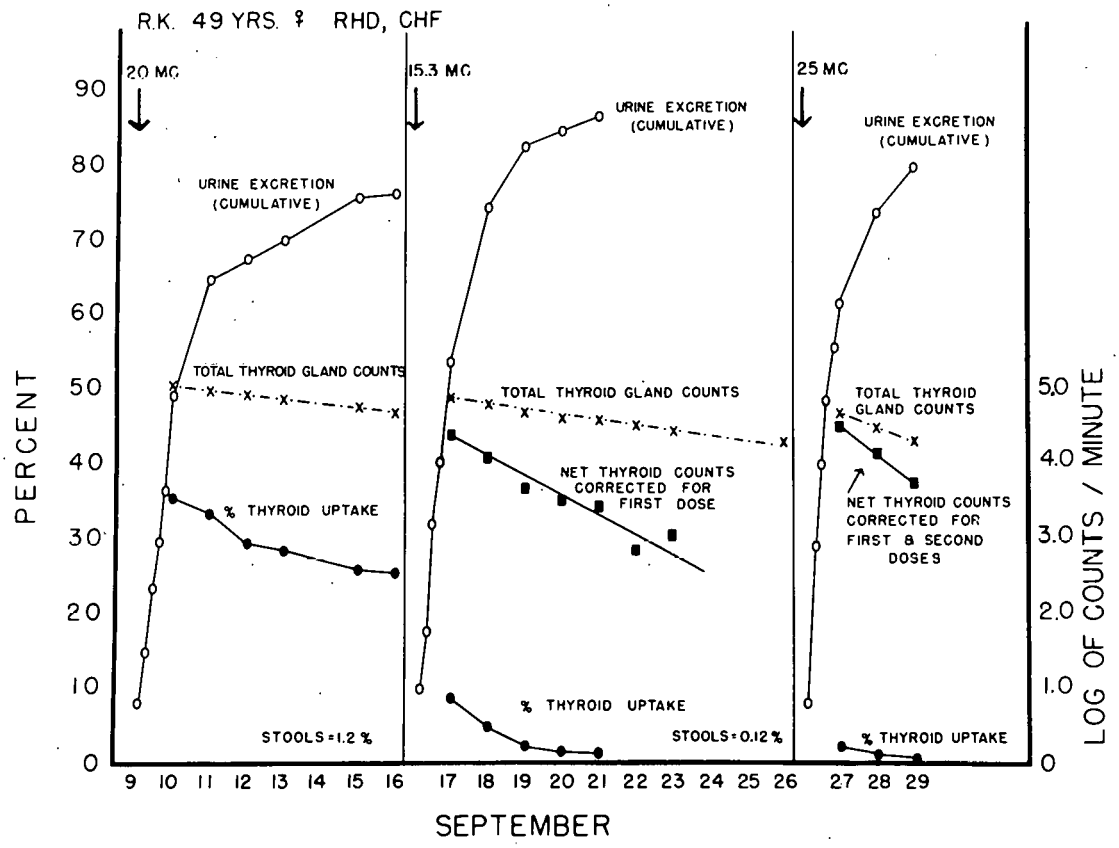


Figure 91. The thyroid gland uptake, net count per minute in the gland, and the cumulative urinary and fecal excretion as per cent of the administered dose of I^{131}.

ing from the first dose, assuming no change in effective half-life, the plot of the net thyroid counts following the second dose shows a much steeper fall-off, with an effective half-life of 1.1 days. The 72-hr. urinary excretion was 83%, and in 4 days, 88% of the dose was out in the urine. A third dose of 25 mc, given 10 days after the second dose, was followed by a negligible thyroid uptake of 1.6%. The effective half-life was only 0.8 days.

The data in Table 55 summarize findings on the thyroidal uptake and effective half-life in 17 euthyroid cardiac patients with angina pectoris to whom multiple doses of I^{131} were administered. The 24-hr. thyroidal uptake of a second therapeutic dose of I^{131}, administered 7 to 14 days after the first dose, was markedly diminished and was turned over at a more rapid rate (i.e., with a shorter E.H.L.) than the first dose. The 24-hr. thyroidal uptake of the initial therapeutic dose of 5.3 to 28 mc of I^{131} averaged 32% (ranging from 16 to 53), and the E.H.L. averaged 6 days (5.3 to 8.0). The uptake of the second dose, however, averaged only 10% (3 to 18), and the E.H.L. averaged 2.1 days (0.4 to 8.0).

Twelve patients with congestive heart failure were also studied (Table 55). Eleven received doses of 16.5 to 31 mc of I^{131}; 1 patient received 8 mc. The average uptake of the initial dose was 35% (ranging from 28 to 40) and that of the second dose was 13% (4 to 23). The E.H.L. fell from a mean of 6.1 days (4.3 to 8.0) to 1.5 days (0.6 to 4.0). Data from

Table 55

THE EFFECT OF REPEATED THERAPEUTIC DOSES OF I^{131} ON THYROID GLAND UPTAKE AND TURNOVER IN EUTHYROID PATIENTS WITH ANGINA PECTORIS OR CONGESTIVE HEART FAILURE

	No. cases	24-hr thyroid gland uptake				Effective half-life (E.H.L.)			
		1st dose		2nd dose		1st dose		2nd dose	
		Range	Aver.	Range	Aver.	Range	Aver.	Range	Aver.
		%		%		%		%	
Angina pectoris	17	16-53	32	3-18	10	5.3-8	6	0.4-8	2.1
Congestive heart failure	12	28-40	35	4-23	13	4.3-8	6.1	0.6-4.0	1.5

over 20 additional patients have confirmed these findings.

Table 56 shows the results of similar experiments in which smaller doses of I^{131} were given. In one patient given two 1-mc doses one week apart, the 24-hr. uptake and the E.H.L. were the same following both doses. In 3 patients given from 2 to 3 mc as the initial dose, the uptake and E.H.L. of a second dose, given 1 week later, were significantly altered as noted above for larger initial doses.

Table 56

EFFECT OF TWO THERAPEUTIC DOSES OF I^{131} ON UPTAKE AND TURNOVER IN EUTHYROID PATIENTS

	Dose (mc)	Uptake (%)	E.H.L. (days)	Estimated rep	Interval (days)
Case 1	0.92 1.04	51.4 53.4	5.9 5.9	2,200	0 7
Case 2	2.1 2.7	34 10	8.6 5.0	5,000	0 7
Case 3	2.5 2.7	30 14	8.6 2.0	5,800	0 7
Case 4	3.0 6.5	35.7 18.4	7 4.0	6,000	0 7

These data are interesting since the thyroid gland 6 to 7 days after a therapeutic dose of I^{131}, appears essentially normal upon histologic examination. Figure 92 shows such a thyroid gland 1 week after a therapeutic dose of I^{131}, which was estimated to have delivered 17,000 rep. While no radiation change is yet visible, such a gland would demonstrate the functional changes alluded to above.

This suggested to us the possibility that the changes might be reversible. We have published data[12] (Table 57) indicating the reversible action of thyrotropin. Since the paper was published, we have studied several additional patients with similar results. If thyrotropin is given before the second of 2 therapeutic doses, the thyroid uptake and the E.H.L. following the second dose are restored to that observed following the first dose.

It would thus appear that a dose of I^{131}, to a euthyroid person, of more than 2 mc with an estimated delivered thyroid radiation of approximately 5000 rep alters the function of the thyroid gland. Using such estimates of thyroid uptake and effective half-life, we came out with a figure of approximately 20,000 rep as required to ablate the euthyroid gland and produce permanent myxedema.

The pertinency of these data to those presented earlier with regard to I^{131} treatment of thyrotoxicosis is not established. We have measured E.H.L. and 24-hr. thyroid uptake in a large series of thyrotoxic patients rendered euthyroid by I^{131}. The studies were done over 1 yr. after the patients were euthyroid. The 24-hr. uptake is higher (41%) than in a group

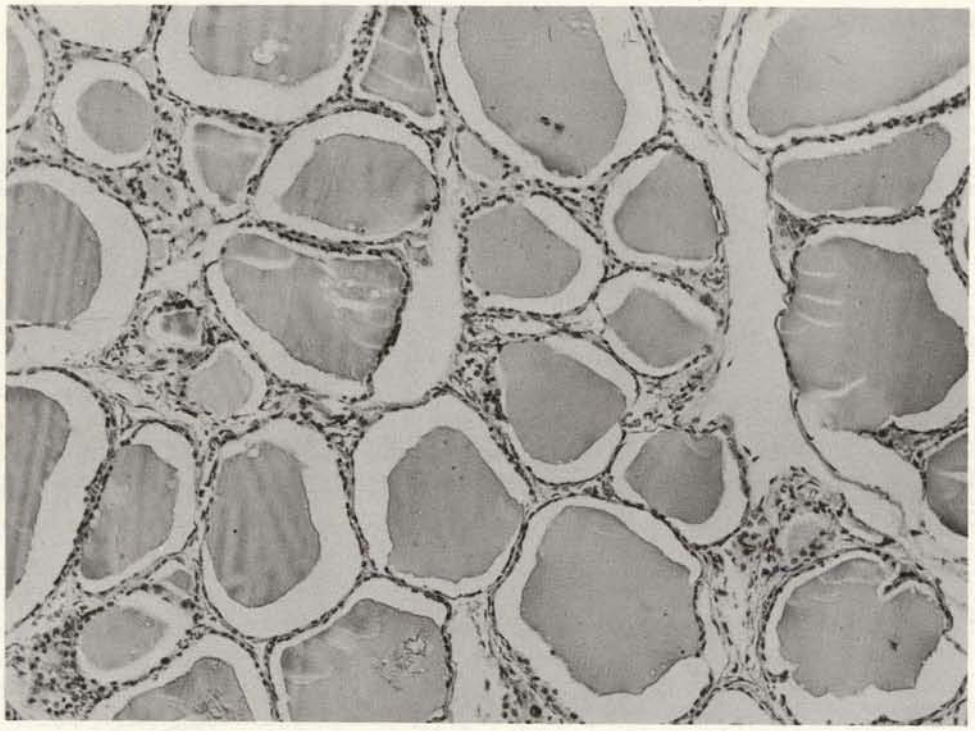


Figure 92. Tissue section from a thyroid gland one week after a therapeutic dose of I^{131} had been given.

of euthyroid controls, and the E.H.L. is significantly faster (4.1 days) than when the patients were thyrotoxic (5.5 days). A similar change in E.H.L. was noted, however, also in patients who remained persistently thyrotoxic, though improved, after a single therapeutic dose of I^{131}.

Finally, for the record, we have autopsy data on 39 euthyroid cardiac patients, ranging from 1 day to approximately 8 yrs. after therapeutic doses of I^{131} were given. The changes in a smaller series with the correlation of estimated radiation delivered have been described previously.[13] The enlarged series presents similar findings. The acute and end-stage changes have been shown previously in Figures 89 and 90. In the later stages, months to years, after I^{131}, many stromal cells and cells lining the remanents of follicles show marked changes including variation in size and staining capacity. Large, bizarre cells with dark nuclei are seen, but mitoses are not found. Not a single tumor in the thyroid or carcinoma in the thyroid gland has been seen. The bizarre cells have been confirmed by Shields Warren as indicating cellular ischemia and not cancer. Nor have there been any changes in the connective tissue which suggest the development of sarcoma in these glands within this period of 9 yrs. Much more data, however, will be required on longer-term cases to be sure that treatment with I^{131} will not be followed by malignant degeneration.

DR. JAFFE: We have reported recently our experience with the use of radioactive

Table 57

REVERSIBLE ACTION OF THYROTROPIN

Case no.	24-hr I^{131} thyroidal uptake (%)	E.H.L. (days)	Therapeutic dose of I^{131} (mc)	Days after initial dose of I^{131}	Comment
1	25	7.4	15.0	0	2 doses TSH on days
	16	7.4	15.0	8	6 and 7
2	40	7.2	14.6	0	2 doses TSH on days
	57	7.6	15.6	8	6 and 7
3	36	7.2	15.4	0	2 doses TSH on days
	48	7.2	16.8	8	6 and 7
4	30	7.3	15.0	0	2 doses TSH on days
	54	5.2	14.6	8	6 and 7
5	24	7.0	22.0	0	2 doses TSH on days
	61	5.0	21.0	15	14 and 15
6	37	6.2	22.6	0	2 doses TSH on days
	17	4.7	21.0	21	20 and 21
7	25	7.3	15.6	0	3 doses TSH on days
	9	4.0	20.0	7	32, 33, and 34
	8	6.0	20.0	14	
	8	4.4	20.0	21	
	32	7.4	12.0	34	
	8	-	31.0	98	
	6	2.4	21.0	160	
8	40	-	10.3	0	3 doses TSH on days
	7	-	0.3	51	52, 53, and 54
	17	-	0.1	55	
	10	-	20.8	56	

iodine therapy for euthyroid cardiac patients with supraventricular tachycardia. Figure 93 is representative of this group of patients. The stars indicate the frequency of attacks. I^{131} was given in a series of 5 to 6 weekly treatments reaching a total of 25 to 30 mc. In this case, the uptake prior to treatment was 18%. Several months after the last therapeutic dose of I^{131}, there was total cessation of attacks. These patients had previously been on quinidine or other medication without success. We now have a fairly large group of these patients who were treated with I^{131} and followed for a period of 5 yrs. The majority has responded favorably. Some had to be retreated with I^{131} after a year or more because they had evidence of further attacks of tachycardia, and most of these patients with recurrences again showed a satisfactory response.

Many of these patients may have a "hot" nodule in one lobe of the thyroid gland which causes a physiologic suppression of the other lobe. Some may also have cardiac disease

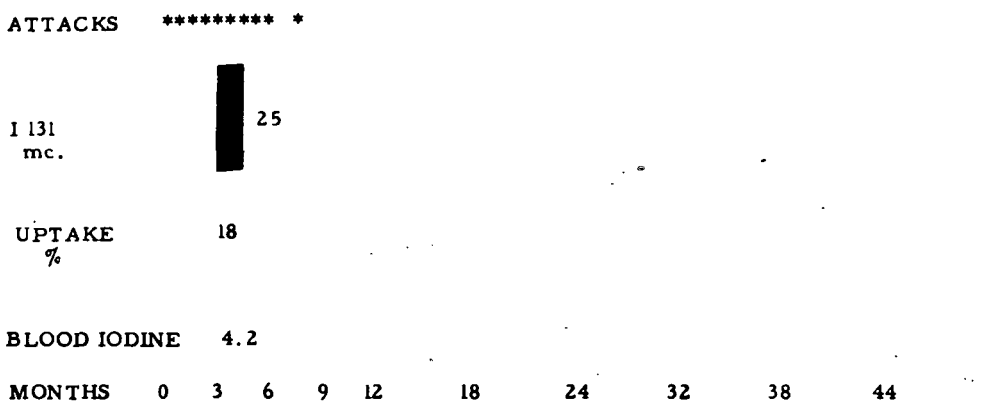


Figure 93. The effect of I^{131} therapy on a euthyroid cardiac patient with supraventricular tachycardia.

or cardiac symptoms. In one case, the scintigram showed absence of uptake on one side, resembling a picture of a surgical lobectomy, but this patient was never treated surgically. The total uptake figure may be in the normal range but that is because the uptake is all confined to one lobe. The PBI may also be within normal limits. Clinically some of these patients may be thyrotoxic, but many of them are euthyroid and yet they have evidence of supraventricular tachycardia. Three months after radioactive iodine you will note that the so-called "hot" nodule has a normal uptake picture and the function of the suppressed lobe has now returned to normal.

In summary, the first group of 23 patients with supraventricular tachycardia had no demonstrable thyroid pathology or disturbance. They have received 1 or 2 courses of radioiodine, each consisting of 25 to 30 mc, and 21 of these 23 patients have had exceptionally good results for a period of 5 yrs. The second group of patients who had a normal uptake of radioiodine and a normal PBI determination were those which, on scintigram examination, showed a concentration of all of the tracer material in one lobe and physiologic suppression of function of the other lobe. Some of these patients had palpable nodules corresponding to the hyperfunctioning area in the scintigram, while in others the entire lobe was enlarged, and in still others both lobes of the thyroid gland were normal on palpation. The scintigram or a manual scanning examination appears to be the only way in which this condition can be recorded and followed clinically after radioactive iodine therapy.

DR. FREEDBERG: There is one point I forgot to mention. That is what the minimal dose is that will produce the change that I described, of reducing the uptake and causing an increased turnover. That dose is 2 mc administered to a normal gland with a normal uptake. We have not seen this with doses of 1 mc administered at weekly intervals for 3 doses. How many more doses one can give without producing this effect I do not know, but we have seen it with a dose of 2 mc in 4 patients.

DR. BECKER: Dr. Freedberg, how big was the dose of TSH, and did it cause any flareup of toxic reaction in patients?

DR. FREEDBERG: The dose is 12.5 units given in divided doses the day before and 10 to 12.5 units given the next morning before the therapeutic dose. This dose did not result in any significant flareup in the patients studied. In one euthyroid patient given TSH to increase uptake in an iodide-blocked thyroid gland, the TSH caused a significant increase in angina pectoris which lasted several days.

DR. BERMAN: I would like to comment on Dr. Freedberg's interpretation of his results.

One cannot necessarily conclude from the change in the E.H.L. of radioiodine in the gland that the radiation or TSH dose has changed the turnover rate of iodine in the thyroid. What could happen, for example, is that the rate of uptake of iodide by the thyroid has been changed. This, in turn, changes the renal excretion rate of radioiodine, resulting in a different fractional loss of radioiodine from the system, and a different effective half-life.

DR. FREEDBERG: We do not have enough data, really, to separate incorporation from synthesis and discharge. The proof of the pudding would be the measurement of labeled products in the blood. The preliminary data we have would indicate that in the non-TSH-treated individual there is only a small amount of protein-bound or butanol-extractable I^{131} following the second of 2 doses of I^{131} of 10 to 15 mc each given 1 week apart. After TSH, with the 24-hr. thyroid I^{131} uptake and the E.H.L. paralleling that observed after the first dose of I^{131}, we have seen a curve of blood concentration of PBI^{131} that is similar to that following the first therapeutic dose. This is not proof because we do not know what the blood products are. But, at any rate, the total curves seem to be the same after TSH.

DR. SINCLAIR: It is a question of what you call turnover.

DR. FREEDBERG: As I mentioned earlier, we are referring to thyroid radioactivity, measured as counts over the thyroid or as per cent of the administered dose.

DR. DOBYNS: Some studies we have done on serial quantitative fractionation of specific iodinated compounds in the blood following treatment doses of I^{131} in euthyroid patients and Graves' disease would indicate that about the time one reaches the point of steeper decline on the thyroid decay curve (7 to 9 days), iodide begins to reappear in larger proportions in the blood and is excreted in larger amounts in the urine. It is now or a little later that compounds such as diiodothyronine begin to appear in the blood. Two factors are thus contributing to the slope of the curve. One is the retrapping of iodine; the other is loss of iodinated compounds. I think that, just as you have said, there is a point at which the iodide-trapping mechanism becomes jammed and this is where the whole pattern changes. I do not have data here to show you, but we have complete serial fractionations of the blood on almost 100 patients done in hours and days and weeks, amounting to 8 to 10 fractionations on each patient. It is very interesting to see how these compounds change in amount or appear and disappear with respect to time. I rather think that the re-

trapping mechanism that appears to fade out of the picture first, or is affected first, occurs about the 7th day for the average treatment doses we give. Thus, a new dose of iodide thrown into the pool is not going to be handled in the same way as the first one.

DR. FREEDBERG: We have seen the same phenomenon from as early as 5 days after a therapeutic dose, to as long as 13 to 14 days afterwards. We do not see at this time a sudden increase in urinary excretion. As I pointed out earlier, it seems for doses of 1 mc or less, given 1 week apart, that the 24-hr. uptake and E.H.L. are the same. The material we are using is carrier free so we assume the change is due to radiation and not to a change of iodide.

DR. KEATING: Mr. Chairman, I submit that the literary turnover of this particular meeting has, as a consequence of fatigue and other forms of attrition, been reduced to a point at which it is virtually athyrotic. I move we adjourn.

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