

## Radioactive Iodine as An Indicator in Thyroid Physiology

### II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits\*

S. HERTZ, M.D.; A. ROBERTS, Ph.D.; J. H. MEANS, M.D.; R. D. EVANS, Ph.D.  
BOSTON, MASSACHUSETTS

*From the Thyroid Clinic of the Massachusetts General Hospital, the Physics Department of the Massachusetts Institute of Technology, and the Department of Medicine of Harvard University.*

#### SUMMARY

USING radioactive iodine as an indicator, the quantity of iodine taken up by the thyroid of the rabbit under various circumstances was studied. After intravenous injection, the percentage collection from any given dose was found to reach a maximum within ten minutes, which was not greatly exceeded for periods of collection as long as several days. The normal thyroid was found to collect up to 80 times the quantity to be expected from uniform diffusion into the general body tissues. In hyperplastic thyroids, this relative concentration may reach several hundred. The variation of this concentration with the injected dosage and the functional state of the gland was determined. The effect of pretreatment of the thyroid in various functional states, with iodine, on the collection of a subsequent dose of labelled iodine was measured.

In certain of these experiments, several differently labelled iodine injections were used on the same animal in order to determine the fate of the individual doses. This labelling was accomplished by using different radioactive isotopes.

From the data thus obtained, we have calculated the strength of samples of radioactive iodine with which it will be possible to administer internal irradiation of the thyroid for therapeutic purposes.

Clinical implications of the results are discussed.

#### INTRODUCTION

In previous papers<sup>1,2</sup> we have described the technic and advantages of the use of radioactive isotopes of iodine as indicators in the study of iodine distribution and have reported preliminary results obtained with this method. This paper is concerned with the detailed results of extended experiments on normal rabbits and on rabbits which had received previous treatment designed to influence the physiologic state of the thyroid.

\*This research was conducted in the Physics Laboratories of the Massachusetts Institute of Technology, supported by grants from the Milton Fund, the Proctor Fund, and the Wellington Fund of Harvard University.

The great majority of the experiments were conducted with the use of the radioactive isotope of iodine of mass 128, which has a half period of 25 minutes. We have also used a few samples of radioactive iodine with the half periods of 12.5 hours, 8 days and 13 days (mass numbers 130, 131, and 126 respectively).<sup>1</sup> Thus most of the experiments have extended over a period usually not greater than one and one-half hours from the time of administration of the radioactive iodine, and a few have been extended for longer periods, up to eight days.

#### PURPOSE OF EXPERIMENTS

It was the purpose of these experiments to investigate the collection of iodine by normal and hyperplastic thyroid glands, in order to establish the normal and pathological behavior toward iodine under various circumstances, and in order to determine the conditions under which it might be possible to use radioactive iodine to administer internal irradiation of the thyroid. The experiments have therefore been concerned with the measurement of the percentage collection of known doses of labelled iodine by the thyroid, as a function of time of collection, quantity of iodine injected, previous history of iodine treatment, thyrotropic hormone administration, cyanide injection, cabbage diet, sex, pregnancy, and certain combinations of these factors.

#### PROCEDURES

The iodine was almost invariably administered intravenously in the form of sodium iodide obtained by dissolving labelled silver iodide in sodium thiosulphate.<sup>2</sup> In a few experiments in which long collection times were possible because of the availability of long-period iodine isotopes, subcutaneous injections were made. Animals were sacrificed by etherization, since the available radioactivities necessitated the removal of the thyroid for measurements.

For purposes of comparison, the dosages of iodine administered (except in some preliminary work) were adjusted to be proportional to the weight of the animal, 2 kg. being taken as a standard. Dosages below 0.5 mg. were not so adjusted, however, it being of interest to determine the collection of the smallest available quantities of iodine. The range of dosages used was from less than 0.1 mg. to 100 mg.

Since it was necessary in these experiments to use the entire thyroid for measurement of the iodine collection, it was impossible to make histological sections for the purpose of comparing the degree of stimulation of the different glands, as we should have desired. In some parallel studies of human thyroid glands, these data have been obtained. We hope soon to report the correlation of the data obtained with measurements of the basal metabolic rate on both animals and humans. In the present experiments, in addition to the information given by the gross appearance of the gland, we have used as a rough measure of the physiologic state of the thyroid the relative weight of the thyroid as compared with the body weight. It is well known that this is by no means a completely satisfactory indication of the physio-

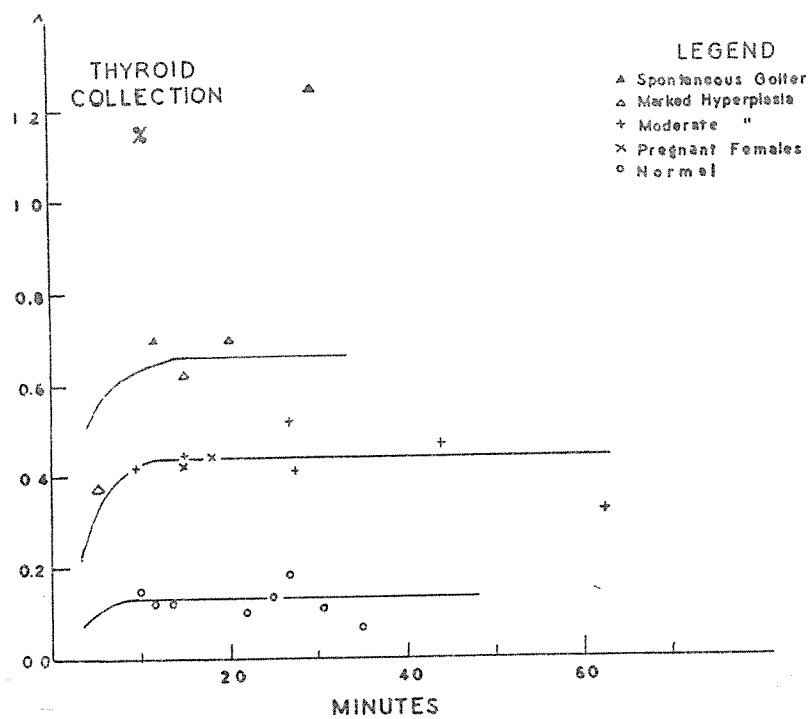
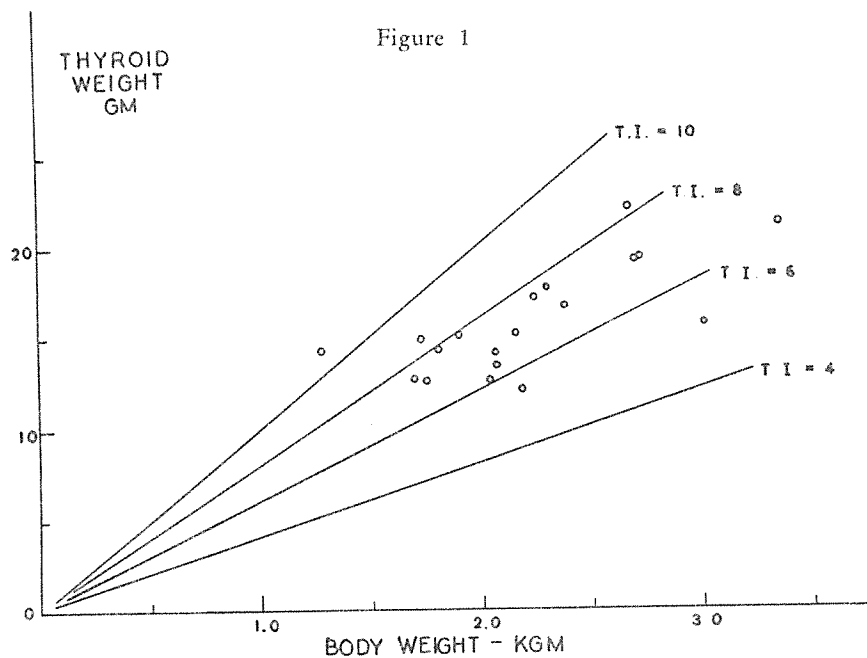


Figure 2  
(CAPTIONS FOR FIGURES 1 AND 2 ON OPPOSITE PAGE.)

logic state of the gland, but nevertheless, with a standard stimulus and large numbers of animals, it was possible to obtain statistically significant results.

For these purposes we have defined a quantity we call the thyroid index, as follows:

$$\text{Thyroid Index} = \frac{\text{Weight of Thyroid in Milligrams}}{\text{Body Weight in Kilograms, } \times 10}$$

where the factor of 10 is introduced to give a convenient numerical result. For the normal animals in our colonies, the thyroid index of almost all animals ranged between 5.5 and 8.0 (See Figure 1). In hyperplastic animals the index ordinarily ranges between 8.0 and 15.0, the highest value observed in our colony being 33.5 for an animal on an exclusive cabbage diet for two months.

In measuring thyroid iodine collection, we have introduced a quantity we call the thyroid concentration coefficient, in order to take into account the variation of size of thyroid glands among animals of the same weight. This quantity is defined by the relation:

$$\text{Thyroid Concentration Coefficient} = \frac{\text{Thyroid Iodine Collection in Per cent, } \times 1000}{\text{Thyroid Index}}$$

The introduction of the factor 1000 has the result of making this quantity represent the concentration of iodine in the thyroid divided by the concentration in an equal weight of body tissue, assuming uniform distribution of the iodine. (Thus it is a measure of the affinity of the thyroid for iodine.) This can be shown as follows:

$$\begin{aligned} \text{T. C. C.} &= \frac{\% \text{ I in Thyroid } \times 1000}{\text{T. I.}} = \frac{100 \times \text{Fraction of I in Thyroid } \times 1000}{\frac{\text{Wt. of Thyroid in gm. } \times 1000}{\text{Body Wt. in gm. } \times 0.01}} \\ &= \frac{10^5 \times \frac{\text{Fraction of I in Thyroid}}{\text{Wt. of Thyroid in gm.}}}{10^5 \times \frac{1}{\text{Body Wt. in gm.}}} = \frac{\text{Concentration of I in Thyroid}}{\text{Av. Concentration of I in Body}} \end{aligned}$$

This method of expressing the iodine collected by the thyroid is particularly useful because it gives directly the concentrating power of the thyroid as compared with the rest of the body. In some preliminary work to determine the approximate character of the iodine collection of various stimulated glands, no indices were constructed, and the data are accord-

(CAPTIONS FOR FIGURES 1 AND 2 ON OPPOSITE PAGE)

Fig. 1. The variation of thyroid weight with body weight for some of the normal animals used. The radial lines are lines of constant thyroid index.

Fig. 2. Preliminary survey of the percentage collection of the thyroid in various time intervals after injection of a 10 mg. dose of iodine. The data show the marked dependence upon the functional state of the thyroid. No precautions were taken to adjust the size of injection to the size of the animal, and the degree of hyperplasia was judged from the appearance of the gland alone.

ingly presented in terms of percentage. A direct comparison between percentage collection and thyroid concentration coefficient may be obtained from Figures 4 and 6. Previously published data<sup>1</sup> have shown that the collection of iodine by the thyroid is much greater than that of other organs.

All animals (except those on a cabbage diet) were maintained on a uniform rabbit chow diet, in a room kept free of any gross contamination with iodine. Thyrotropic hormone, cyanide and iodine other than the labelled iodine were injected subcutaneously or intramuscularly. Animals on a cabbage diet were fed exclusively on cabbage, no water being given.

Cyanide-injected animals were maintained on a normal diet, and were given daily injections of 0.1 cc. of methyl cyanide daily for from two to four weeks. Animals that were given 0.25 cc. daily exhibited a very high mortality rate without a great change in thyroid response.

Several different preparations of thyrotropic hormone have been used during the course of the experiments. These include suspensions of fresh beef anterior pituitary, of dessicated anterior pituitary powder supplied by Armour and Co., material prepared according to the technique of Lambie and Trikojus<sup>4</sup> (in both the soluble and insoluble forms), and a thyrotropic extract prepared and kindly furnished to us by Dr. Oliver Kamm of Parke Davis and Company. Of all these the last named was found to be the most active and satisfactory preparation. With this material 50 to 100 per cent increase of thyroid size in normal adult male rabbits may be obtained with two successive daily injections, corresponding to a nominal daily dose of 25 guinea pig units. In early experiments, Ayerst, McKenna and Harrison thyrotropic preparations were used, but were found to be inactive in male rabbits, in dosages up to 10 cc.

#### PRETREATMENT WITH IODINE

A series of experiments were undertaken to determine the effect upon the collection of a labelled dose of iodine of previous iodine treatment. In these experiments the labelled dose of iodine was always 5 mg., while the amount used in pretreatment was varied from 5 to 100 mg. The time elapsing between pretreatment and injection of the labelled dose of iodine was varied from several minutes to several days.

#### EXPERIMENTS WITH MORE THAN ONE RADIOACTIVE ISOTOPE

In some of these experiments it was possible to label the dose used for pretreatment as well as the succeeding dose, using a different radioactive isotope for each dose, and distinguishing between the two or more radioactivities found in the thyroid by following the decay curve of the total radioactivity in the gland, and analyzing it into its several components. In the analogy of labelling, this corresponds to the use of labels of different colors for the different doses.

## RESULTS

Most of our data are presented in graphic form, in Figures 1 to 10.

Using the long-period isotopes referred to above, we have obtained some data on the collection of single doses of iodine in hyperplastic thyroids in periods up to eight days. The results seem to show that the collection in Type 1 animals (see Figures 4 to 6 for explanation of different types) tends to increase until the total collection has reached the value of about 40 to 50 micrograms, and then does not increase further. The length of time this takes depends mainly upon the total quantity of iodine injected. From Figure 9 it can be seen that this may occur in as little as 15 minutes. The smallest quantities of long-period labelled iodine injected have been of the order of 1.0 to 1.5 mg. The thyroid collection of this quantity may go as high as six per cent within a day, in animals on a cabbage diet. This is to be compared with collections of as much as six per cent within 15 minutes with injections of ca 0.2 mg.

In an extension of the results given in Figure 10, six animals have been injected with two successive labelled doses of iodine and the collection from each dose measured. The results seem to show that if a moderately large collection occurs from the first dose, the collection of the second dose is inhibited. Thus an animal which in 19 hours collected 53 micrograms from a 4 mg. injection collected less than 4 micrograms from the subsequent 5 mg. injection. On the other hand, an animal which had collected only 20 micrograms from a 5.5 mg. injection in 31 hours, collected 7 micrograms from the subsequent 5 mg. injection. The collection time of the second injection was always 15 minutes. In one animal whose collection time was eight days, the collection was not much more than it would have been in 15 minutes.

In most of the experiments on pretreatment with iodine, the premedication was accomplished with ordinary iodine. Only a few of the results are expressed in Figure 10, since it appears that the effects of premedication depend upon a large number of other factors in animals with hyperplastic thyroids. The subsequent collection appears to depend upon not only the quantity of the premedicating dose, but also upon the thyroid index of the animals, their type of thyroid stimulation, and to some extent the time elapsing between the premedicating dose and the labelled dose. The problem is still under investigation, but at present sufficient data are available to enable us to say that in normal animals a dose of about 50 mg. is necessary to reduce the collection of the labelled dose to one-half the value expected of a normal untreated animal. In the case of Type 1 animals, only 8 mg. will do the same within four to six hours (Fig. 10).

A number of control experiments with radioactive bromine have been performed. The thyroid collection in both normal and hyperplastic animals is less than one-tenth of that from the same quantity of iodine, and the presence of the bromine could be demonstrated in the cerebrum within

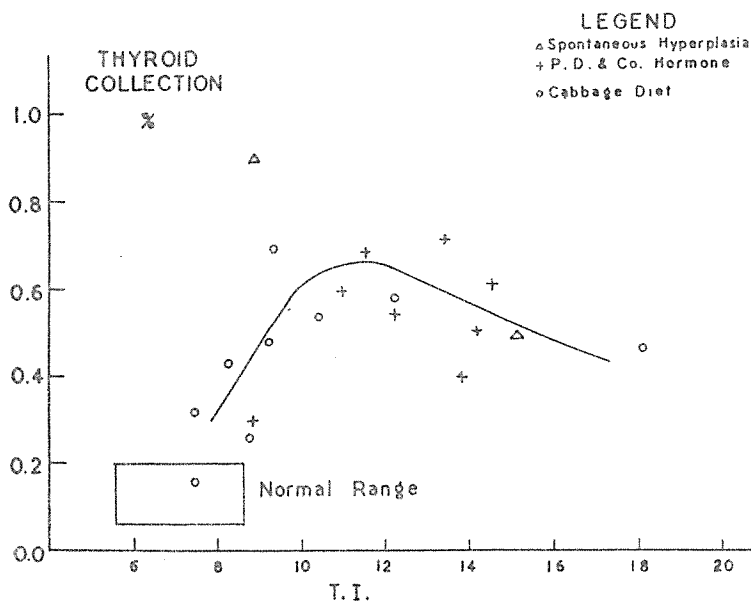
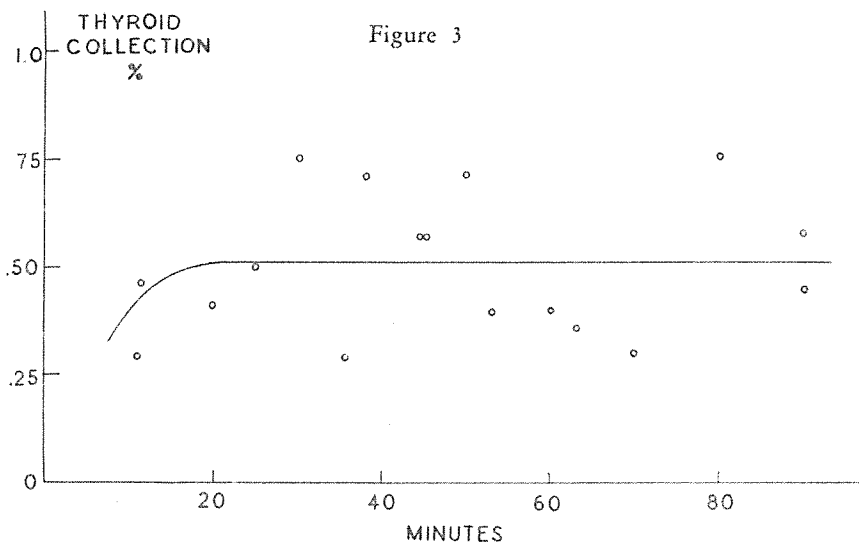


Fig. 3. Percentage collection of the thyroid of normal males of injections of between 0.1 and 0.4 mg. of iodine. No increase of collection over that of the first ten minutes is observed for intervals up to an hour and a half.

Fig. 4. Percentage collection of hyperplastic thyroid glands of male animals. Hyperplasia induced by cabbage diet, by injection with Parke Davis and Company thyrotropic hormone, and of spontaneous occurrence. Injection 5 mg. per standard 2 kg. animal. Collection time 15 minutes. The differently treated animals show experimentally indistinguishable responses, with a maximum collection at T.I. ca 11 or 12. These animals are referred to as Type 1.

15 minutes, in contradistinction to the behaviour of the iodine, which could not be detected there.

#### DISCUSSION OF RESULTS

From Figures 2 and 3 we see that the collection of iodine in both the normal and hyperplastic gland reaches a value within ten minutes which is not thereafter exceeded for at least one and one-half hours. This has been verified for all the values of injection for which experimental points are plotted in Figure 8. In a few cases, collection times of less than five minutes have been used; collection has been detected in animals that died within two minutes of injection. It appears, therefore, that the *initial collection* (i.e., the collection within one and one-half hours) *is taken up in a time determined mainly by the time required for the injected material to reach the thyroid*. In the few experiments performed with long period iodine, we have found that in general the increase of collection, if any, is comparatively slow following the initial collection.

The percentage of iodine collected from any given injection by the thyroid is definitely dependent upon the dosage, in all types of thyroids. Figure 8 shows this dependence. For normal thyroids, *the percentage collection increases as the dosage is decreased*. The total quantity of iodine so collected, however, is small even when the injected dose is 10 mg. or more. On the other hand, the efficiency of collecting a dose of 0.1 mg. is much higher (Fig. 8). In terms of the concentration coefficient, the T.C.C. at 0.1 mg. is about 80 for normal glands, while for an injection of 100 mg. it may be as low as two, or less. This relatively large percentage uptake from small injections seems qualitatively consistent with the ability of the normal gland to maintain itself upon the small quantities of iodine normally found in the diet.

From Figures 4, 5, and 6, it appears that under various conditions of stimulation the thyroid can respond in (at least) two different ways, with respect to the iodine collection of doses of 5 mg. In one type, which we have called Type 1, the T.C.C. is always higher than normal, and in the other, Type 2, the T.C.C. is significantly lower, and falls below normal for large values of the T.I. (In fact, for several of the animals—those in the dotted rectangle in Figure 5—the T.C.C. is below normal although the gland has increased only slightly in size. This will be discussed a little later on.) The two different types are defined by the character of their pretreatment, except in the case of animals with spontaneous hyperplasia, which were found to fall in both categories. There is for each type a maximum T.C.C. at a particular value of T.I. It is quite striking that glands of the same size, e.g. T.I. 13, do not exhibit the same iodine collection, although their gross appearances are similar, both appearing hyperplastic. The decrease of T.C.C. for thyroid indices larger than ten, can be interpreted in different ways. If we admit that the uptake of iodine under the conditions stated is a measure of the functional activity of the thyroid, then this decrease may be interpreted as due either to the existence of a

Figure 5

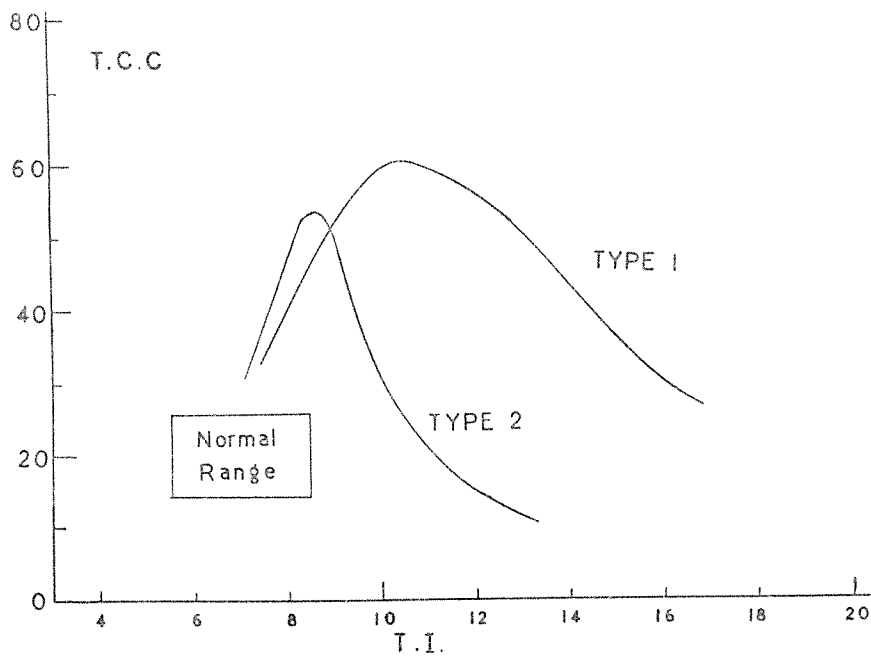
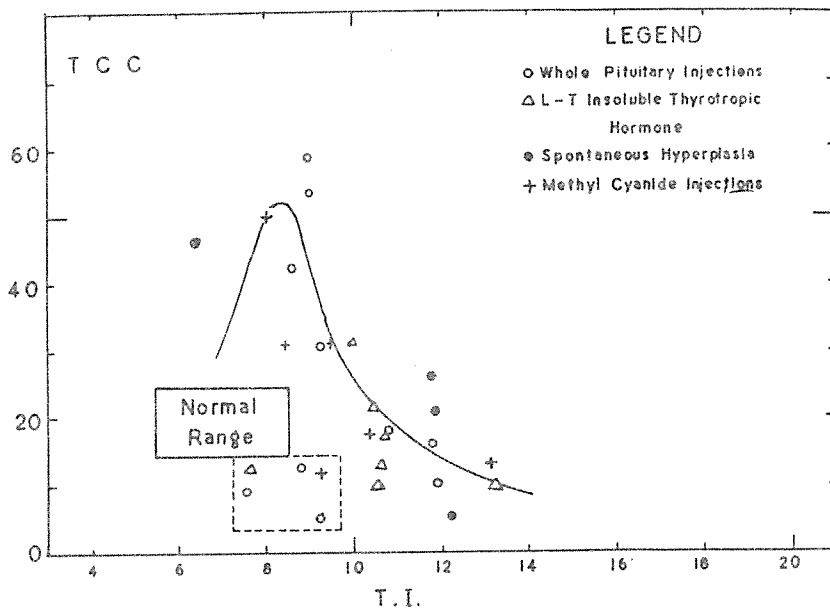


Figure 6  
(CAPTIONS FOR FIGURES 5 AND 6 ON OPPOSITE PAGE)

threshold, or to functional exhaustion of the gland (or both). If we assume it to be due to a threshold, then we must suppose that in general the higher the thyroid index in Type 2 animals, the higher the threshold for iodine uptake. In this case we should expect the shape of the curves for Type 2 animals to change, as the dosage of iodine is changed. Figure 7 shows the altered shape of the curves for very small injections. In this case, the Type 1 animals follow the same sort of curve as in Figures 4 and 6, and exhibit very high collections, reaching in certain cases as much as six per cent of the injection in 15 minutes. On the other hand, the Type 2 animals always collect less than the normal at this injection level. This curve casts some light upon the animals referred to above, represented by the points in the dotted rectangle in Figure 5.

These animals have thyroid indices only slightly greater than normal, but their collections are below normal even with a 5 mg. injection. A similar curve at an injection of 10 mg. does not show any such points. Therefore, we have drawn the curve in Figure 5 through the upper points, considering these animals to have a threshold for iodine collection which is greater than the average at their thyroid index. In some of the animals which received very small injections, the collection of iodine by the thyroid was so small that it was undetectable (less than 0.05 to 0.1 per cent of the injection) and only maximum values for the iodine collection could be given. The contrast between the Type 1 and Type 2 animals is even more striking at this value of injection than at the higher injection value.

Figures 8 and 9 again show the threshold effect, which can best be discussed with reference to the latter. In this graph we see that the total iodine collected by Type 2 glands of a given size (T.I. 10) is rather high and fairly constant for injections above 10 mg., but that it drops sharply between 1 and 10 mg., becoming consistently lower than the normal collection somewhere near 1 mg. On comparison with the behavior of the Type 1 animals it appears that this is quite definitely a threshold effect and perhaps even an "all-or-none" effect. The relatively gradual decrease in total iodine collection of the Type 1 animals shows that if similar considerations apply to these glands, they do not begin to do so in the dosage range investigated.

The functional exhaustion involved in the Type 2 animals is not a complete exhaustion, but a threshold effect, because at injections of 10

(CAPTIONS FOR FIGURES 5 AND 6 ON OPPOSITE PAGE)

Fig. 5. Thyroid collection coefficients of male animals treated as follows: saline suspensions of fresh beef anterior pituitary, insoluble thyrotropic hormone prepared according to the method of Lambie and Trikojus, methyl cyanide injected, and untreated animals with spontaneous hyperplasia. Injection 5 mg. per standard two kg. animal. Collection time, 15 minutes. For a discussion of the points in the dotted rectangle, which were not taken into account in drawing the curve, see the section entitled "Discussion." These animals are referred to as Type 2.

Fig. 6. Thyroid concentration coefficients for the data of Figures 4 and 5.

Figure 7

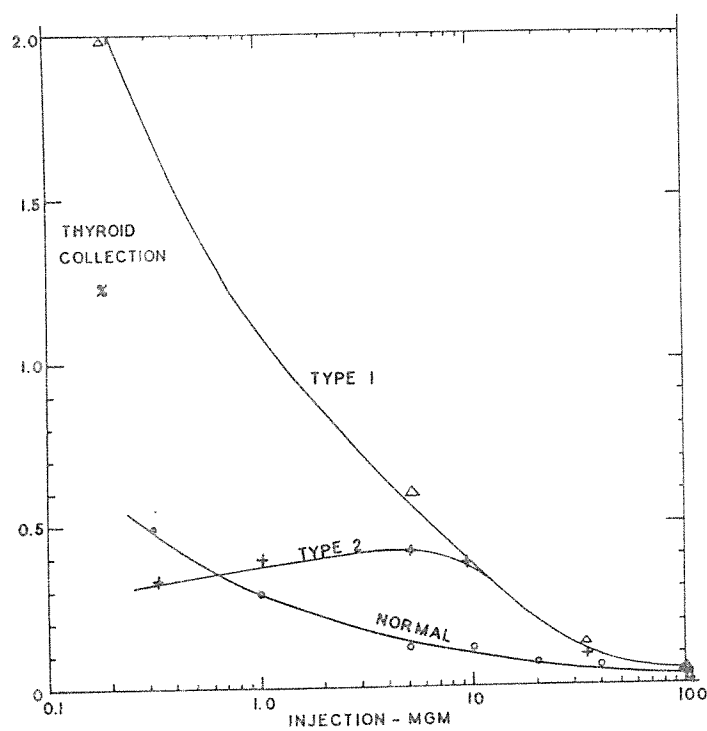
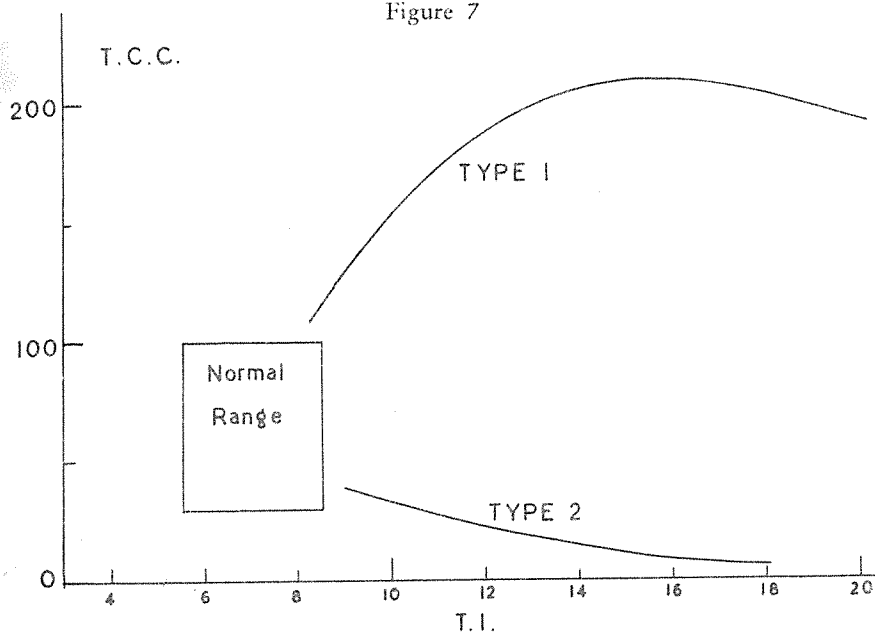


Figure 8

(CAPTIONS FOR FIGURES 7 AND 8 ON OPPOSITE PAGE)

mg. and higher values, the collection of these animals is above normal in all cases, and is indistinguishable from the behavior of the Type 1 animals.

It is interesting to note that for large doses, the collection of iodine in both types of glands attains a nearly constant value at about 40 to 50 micrograms. If the wet weight of a rabbit thyroid is about 200 mg., of which 60 per cent is water, this quantity of iodine represents a collection of 0.05 per cent of the dry weight, or a quantity of the same order of magnitude as the

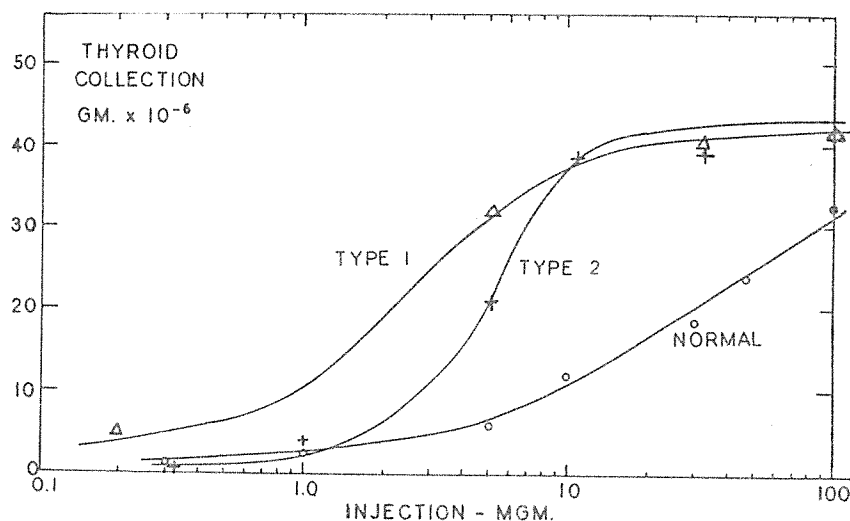


Fig. 9. Total iodine collection of the thyroid from different injections in 15 minutes. The data are the same as those plotted in Figure 8.

original iodine content of a hyperplastic gland. Thus the hyperplastic gland is capable of increasing its iodine content 100 per cent within a few minutes.

We do not wish to suggest that the two types of hyperplastic glands discussed here are strictly defined separate categories. On the other hand,

(CAPTIONS FOR FIGURES 7 AND 8 ON OPPOSITE PAGE)

Fig. 7. Same type of data as Figure 6 for injections of 0.2-0.5 mg. per standard 2 kg. animal. In Type 2 animals are now included some which received a dilute acetic acid suspension of Armour's desiccated pituitary tablets, and some receiving the soluble thyrotropic hormone prepared according to the method of Lambie and Trikojus.<sup>4</sup> The curve for Type 1 animals is only approximate in character, since the scattering of the values of the thyroid collection coefficient is great, the values ranging from 100 to 500. The number of animals used was 12 Type 1, 20 Type 2.

Fig. 8. Variation of the percentage iodine collection of the thyroid in 15 minutes with the quantity of iodine injected. The curves for hyperplastic animals are for average thyroid index 10. Total number of animals used: 39 Type 1, 68 Type 2, 69 normal.

the curves of Figure 9 seem to indicate that perhaps there can be continuous gradations of all types between the limits plotted in the graph, and even outside these limits. Evidence for this is given by the shape of the curves giving the variation of collection with thyroid index, which indicate that the threshold for iodine collection is somewhat displaced for values of the thyroid index other than ten. It has, of course, been previously known that various types of thyroid hyperplasia exist which are functionally different. The dissimilarity in behavior toward

iodine is another indication of this multiplicity. We are now studying the relation between the iodine collection of the thyroid and the basal metabolic rate.

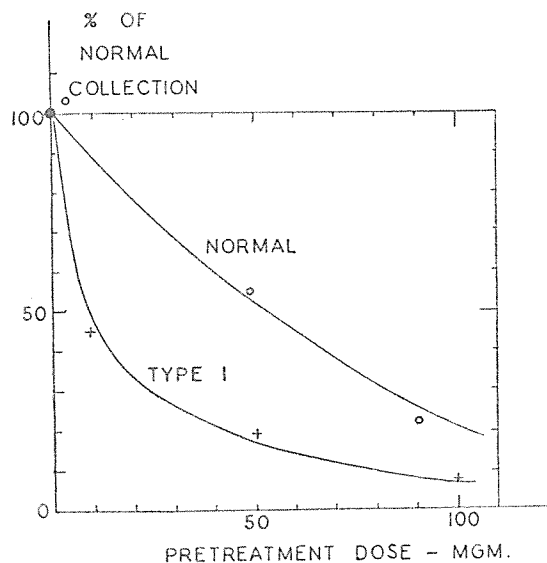


Fig. 10. The effect of iodine premedication upon the collection of a subsequent 5 mg. labelled iodine injection in 15 minutes. The collection is given in terms of the collection without previous treatment, which is set at 100 per cent. The time elapsing between the two doses is between one hour and five days, in normal animals. The curve for Type 1 animals is for thyroid index 10, and for an interval of time between the premedicating dose and the labelled dose of 4 to 6 hours. The number of animals used was nine normal, 12 Type 1.

this is probably accomplished by some mechanism which is accompanied by thyroid collection of iodine. Since in the rabbit the thyroid saturation point is reached so quickly, it seemed to us likely that a single dose of iodine administered to a patient with Graves' disease could be expected to produce a maximal drop in the B.M.R. This has actually been the case in the two patients on whom this treatment has thus far been tried.

The data we have obtained concerning the presence of a threshold in

The observation that it is possible to "saturate" the thyroid with just one injection (as evidenced by the greatly reduced collection of a second dose) has led us to the following considerations. It has been shown<sup>1</sup> that the decay curves of the B.M.R. of thyrotoxic patients following the administration of iodine are approximately the continuation of the decay curves of the B.M.R. following the cessation of thyroxine administration in myxedema. The action of iodine in Graves' disease is, therefore, probably that of stopping the excess delivery of thyroxine. It now appears that

certain kinds of hyperplasia, when taken together with the well-known low thyroid iodine and high blood iodine found in Graves' disease, point toward a relatively high threshold for iodine uptake by the thyroid in this illness. We have shown that in certain animals the thyroid is less able to utilize a small quantity of iodine than a normal gland, but has the capacity of taking up much more than a normal gland from a large dose. This seems to us to throw light on the mechanism of Graves' disease, in that it explains how a gland known to have a great affinity for iodine, as the thyroid does in this case, still does not cure itself by taking up the small quantities of iodine normally found in the diet, but can be definitely benefited by the administration of a relatively large quantity of iodine.

In this discussion we have so far assumed that the appearance of the labelled iodine in the thyroid after injection is actually due to addition of new iodine to the gland, and not to simple exchange of the iodine previously present with the labelled iodine. We have several reasons for supposing this to be the case, although even if it were not, the iodine exchange could be used as an indication of the thyroid function, or to introduce internal irradiation, just as well as iodine collection. Our reasons for believing that we are dealing with collection rather than exchange are the following: hyperplastic glands collect more iodine than normal glands at some injection values, less at others. The amount exchanged by a gland ought ultimately to be independent of dosage, and to depend mainly upon the iodine content of the gland. This does not appear to be the case. Furthermore, the collection of the second dose of iodine is almost always much less than the collection of the first dose. The amount exchanged ought to be independent of whether the dose is the first or any other in order.

In view of the fact that there is a difference in iodine collection at the same thyroid index, at low injection values, in animals treated with Parke Davis thyrotropic hormone and animals treated with other thyrotropic hormone preparations, including the saline suspension of fresh beef anterior pituitary, it appears that there may be separate factors producing growth and functional stimulation with respect to iodine collection, respectively. This is in accord with the clinical observation that the size of the thyroid, taken by itself, is not indicative of the functional state.

The difference between the behavior of cabbage diet animals and animals injected with methyl cyanide is worth noting, in view of the supposed cyanide nature of the goitrogenic substance in cabbage.<sup>6</sup>

#### RADIATION THERAPY WITH RADIOACTIVE IODINE

From the data on iodine collection that we have obtained, and the known energy of the radiations from the various radioactive isotopes of iodine, it is possible to calculate how strong the radioactivity of an administered dose of radioactive iodine must be in order to give the desired amount of radiation within the thyroid. Since the thyroid concentration coefficient may be as much as several hundred, it is easy to see that the

ratio of thyroid dosage to the dosage of other tissues may be made just as high, thus giving a very large safety factor for such irradiations.

If we assume that it is desired to administer such an amount of radioactive iodine as to yield a dose of 100 r. within the thyroid, then the amount of initial activity required in the thyroid is calculated in the following way: One roentgen unit is defined as the quantity of radiation which will produce a free charge of ions of one sign of 1. e.s.u. per cubic centimeter of air at 0°C. and 760 mm. Since the energy necessary to produce one ion pair in air is about 32 electron volts, the energy dissipated by one roentgen per cm.<sup>3</sup> of air is:

$$1 \text{ r.} = \frac{32 \text{ e.v.} \times 1 \text{ e.s.u.}}{300 \text{ volts/e.s.u.}} = 0.107 \text{ ergs/cm.}^3 \text{ of air}$$

and since one MEV (million electron volts) is equal to  $1.6 \times 10^{-6}$  ergs,

$$1 \text{ r.} = 6.7 \times 10^4 \text{ MEV/cm.}^3 \text{ of air}$$

If we take instead one gram of air (800 cm.<sup>3</sup>), then we find:

$$1 \text{ r.} = 800 \times 6.7 \times 10^4 \text{ MEV} = 5.5 \times 10^7 \text{ MEV/gm. of air}$$

In tissue the energy required to produce an ion pair may be taken to be the same as in air,<sup>7</sup> and thus the above expression is valid for tissues as well as for air and we can drop the notation as to the medium in which the ionization is produced.

The unit of intensity of radioactivity is the curie, defined as that activity from which the same number of particles are emitted per unit time as from a gram of radium, i.e. about  $3.5 \times 10^{10}$  per second. The millicurie (mC) is one-thousandth of a curie; thus a millicurie of radioactive iodine will emit  $3.5 \times 10^7$  beta rays per second. We shall neglect the effect of the gamma rays produced by the radioactive iodine, since a large proportion of them will escape from the irradiated tissue. Furthermore, the 25 minute isotope emits gamma rays of low intensity as compared with the beta rays.

Now the beta rays from a radioactive substance do not all have the same energy; therefore, for purposes of this calculation, we must use the mean energy of the beta-ray spectrum. For the iodine isotopes which are of greatest interest, these are as follows:

$$25 \text{ minute I} : 0.7 \text{ MEV}^8$$

$$8 \text{ day I} : 0.3 \text{ MEV}^3$$

Thus the radiations from one millicurie of each of these isotopes, dissipated in one gram of tissue, are equivalent to the following dosages:

$$25 \text{ min. I} : 0.7 \text{ MEV/beta ray} \times 3.5 \times 10^7 \text{ beta rays/sec.} = 2.5 \times 10^7 \text{ MEV per sec.}$$

$$8 \text{ day I} : 0.3 \text{ MEV/beta ray} \times 3.5 \times 10^7 \text{ beta rays/sec.} = 1.0 \times 10^7 \text{ MEV per sec.}$$

Now we have supposed that one r. is equal to  $5.5 \times 10^7$  MEV/gm. of tissue. Thus activities of:

$$25 \text{ min. I} : \frac{5.5 \times 10^7 \text{ MEV/r.}}{2.5 \times 10^7 \text{ MEV/mC sec.}} = 2.2 \text{ mC will give 1 r. per sec. per gm.}$$

$$8 \text{ day I} : \frac{5.5 \times 10^7 \text{ MEV/r.}}{1.0 \times 10^7 \text{ MEV/mC sec.}} = 5.5 \text{ mC will give 1 r. per sec. per gm.}$$

or:

$$3.6 \text{ mC of 25 min. I} = 100 \text{ r. per minute}$$

$$9.2 \text{ mC of 8 day I} = 100 \text{ r. per minute}$$

Now the *mean* lives of these two isotopes are 36 minutes, 11.5 days (16,500 minutes), respectively. Thus the initial activities necessary to obtain a total irradiation equivalent to 100 r., as the activity decays to zero, are:

$$25 \text{ min. I} : 3.6 \text{ mC} / 36 \text{ min.} = 0.1 \text{ mC per gram}$$

$$8 \text{ day I} : 9.2 \text{ mC} / 16,500 \text{ min.} = 5.6 \times 10^{-4} \text{ mC per gram}$$

These activities are very different from each other, and we must now consider the Bunsen-Roscoe reciprocity law. It is a question still under debate as to whether a weak source supplying radiation for a long time will have the same effect as a strong source supplying the same total radiation. The initial rates of irradiation for the above activities are respectively:

$$25 \text{ min. I} : 2.7 \text{ r. per minute}$$

$$8 \text{ day I} : 0.4 \text{ r. per hour}$$

Normal tissues tolerate safely a dosage of 0.1 r. per day for indefinite periods; it is, therefore, questionable whether the eight-day iodine of the strength calculated above is supplying its radiation fast enough to have the desired effects. This is something to be decided by experiment. On the other hand, the short period iodine will approximate quite well the short intense dosage obtained in x-ray therapy.

Considering only the 25 minute period, then, the necessary activity per gm. of tissue is 0.1 mC., for an initial intensity of ca 3 r. per minute. If we assume a thyroid to collect one per cent of the administered iodine, as the results of these experiments permit us to suppose likely, the injected dosage must then be 10 mC. per gm. of tissue. For the rabbit, with a thyroid of ca 0.2 gm., we must correct the value thus obtained for the "leakage" of radiation outside the thyroid tissue, since some beta rays can escape from the thyroid because of its relatively small size, and will dissipate part of their energy in the surrounding tissue. This will certainly be taken care of by adding 50 per cent to the required dosage. Thus, for the rabbit, we may calculate that the required dosage to provide 100 r. of radiation in the thyroid is about 3 mC. of the 25 minute isotope of iodine.

If we assume that similar collections may be obtained in human thyroids, then a 75 gm. thyroid will require an administered dosage of ca 750 mC.

*Acknowledgements:* The experiments with the long-period isotopes of iodine were made possible through the generosity of Professor E. O. Lawrence and Dr. Joseph Hamilton of the University of California, and Dean L. A. DuBridge of the University of Rochester, who supplied these isotopes from their cyclotron laboratories.

We are indebted to Dr. Gregory Pincus and Dr. Mark Graubard of Clark University for their kind assistance in maintaining animals on a cabbage diet, and for administering cyanide injections. We are particularly grateful to Dr. Oliver Kamm, of Parke Davis and Company, who supplied us with an active thyrotropic hormone preparation.

#### REFERENCES

1. Hertz, S.; Roberts, A.; Evans, R.D.: *Proc. Soc. Exp. Biol. Med.*, 38:510, 1938.
2. Roberts, A., and Irvine, J. W.: *Phys. Rev.*, 53:609, 1938.
3. For a list of available radioactive isotopes of iodine and their properties, see Livingood, J., and Seaborg, G.: *Phys. Rev.*, 54:775, 1938.
4. Lambie, C. G., and Trikojus, V. M.: *Biochem. J.*, 31:843, 1937.
5. Means, J. H., and Lerman, J.: *Ann. Int. Med.*, 12:811, 1938.
6. Marine, D.; Spence, A. W.; Cypra, A.: *Proc. Soc. Exp. Biol. Med.*, 29:772, 822, 967, 1932.
7. Failla, G.: in Duggar, *Biol. Effects of Rad.*, V.I, 121, Mc-Graw Hill, 1936.
8. Alikhanov, A. I.; Alikhanian, A. I.; Dzelepov, B. S.: *Nature*, 135:593, 1935.