RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

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In previously published experiments of this series [1] radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for discussion and determination of their suitability for this type of treatment. In each instance a dose of radioactive iodine, which had been made by the cyclotron at the Massachusetts Institute of Technology or by the Harvard University cyclotron, and separated chemically as sodium iodide, was then orally administered.

The samples of radioactive iodine used were obtained by deuteron bombardment of tellurium and at the time of administration consisted of a mixture of different radioactive isotopes of iodine. Over 90 per cent of the activity at this time consisted of the 12.6 hour isotope I^{130} and most of the remainder of the 8 day isotope I^{131}. The total activity administered varied between 0.7 and 28 millicuries. In 19 cases the total dose was administered to the individual patients as one dose; in 10 cases divided dosages were employed.

From the data already obtained from tracer studies it was considered desirable to keep the total amount of iodide administered below 2 mg. of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first seventy-two hours after the administration of radio-iodine. An indirect estimate of the thyroid retention of radioactive iodine was thereby obtained, since an approximate balance exists between administered iodine on the one hand and the sum of thyroid iodine retention and urinary excretion on the other.

Urinary studies were carried out on aliquot portions of carefully collected twenty-four hour specimens, which were kept iced and corked during the collection periods.

It was early found [2] that significant amounts of the original dose were to be found only in the first three days' specimens. Fecal excretion was tested and was found to be so low as to be negligible for the purpose of these experiments.

In a few cases external gamma ray counter measurements were made of the activity of the thyroid of patients following the administration of radioactive iodine. Such measurements are difficult, for obvious reasons, to evaluate quantitatively. However, day to day measurements of this type can give good data on the variation of thyroid iodine content. They were performed in order to follow the loss of iodine from the thyroid following the initial uptake and to evaluate the effect of routine iodinization following the administration of radioactive iodine.

External counter measurements were roughly calibrated against actual direct measurements on the thyroid glands at operation and after chemical separation [2] in 2 patients, previously scheduled for surgery, who received therapeutic amounts of radioactive iodine.

Following the administration of radioactive iodine, routine iodine (nonradioactive) in the usual dosage of saturated solution of potassium iodide 5 minims (0.3 cc.) twice a day was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate of the patients treated was tested frequently both before and after the radioactive iodine administration. Basal metabolic levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the basal metabolic rate, weights, pulse rates and physical findings were recorded and the total clinical picture was used to evaluate the effects of treatment. No adverse effects, such as fever, nausea or irradiation sickness, were noted in this series of patients. No complaints were recorded regarding the taste of the medicament (since it is tasteless), nor were any local effects, either in the oral cavity or over the thyroid, encountered at the dosage levels used. No increase in the degree of thyrotoxicosis following the radioactive iodine treatment, per se, was recorded, although several test patients were kept uniodinized for three to four weeks prior to routine iodinization.

In most cases, after a period of two to four months following the radio-iodine administration, routine iodine therapy was stopped when an essentially normal basal metabolic rate had been maintained on iodine for a few weeks or months. Such basal metabolic rate response was taken to be indicative of good control of

A report to March 15, 1946.
From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital and the Radioactivity Center, Massachusetts Institute of Technology. This material was presented in part to the American Society for Clinical Investigation in May 1942 (see abstract of proceedings, Physiol. Rev. **62:** 4, 1942). The work was aided by a grant from the John and Mary R. Markle Fund in the names of Professors J. H. Means and Robley D. Evans and was accomplished by close cooperation of the Radioactivity Center of the Massachusetts Institute of Technology, Cambridge, Mass., and the members of the medical staff of the Massachusetts General Hospital, Boston.
This work was performed at the Massachusetts General Hospital and the Massachusetts Institute of Technology under a grant from the John and Mary R. Markle Fund. Cooperation and assistance in this work were given by Professor J. H. Means, Professor J. W. Irvine, Dr. Wendell C. Peacock, Professor M. Stanley Livingston, Professor Robley D. Evans, Drs. R. W. Rawson and Jacob Lerman, the technical assistants Mrs. Phyllis Brown Shattuck, Miss Ann Gaurdo and Miss Mary Lennon as well as the nursing, surgical and medical staffs of the Massachusetts General Hospital. The speech of President Karl T. Compton of the Massachusetts Institute of Technology before a Harvard Medical School colloquium in the fall of 1936 served to inspire the senior author in the initiation of this investigative program.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38:** 510 (May) 1938. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Am. J. Physiol. **128:** 565 (Feb.) 1940; Tr. Am. A. Study Goiter, 1939, p. 260. Hertz, S.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Observations on Rabbits and on Goiter Patients, Am. J. Roentgenol. **46:** 467 (Oct.) 1941. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21:** 624 (Sept.) 1942. Hertz, Roberts and Salter.[2] Hertz and Roberts.[6]

2. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21:** 25 (Jan.) 1942.

the thyrotoxicosis at that time. Failure of the basal metabolic rate to rise on the cessation of iodine treatment was then interpreted as positive evidence of remission of the disease. A rise of the basal metabolic rate on cessation of iodine therapy was considered evidence of failure of the regimen of internal irradiation. A lowered basal metabolic level, with weight gain, symptomatic relief and lowered pulse, were considered indicative of a decrease of the severity of the disease.

As with other forms of treatment for hyperthyroidism, a prolonged follow-up of six months to one year (or more ideally two to five years) following, clinical evidence of remission was required before classification of cases as "cures."

CALCULATION OF RADIATION DOSAGE

In order to obtain a basis of comparison among patients and between radioactive iodine on the one hand and x-ray therapy on the other, the probable values of radiation dosage delivered in the thyroid were calculated. Such calculations are based on the following data:

1. Fractional uptake of radioactive iodine by the thyroid.
2. The known energy of the radiations from I^{130} and I^{131}.
3. The clinical estimation of the weight of the thyroid of the patient.
4. The known pattern of uptake and retention of radioactive iodine [3] by the hyperplastic thyroid gland of hyperthyroidism.[2]

By using the known values of ionization produced by 1 millicurie of radiation and the properties of I^{130} and I^{131} the following formulas can be derived for the total radiation delivered in decaying to zero:

$$\text{Radiation (in roentgen units)} = \frac{10{,}000 \text{ (dose of } I^{130} \text{ in mc) (fractional uptake in thyroid)}}{\text{weight of thyroid in grams}}$$

For I^{131} the constant 10,000 is replaced by 117,000. Thus for I^{130} a net collection of 3 millicuries in a 30 Gm. thyroid will give a total of 1,000 roentgens in decaying to zero.[4]

The effectiveness of radiation therapy is known to depend on the rate of delivery, especially at low rates. In the case of I^{130} the initial rate of delivery of a 1,000 roentgen dose is 55 roentgens per hour. For I^{131} it is only 3.6 roentgens per hour. Thus, while in these experiments the total radiations delivered by the two isotopes are comparable, the rate is so much slower for the long-period isotope that its effectiveness is at least open to question. Furthermore, an appreciable fraction of the activity leaves the thyroid during the decay of the long period iodine.[2] We shall assume throughout that it is the I^{130} radiation which is most effective.

Calculations of the type described are subject to large errors. These arise mainly in the estimate of the thyroid weight, in the determination of thyroid iodine uptake and in the assumption of a uniform picture of iodine retention.[2] Errors of 50 per cent or more in the estimate of the thyroid radiation are therefore to be expected.

3. This pattern was determined by the use of tracer quantities of radioactive iodine. It is not strictly correct to assume, as we have, that the pattern will be the same when quantities of activity sufficient to have a biologic irradiation effect on the thyroid are present. However, in the absence of other data we have assumed that the pattern is the same. If this is in error it will introduce another error into the calculation, already admittedly approximate, of the dosage delivered to the thyroid.

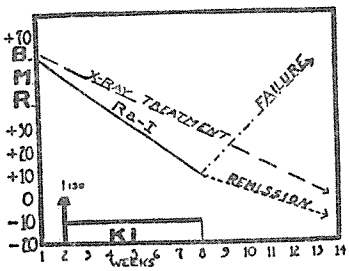
4. The millicurie values of activities cited in this paper are absolute values based on the number of disintegrations occurring in the radioactive substance, determined by methods like those described by Deutsch, M.; Downing, J. R.; Elliott, L. G.; Irvine, J. W., Jr., and Roberts, A.: Physiol. Rev. **62**: [illegible]942.

RESULTS

The accompanying graph is a schematic representation of the expected course of the basal metabolic rate in successfully and unsuccessfully treated cases. The upper broken line represents the course of the basal metabolic rate of a patient treated successfully by means of orthodox external x-ray therapy. The latter is given as a basis for comparison of the time interval required for obtaining a remission by the internal and external forms of thyroid irradiation in typical cases of hyperthyroidism.

The results obtained with 29 patients are summarized in tables 1 and 2. Table 1 affords an analysis of 9 cases in which cure was not obtained by the radiational effect of radio-iodine. Table 2 gives an analysis for 20 cases considered to be cures. These cases are so classified after follow-ups and examinations extending to March 1946.

The excretion studies and the external gamma ray counter measurements showed early in these experiments that there is no peak in the excretion of iodine in any of 14 cases tested, nor is there any sudden drop in the radioactive iodine content of the thyroid when a patient who has been given radioactive iodine is started on routine iodinization. On the contrary, these experiments showed that iodinization either has no effect on the normal slow loss of iodine from the thyroid or tends to "freeze" the radioactive iodine collected by the gland, i. e. to foster its longer retention therein. As much as 25 per cent of the initially collected radioactive iodine may remain in the thyroid twenty-five days after an initial collection and subsequent iodinization.[2] It is clear that such prolonged retention is advantageous from the standpoint of efficient use of the radioactive isotopes administered. Urinary studies in a typical case gave the results recorded in table 3.



Course of the basal metabolic rate in successfully and unsuccessfully treated cases of hyperthyroidism: solid line, treatment by radioactive iodine; upper broken line, treatment by external x-irradiation. The arrow indicates the point at which I^{130} was administered to the patients treated with radioactive iodine. The lower rectangle indicates the administration of ordinary iodides. A rise in the basal metabolic rate on omission of iodide therapy is significant of continued thyrotoxicity and failure of the therapeutic program; the absence of any such rise in any case is interpreted as evidence of remission of the disease as a result of the type of treatment received by the patient.

The reasons for adopting the procedure of full iodinization following the radioactive iodine dose were, in the main concern, that if the radioactive iodine was not effective the patients might be injured by uncontrolled thyrotoxicosis. In addition, no adequate control was possible of the iodine intake of patients (from extraneous sources) while ambulatory and awaiting the radiotherapeutic effect.

In spite of the fact that the interpretation with regard to cure might be rendered slightly less unequivocal with the use of this procedure, one can depend on the familiar fact that routine iodinization, per se, has been known for years to be a rather unsatisfactory sole treatment for the great majority of unselected thyrotoxic patients.[5]

5. Thompson, W. O.: Toxic Goitre: The Present Status of Treatment, Canad. M. A. J. **42**: 224 (March) 1940.