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ASSURANCES AS TO THE ADVANTAGES AND SAFETY OF RADIOACTIVE IODINE TREATMENT OF HYPERTHYROIDISM*

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INTRODUCTION

Although the use of radioactive iodine in the therapy of patients with Graves' disease and in the study of thyroid physiology now over eight years old the method of treatment has only recently been as widely applied as the results would dictate. The limitation of this form of treatment was largely due to the small availability of isotopes for this purpose until a wide expansion of the field was made possible by supplies from such agencies as the Atomic Energy Commission's installation at Oak Ridge, Tennessee. It is fair to say that no longer need availability or expense deter the extended use of radioactive iodine for specified purposes. Safety in handling the isotopes and expense are largely solved.

Another deterrent to the wider use of the isotope therapy has been the undercurrent rumors that radioactive iodine "might cause renal damage" ("radiation nephrosis"), be "damaging to the genetics of the race," "cause sterility," or, indeed, "be carcinogenic over a long period."

Presented at the Seventieth Annual Meeting of Louisiana State Medical Society, at Baton Rouge, La., April 25, 1950.

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In view of the wide demand for and growing use of radioactive iodine in many clinics in this and other countries, it is important to set down the known facts on this subject rather than to rely on rumor or armchair suspicions in determining these cogent considerations in the care of patients who are ill with hyperthyroidism. This is particularly salient, inasmuch as the treatment by means of radioactive iodine is economical of the patient's time and money, and of hospital beds as compared with surgical management; and it is conservative of long periods of invalidism and protracted medical observation required by antithyroid drug therapy. Since I^{131} therapy is virtually 100 per cent efficacious under properly standardized conditions, the deterrents to I^{131} must need be removed as rapidly as is warranted by sound clinical judgment on the basis of accurate information.

Further, since an estimate of over 4,000 patients have already been treated by many observers, E. F. D. 5, 6, the fears of some of these patients which have been "doctor-induced" must be allayed as soon as possible. Individuals who have been cured of their hyperthyroidism by I^{131} , and who are otherwise happy to have received the therapy, have developed deep-rooted anxieties concerning the "bogey" of damage of "one sort or another" which well meaning, (usually surgically minded) members of the profession have raised. The harm done in such an inadvertent manner has been obviously uncalled for and certainly inhumane when it results from lightly considered and ill advised rumor in place of logically con-

ved opinion and adequately collected data.

Therefore, let us examine the rumors, and what may be their basis, as well. Let us state the pertinent data upon which unused advice may be rendered to the hyperthyroid patient who is a candidate for treatment.

There was a period within my own memory in the history of the therapy of this disease during which the choice of method was made upon the basis of mortality statistics. Opinions have changed to such a degree, as a result of research during the past twenty-five years in this field, that we now think of these matters not in terms of "what are our patients' chances of survival under therapy" but rather in terms of "what are their chances of becoming free of persistence, complication, recurrence or other ill effects of the type of therapy employed." Mortality from hyperthyroidism per se has been erased to the vanishing point except in neglected cases. The death of a thyrotoxic patient is now as inexcusable as is death from diabetes when there is no complicating disease. To state that radioactive iodine therapy may avert all surgery on the thyrotoxic subject is not yet justified, but it is important to realize that many operations now being done on the thyroid are needless" in the sense that our knowledge of the disease is sufficient to enable us to avoid any of them!

THEORETICAL CONSIDERATIONS

It is important to understand the theoretical background of the individual forms of therapy for Graves' disease in order to evaluate their relative safety and efficacy for the patient. In general terms, all the methods being used have as their goals the ultimate decrease in the overproduction of thyroid hormone and the avoidance of harmful effects which might be incident to the particular approach used to achieve this primary purpose. Surgery attempts to reduce the total mass of hypersecretory tissue present in these patients by mechanical removal of as much tissue as the skill of the surgeon will allow without damage to the recurrent laryngeal nerves, the parathyroid

glandules, and the cardiac and adrenal mechanisms. Technical achievements and proper preparation of the patient by antithyroidal drugs, iodine, general nutritive measures, and cardiac therapy have contributed greatly to the safety of the surgical approach in large centers and in most small hospitals.

However, despite these advances the mortality following subtotal thyroidectomy still varies from 0.5 per cent to 10 per cent, or higher, in individual hospitals in the U. S. A. and Europe. (published and unpublished data.) A survey of these statistics reveals that the deaths have not been limited to the severely ill and aged patients as might have been expected; but deaths have included many mildly toxic cases and individuals of youthful age. By and large, the incidence of thyroid storm as a cause of death has been effectively eliminated by proper preoperative preparation of patients. The deaths have been due in the main to surgical and anesthetic accidents such as bilateral adductor paralysis of the vocal cords, postoperative hemorrhage, tracheal collapse, pulmonary and cardiac infarctions; traumatic shock of irreversible type, sepsis with mediastinitis, parathyroid tetany, air embolism to the brain, and ether convulsions.

Antithyroid medication is presumed to act by interference with the mechanism of fixation of inorganic iodide following conversion in the thyroid to iodine. This results in decrease of thyroglobulin production by imposing a barrier to the enzymatic conversion of iodine into protein-bound iodide. It is evident that this offers the surgeon an excellent aid in the preoperative control of the thyrotoxic element of the disease but it is equally important that the frustrated hyperplasia resultant from exhibition of antithyroid drugs leads to enlarged and markedly vascular glands for the surgeon's mechanical approach. The addition of iodide to the antithyroidally prepared gland has obviated this disadvantage to the surgeon by promotion of the involution of such frustrated hyperplasias. The consequent reduction of vascularity has

restored the surgically controlled presence of a well

The proponents of thyrotoxicosis administration have reported a high per cent of cases after periods of treatment of several months. But closed us personally reported a per cent of such a high percentage of remissions has decreased to the point of being clinically judged to be on a permanent basis.

Hence we place our reliance on prolonged antithyroid medication and reduction of "cure" in patients below 35 to 40 years of age. These results are the greatest of persistence in a patient, the doctor's considerable drain on the patient's resources, it becomes obvious that drugs thus far developed have done much to our understanding, and preparation of patients with thyrotoxicosis. Surgical treatment of patients is not a radical approach. It is felt that they aid in control of the disease until natural involution periods of one to two years similar to that in patients without surgery in the past. Their discovery has broadened our knowledge of the disease, but it is evident that it has not established a final common pathway of the disease has been eliminated.

We still need to establish a method of hyperactive thyroid gland control through which the disease are directed to remission of thyrotoxicosis. The very adequate antithyroidal drugs afford a possible the prolonged

restored the surgical advantage of a beautifully controlled thyrotoxic element in the presence of a well involuted gland.

The proponents of the long term therapy of thyrotoxicosis by antithyroid drug administration have found between 60 to 80 per cent of cases in permanent remission after periods of therapy lasting eight to ten months. But close follow-up thereafter has led us personally to the conclusion that the per cent of such antithyroidally induced remissions has decreased with the passage of time to the point where 40 per cent are clinically judged to have taken place on a permanent basis.

Hence we place the efficacy rate of prolonged antithyroidal therapy based on induction of "cure of the disease" somewhat below 35 to 40 per cent. Considering that these results are obtained only with the greatest of persistence on the part of the patient, the doctor, his employers, and with considerable drain upon financial resources, it becomes obvious that while antithyroidal drugs thus far developed have contributed much to our understanding, clinical management, and preoperative preparation of patients with thyrotoxicosis, an ideal non-surgical treatment for the great majority of patients is not attained by the antithyroidal approach. It is our personal opinion that they aid in control of the havoc of the disease until natural remission occurs (in periods of one to two years), in a manner similar to that in which did iodide therapy without surgery in a limited fashion prior to their discovery. This approach has broadened our knowledge of the mechanism of the disease, but as in the former methods it has not enabled us to eliminate the final common pathway—the inherent cause of the disease has not been discovered or eliminated.

We still need to attack the end result, the hyperactive thyroid gland, which is the end organ through which the various results of the disease are developed. The tendency to remission of thyrotoxicosis is favored by the very adequate control which antithyroidal drugs afford us. They make possible the prolonged psychiatric and nutri-

tional approaches which usually must accompany them for best results. Prolonged therapy is, on the contrary, not possible in patients presenting themselves in a neglected state, with severe and debilitating complications of heart disease, diabetes, and like conditions. Antithyroidal drugs have a definite, though quite low incidence of drug sensitivity and toxicity; or bone marrow, hepatic and adrenal depressant effects which obviate their prolonged use. It is true that rarely does one encounter a case in which the acute antithyroidal effects are not obtainable as was the case with iodide suppression of thyrotoxicosis. Often increases in dosage are needed and prolonged or delayed responses have been seen to occur when, at first, the antithyroidal approach seemed lacking in effect. However, we have, as have others, seen patients whose disease became very prominent after initially good control of same. Suggested increases in dosage at such times have resulted in further amelioration. In our experience subtotal "escape" from the action of antithyroidal drugs has been evident in increasing numbers of patients who have by consequence thereof been referred to us for I^{131} therapy after prolonged disability.

EXPERIENCE WITH EXTERNALLY ADMINISTERED X-RAY THERAPY FOR TOXIC GOITER

In a few quarters treatment by means of external x-irradiation has continued to be practiced. Particularly interesting in this regard were the results of a recently conducted survey reported by Edith H. Quimby and Sydney C. Werner of Columbia University, which was published in the Correspondence Columns of the *J. A. M. A.*, (July 23, 1949; 1046-47). Responses to a detailed questionnaire from 70 radiologists and 31 internists especially interested in treatment of thyroid disease led them to conclude that "if the complication (of cancer) exists following irradiation it is very rare." In discussing the possible late effects of x-irradiation they found only 3 cases in which the history could be interpreted on any valid basis to have suggested that radiation was implicated in the production of cancer in toxic goiter x-ray therapy. Since their survey is estimated to

have encompassed the experience in several thousands of cases over a period of thirty or more years, it would appear that the incidence of cancer in x-ray treated cases was not appreciably higher than is the spontaneous incidence of cancer in toxic goiter glands reported by Pemberton from the Mayo Clinic in cases which had received no radiation.

There is no reason to assume that the tissue ionization produced by a stated number of roentgen equivalents is different,—be they delivered by means of an x-ray tube or by the administration of a beta emitting short, half-lived isotope such as I^{131} . The data accumulated in Quimby and Werner's report with regard to the incidence of malignancy in heavily treated cases by x-ray would argue in favor of a special sensitivity of the skin to x-ray carcinogenesis as opposed to a rather remarkable insensitivity of the hyperplastic and normal thyroid glands of the human being.

EIGHT YEARS EXPERIENCE WITH RADIOACTIVE IODINE THERAPY

Since 1941 we have observed the salutary effects of radioactive iodine on patients with toxic goiter, but in no instance to date has there been seen the development of any evidence of malignancy of the thyroid. Even in instances in which overdosage has led to the development of myxedema the development of cancer has not occurred. It is reassuring that the x-ray treated cases over a much longer period of time have also been free of this complication.

It might be reasoned by some that by adopting the medical approach,—either prolonged treatment by means of antithyroidal drugs or radioactive iodine, we lay our patients open to the possibility of failure to recognize an early coincidental cancer of the thyroid in a hyperplastic gland. We have borne this clearly in mind and have recommended the removal of any persistent goiter following the successful relief of thyrotoxicosis by either of the two methods.

It might be argued that the radioactive iodine would be effective prophylaxis and preparation for radical care by surgery in such cases of persistent goiter following successful I^{131} therapy and that this extra

precautionary step might lead to the earlier detection and more adequate cure of coincidental cancer of the thyroid in these cases.

On the other hand, we have seen the persistence of goiter so frequently after the detoxified state has been reached in the antithyroidal management of thyrotoxic patients that we would predict that over 50 per cent would come to operation even though complete remission be induced in them because of such persistent thyroid masses. The obvious disappointment of such patients on hearing that operation is needed for safety, after one to two years, or longer, of treatment by antithyroidal drugs made them subjectively well, remains a disadvantage of such a program.

THE THERAPEUTIC APPLICATIONS OF RADIOACTIVE IODINE IN THE TREATMENT OF THYROID DISEASES

In July 1948, a conference was held at the Brookhaven National Laboratory, Upton, New York. The proceedings at that conference on the subject of radio iodine have been published as U. S. Report B.N.L.-C-5. This published material summarizes much of the physiologic and laboratory aspects to that date. The concentration of radioactive iodine by goiters, and the mechanisms of antithyroidal medications, as well as the methods for standardization of radioactive iodine administration and therapeutic dosage were covered. Uptake and excretion studies were reported both in benign and malignant conditions of the thyroid and in other endocrinopathies. The reader is referred to this publication as authoritative on these various subjects.

The author had the privilege of acting as chairman of the session devoted to the study and treatment of cases of hyperthyroidism by means of radioactive iodine. The reader is referred to these discussions which are of historical interest,⁴ as well as of academic value in relation to this form of treatment.

Succinctly summarized, the session indicated beyond any question of a doubt that *properly assayed dosage and selection of patients with toxic goiter for treatment led to entirely satisfactory cures in the great majority of patients treated by means of*

radioactive iodine. The medical approach were repeated and to the excess (Chapman) between the two for the treatment. Methods of administered medication to the thyroid gland come more specific cases is becoming

It was the coming the problem of radio iodine the qualitative statement aspect of the had not approached would wish to diagnostic thyroid metabolic rate man predicted ducted turnover bound I^{131} not turn out to be of thyroid function cannot be adequate methods tein-bound I^{131} . These methods able,⁸ and its method applied principle will clinics where studied or is

The treatment is based primarily that utilized by treatment of radioactive iodine regard to the location of the thyroid, have as radioactive possible and radioactive iodine there is any satisfactory active iodine we say that the radiation should form of treatment

inactive iodine. Various methods of approach were utilized, as for instance the oft repeated and small dose (Soley) as opposed to the excessively large dose of other (Kapman) investigators. Somewhere between the two schools lies the ideal dosage for the treatment of hyperthyroid cases. Methods of measurement of both the administered material, and also, the uptake in the thyroid gland being treated have become more standardized and improved so that a specific dosage for individual thyroid cases is becoming more clarified.

It was the consensus of the group discussing the problem of the diagnostic use of radioactive iodine that we had reached a roughly definitive stage in our knowledge of this aspect of the use of radioactive iodine, but we had not approached the point at which one would wish to give up the older forms of diagnostic thyroid testing, such as the basal metabolic rate determination. The chairman predicted, however, that properly controlled turnover rates, utilizing protein-bound I^{131} neosynthesis, might very well turn out to be the most sensitive indicator of thyroid function. This great desideratum cannot be achieved, however, until adequate methods for the determination of protein-bound I^{131} have been worked out. These methods are now becoming available, and it should not be long before a method applied to finger blood utilizing this principle will be a routine measure in all cases where radioactive iodine is being used or is available.

The treatment of cancer of the thyroid is based primarily on the same principle as is utilized by Hertz and Roberts in their treatment of thyrotoxicosis by means of radioactive iodine. The situation with respect to the locally static case of carcinoma of the thyroid is clear. The patient should have as radical a removal of tissue as is possible and have subsequent dosage of radioactive iodine administered as long as there is any significant retention of radioactive iodine within the body. It is fair to say that the administration of external irradiation should be considered an outmoded method of treatment wherever radioactive

iodine is available. No patient should be discharged as cured of cancer of the thyroid until he has developed total myxedema and in the absence of any metastatic lesion is placed upon thyroid medication and requires it as a permanent form of substitution therapy.

In the case of metastatic cancer of the thyroid with lesions in lung, bone, or other organic metastases, the problem remains one of radioactive iodine in repeated dosage with either local excision of the tumor or massive dosage destruction of the local normal tissue with subsequent repeated dosages of radioactive iodine until no further retention of the material is demonstrated. Since not all tumors are equally avid for radioactive iodine, a very useful procedure has been employed; namely, that of giving thyrotropic hormone or a preliminary treatment of the patient with propylthiouracil for the purpose of promoting increased uptake by lesions which were not originally iodo-receptive.¹¹

On the whole the results of radioactive iodine treatment of cancer of the thyroid, while promising, have not indicated any great percentage of cures in the short time in which the procedure has been used.

However, the original patient of S. M. Seidlin¹¹ of Montefiore Hospital is still alive after having received treatment in 1943 for metastatic thyroid cancer with associated thyrotoxicosis. He has been totally myxedematous and has, as noted by x-rays, remained free of any new lesions. Most of his old lesions have decreased to the vanishing point with respect to both radiologic appearance and I^{131} uptake on repeated tracer studies. It seems quite clear that all functioning thyroid tissues which were present in this man have been markedly necrotized by the action of the beta radiations of the radioactive iodine which he has received. Of course, it will take a number of years to demonstrate many such cases as this original one. The author has had contact with this patient since the inception of treatment in 1943, along with Dr. Seidlin, and saw him alive and well as recently as May 1949, a period of six years following

the inception of his therapy by means of radioactive iodine.

DOSAGE CONSIDERATIONS IN THE USE OF
RADIOACTIVE IODINE

The primary guide for dosage in the treatment of patients with hyperthyroidism still remains the uptake of radioactive iodine by the thyroid per gram of estimated tissue as checked by external Geiger-Mueller counting and urinary excretion studies. It is our opinion that no patient should be treated without a preliminary tracer study utilizing 100 microcuries of I^{131} for this purpose. The importance of standardizing the dosage on the basis of the tracer behavior of the individual case has been brought out many times in our own and others' experiences; the success or failure of the treatment may be dependent upon such an adequately conducted tracer study preliminary to the therapeutic dose, since the receptivity of the gland for the therapeutic dose is the major consideration with respect to both the size of the dose and its probable effect upon the patient.

Improved methods of measurement of radioactive iodine uptake by the thyroid and other sites of the body are now in development and will be generally available shortly; namely, four-way Geiger counters named by us "Multi-counters" to be used in conjunction with Multi-scalers which read up to 40,000 counts per minute in an accurate and duplicable manner. Urinary studies by the Marinelli technic utilizing a candle type beaker and gamma ray detector have been found to require less time and to be adequate for the usual clinical applications, instead of beta ray counting.

With regard to the dosage for patients with cancer of the thyroid with metastases, each individual case must be treated in accordance with observations in that particular individual. The data so far published do not allow any law to be set down with regard to cancerocidal dosage. However, gross dosage from 100 to total 934 (Seidlin) millicuries have been utilized without undesirable irreversible changes in the patient. Leukopenia should be watched for and also anemia be corrected before aplas-

tic changes have ensued in the bone marrow. The incidence of aplasia of the bone marrow is more suspected than real as there have been no specific reports of death due to any such toxic effect of even these large doses of radioactive iodine.

Nor has the use of these tremendous dosages of radioactive iodine been attended by any renal damage. It is apparent, therefore, that the minor dosages used in patients with thyrotoxicosis are unlikely to be of any renal importance. The extreme dilution of the radio isotope in the urine is a likely explanation of this failure of any renal or bladder damage by the radioactive iodine being excreted through that pathway.

Repeated sperm counts and also the menstrual histories of patients treated by means of radioactive iodine have indicated no damage to either the testicles or the ovary in any functional sense. Normal pregnancies have followed both the treatment of male and female parents with thyrotoxicosis by means of I^{131} .

LONG TERM RESULTS OF TREATMENT OF PATIENTS
WITH GRAVES' DISEASE BY RADIOACTIVE IODINE

In the original reports by Hertz and Roberts were included the results obtained to date of March, 1946 for a series of 29 patients treated from March, 1941 to April, 1943, a period of observation covering 3 to 5 years. The results of follow-up conducted as of December 15, 1949 (6-8 years) may be summarized as in Table I.

From Table 1 it can be realized that the operations upon the 5 cases in the original series might have been avoided if confidence in the procedure of I^{130} and I^{131} treatment in 1943-44 had reached its present high level. Retreatment has been needed in 3 patients who received noneffective first dosage; but in no instance was a third treatment found necessary in the original group.

At the dosage level employed in series 1, and with retreatment of the nonoperated "failures," the score for successful treatment of individuals with thyrotoxicosis in this first group has been raised to 24/29. It is fair to assume with our present knowl-

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TABLE 1

SIX TO EIGHT YEARS' FOLLOW-UP OF RESULTS ON THE ORIGINAL PATIENTS WITH GRAVES' DISEASE TREATED BY MEANS OF I-130, RADIOACTIVE IODINE MARCH 1941 TO DECEMBER 15, 1949

Clinical Result as of December 15, 1949	Case No.	No. of Cases
Free of rectal cancer (independent of treatment)	22	1
Free of persistence or (?) recurrence after I ¹³⁰ by I ¹³¹	2, 3, 26	3
Remained well after I ¹³⁰ , I ¹³¹ induced remission		17
Retreated for recurrence (? one)	3(?)	0
Developed myxedema after long latent period	12	1
Exophthalmopathic (controlled on medical measures)		
slowly improving on iodide and thyroid	4	1
Retreated, myxedema and hypothyroidism	1, 5, 10, 14, 16, 19	6
Total of original series (1941-43) Mass. General Hospital		29

of dosage and confidence in our technique that the 5 operated cases might well have responded to a second dose of I¹³⁰ in the absence of operation if such a program had been chosen instead.

The development of evidence of thyroid deficiency after the combined treatment of iodine plus operation is of special interest in the light of earlier experiences with combined x-ray and operative treatment reported from the Massachusetts General Hospital by Pittman.

Although 3 cases were retreated for persistence of thyrotoxicosis, it is striking that no instance of true recurrence of the disease occurred. One patient died of independent cancer of the colon (case 22) with recurrence of thyrotoxicosis. No other patient of the series died either during or after treatment. No complications were encountered. No case has developed cancer of the thyroid, anemia, evidence of renal or hepatic damage. No instance of exophthalmos, tetany, or vocal freckle has been encountered in this series since any other treated by I¹³¹ and published to the present time.

Caplan and Evans reported in some detail in 1946^{12, 13} on the use of higher doses of I¹³¹ as the sole agent, i.e., no additional iodide therapy during the radiation period. Between May 1943, and March 1949 they treated 22 patients having hyperthyroidism with such increased dosage in the absence of other therapy. They reported that 14 responded well to a single dose, 3 were given 2 doses and 5 required

3 doses. Myxedema occurred in 4 of their cases. Six of their patients developed radiation sickness; and fibrosis of the thyroid was demonstrated by them by biopsy of 2 patients. A comparison of these two series has led us to believe that the dosage was excessive in the latter series and the advantages of control of the disease by iodine administration three to four days after the radioactive dose are sufficiently great to warrant the adoption of this routine as standard, providing that such full iodination does not modify the thyroid retention of radioactive isotope in any serious manner.

Freedberg, et al¹³ under our supervision, reported that such modification of the retention of I¹³¹ in the thyroid after a therapeutic dose does not occur if the iodination is accomplished after the third day following the I¹³¹ therapeutic dose. These authors pointed out that a small peak in urinary excretion of I¹³¹ does occur following iodination in this manner, but that this is at the expense of extrathyroidal or total body distributed I¹³¹. It is likely that this is an additional advantage to post-I¹³¹ iodination rather than a deterrent to the therapy. From the results, now, in the treatment of over 750 cases treated by ourselves and by R. H. Williams, Werner and Quimby, and Soley, it becomes quite evident that the procedure of iodination does in no way interfere with the desired radiation effects of I¹³¹, and that it lends safety to the clinical care of the severely toxic and

TABLE 2

Detailed Analysis of the Clinical Courses of a Representative 13 of 99 Complicated Cases of Graves Disease with their Special Indications for I¹³¹ Treatment. (1946-1948)

Initials Age Sex	Diagnosis	Duration years	Complications and/or Special Indications	CLINICAL AND LABORATORY DATA BEFORE I ¹³¹ TREATMENT					I ¹³¹ milli- curies	Carrl Nal mgm	Excretion in 72 hrs. % Dose	Estimated Radiation Delivered to Thyroid r. e. p.*
				Thyroid Size Est'd. Grams	BMR Level	Circ. Time Secs.						
E. F. ¹ 45 M	Diffuse Toxic Goiter	1	Poor control on iodide Incr'd. size of goiter and exophthalmos on propyl- thiouracil. Refused surgery	75	+45	13	4.0	0	51	2600		
R. S. ² 23 M	Diffuse Toxic Goiter	½	Poor control on iodide	75	+40	14	8.0	0	33	4600		
F. A. ³ 44 M	Diffuse Toxic Goiter	½	Incomplete control by propyl and iodide Refused surgery	90	+45	14	8.4	0		
I. B. ⁴ 38 F	Diffuse Toxic Goiter	1 & ½	Refused surgery	100	+40	11	8.0	0		
Retreatment ⁵			Improved but persistent thyrotoxicosis	60	+25	9	6.3	0	14	10,600		
M. N. S. ⁶ 45 M	Diffuse Toxic Goiter	½	None	75	+30	8.0	0		
L. D. ⁷ 45 F	Diffuse Toxic Goiter	1	Psychosis Involuntional Melancholia. Drug addiction Refused surgery	40	+40	12	6.4	0		
C. K. ⁸ 41	Recurr. Postop. Diffuse Tox. Goiter	1 ¼	Progressive exophthalmos	90	+45	12	8.0	0	25	7800		
S. H. ⁹ 57 F	Diffuse Toxic Goiter	1	Psychosis-involuntional melancholia Hypertension B. P. 200/105	75	+60	14	7.5	0	25	8800		
W. P. ¹⁰ 35 M	Diffuse Toxic Goiter	3	Bronchial asthma Anxiety neurosis, severe	75	+25	10	6.0	0	6	7900		
K. H. 44 M	Diffuse Toxic Goiter	¼	None	45	+30	13	4	0	8	7500		
M. P. ¹¹ 37 F	Recurr. postop. & post x-ray Diffuse Toxic Goiter	6	Failure of control by x-radiation and by iodides	75	+25	16	4	0	5.41	2900		
S. B. ¹² 27 F	Diffuse Toxic Goiter	¼	Healed tuberculosis Sensitivity to propylthiouracil	60	+26	11	4	0	1	6200		
F. F. ¹³ 56 F	Recurr. postop. Diffuse Toxic Goiter	22	4 thyroidectomies. Persistent after x-ray therapy. Granulo- cytopenia following thiouracil. Incomplete relief by propyl- thiouracil and iodide	60	+30	8	12	0	5	17,500		

COMMENTS

.... = not obtained or unknown
+0 = none
r.e.p.* = roentgen equivalent physical

¹11 months after I¹³¹ BMR +1. Euthyroid. Exophthalmos improved.

²Transient myxedema, 14 months after I¹³¹, off thyroid 6 weeks, BMR -21, serum cholesterol 276 mgm. %.

³BMR +3 1 year after I¹³¹. Off medication 3 months.

⁴Improved but persistent thyrotoxicosis 5 months after I¹³¹. Retreated 11 months later. (Prot Bound Iodine 15.8. gamma %).

⁵Euthyroid (eight weeks after second treatment)

⁶Lost to follow-up. L. M. D. reports that patient is well.

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Estimated
Radiation
Delivered
to Thyroid
r. e. p.*

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TABLE 2

ailed Analysis of the Clinical Courses of a Representative 13 of 99 Complicated Cases of Graves' with their Special Indications for I¹³¹ Treatment. (1946-1948)

Estimated Radiation Delivered to Thyroid r. e. p.*	Propylthiouracil				Clinical Status	EVALUATION 6 MONTHS AFTER I ¹³¹				
	Stable Begun Days After I ¹³¹	Iodide Weeks Used	Begun Days After I ¹³¹	Weeks Used		BMR Level	Circ. Time (Secs.)	Wgt. Gain Lbs.	Thyroid	
2600	1	6	0	0	Euthyroid	+5	16	24	Normal	
4600	1	11	0	0	Myxedema	On Thyroid	26	35	Normal	
.....	1	12	0	0	Euthyroid	30	
.....	1	10	0	0	Persistent Thyrotoxicosis	+20	14	0	60	
10,600	0	0	0	0	Euthyroid	8	Normal	
.....	1	1	0	0	Euthyroid	Normal	
.....	1	8	0	0	Euthyroid	+7	22	
7800	3	12	0	0	Euthyroid	+5	18	17	Normal	
8800	0	0	0	0	Euthyroid	+4	16	13	Normal	
7900	0	0	0	0	Euthyroid	-3	17	8	Normal	
7500	3	7	0	0	Euthyroid	
2900	3	5	0	0	Euthyroid	+8	17	0	Palpable Tissue Persists	
6200	0	0	0	0	Myxedema	30	12	Normal	
17,500	8	0	0	Euthyroid	15	15	Normal	

COMMENTS

stabilism without clinical evidence of myx- months after I¹³¹ BMR -20. Cholesterol circulation.

sive decrease of exophthalmos. 8½ er I¹³¹; patient euthyroid.

is after I¹³¹ BMR -22. Serum cholesterol %. Clinically myxedematous. B. P.

¹⁰Euthyroid 9 months after I¹³¹. Exophthalmos completely disappeared.

¹¹(1) 4 weeks off iodide. (2) Marked decrease in size of goiter. Left lobe still palpable. Repeat I¹³¹ tracer showed 26% excretion in 72 hours.

¹²Euthyroid (BMR +0) with no palpable thyroid 4 weeks after I¹³¹ without added therapy. Rapid response.

¹³Myxedema—on permanent thyroid medication. (9 months after I¹³¹ therapy).

sperately ill cardiac and diabetic subjects with thyrotoxicosis.

The most complicated and debilitated patients have been handled with I^{131} . Patients with serious complications such as colostomy, congestive heart failure, Addison's disease, renal disease, multiple antecedent operations, drug sensitivities to iodide, and propylthiouracil, as well as patients with severe infections, have responded favorably to I^{131} therapy followed by routine iodination (see Table 2). Detailed reports of these subsequent series of patients are available.^{E. 16, 17.} In no instance was it thought that iodination contributed negatively to the care of the patients in such instances in which iodination was not carried out prior to the seventy-two hours following the therapeutic I^{131} dose.

In emergency cases it is our view that, if allowance is made for the possibility of a moderate loss of I^{131} by iodination during the first forty-eight hours following I^{131} , by adjustment of the dosage of I^{131} upwards it is permissible to carry out full iodination relatively early in order to bring the patient's disease under as rapid control as is possible by any known technic.

We are now in a position to caution against certain pitfalls in the practical management of patients with I^{131} . We have discovered a few of these by the experience of analyzing the new failures of our own and others' cases.

A priori and by actual experience we agree with Werner, who states that the most common cause of failure of a single dosage to remit the disease is inadequate dosage. Our present dosage scheme calls for 200 to 250 μ C/gram of estimated thyroid weight. By clinical practice it is possible to calibrate one's palpation of the thyroid, as has been shown by Soley, to a fair accuracy in such estimation of thyroid weight. Werner's models are also helpful adjuncts in such self education in this important aspect of thyroid examination. Unless the thyroid is of inordinate size, i.e., over seven to ten times normal, it is unlikely that over 12 to 15 MC. total dosage will be required. We have had cases in

which response has occurred to as little as 1 MC. for an impalpable gland, (probably less than 25 grams); and yet we have seen failure on the first dose from as much as 12 MC. for a patient with a 90 to 100 gram goiter. In such instances we believe it better to err on the side of low dosage and to depend upon the use of a second dose, if it proves to be needed in follow-up.

In our present state of knowledge and with improved equipment soon to be made generally available, it should be made a rule that no patient with thyrotoxicosis should be treated with I^{131} without a preliminary tracer dose of 100 μ C. and determinations of both the thyroid uptake and urinary excretions over a period of forty-eight to seventy-two hours.

We have found a close correspondence between the handling of tracer and therapeutic doses by patients in our large series. The importance of these preliminary tracer studies is heightened by certain instances in which patients were taking iodinated salt, kelp or cough mixtures prior to presentation for I^{131} treatment. Early studies in both animal and man indicated the importance of having the systems free of extraneous iodide ingestion prior to therapeutic uptake of I^{131} .¹⁻⁴

In one case 3 doses of I^{131} had been administered at another clinic without tracer or excretion studies. This patient responded very little to those doses and presented herself to us for study because of this alleged resistance to I^{131} treatment. We performed a tracer study and found her gland unresponsive to I^{131} . On analysis it was elicited that for over four years she had used iodized salt regularly and had been continuously on this source of iodide during her entire I^{131} trials. When iodized salt was stopped for a month and a repeat tracer dose given it was discovered that her uptake was consistent with her moderate thyrotoxicosis; and a subsequent therapeutic dose was fully effective when taken on an "empty thyroid," i.e., free of extraneous iodide.

Patients who have received the antithyroidal agents, such as thiouracil and pro-

pylthiouracil, alone, are less of a problem in iodide medication in view. It is, however, a goiterogen best started days prior to the treatment as patients who are on these drugs do not have uptakes of I^{131} by the gland. In part, this has accounted for a number of "failures" of I^{131} therapy. This emphasizes the value of a preliminary study as a control experiment.

Tracer studies are a source of information in the treatment of hyperthyroidism. They are used in individual cases, though Werner's studies of the tracer behavior of hyperthyroidism is not based on iodine uptake studies. They are diagnostic aids in the treatment of toxic goiter. They give promise that they will be used into protein-bound tracer dose may be available for this purpose. Microtechnics on this subject are being developed. This is a very new time.

Complications of I^{131} treatment are continued to be few. Roughly 10 patients have had edema. Of these 10 patients, 5 are permanent in character and in 100 requires permanent sort in our treatment. They may eventually be improved and as the number of patients becomes

Minor tenderness, cough and, rarely, thyrotoxicosis have been reported in a group; but no case has caused concern with the treatment. Measures and the iodination. We have seen leukopenia or anemia

racil, alone without iodides offer a problem than those previously on medication from the above point of view. It is, however, imperative that the patient be stopped for at least three days prior to the tracer or therapeutic dose. Patients who are under the influence of other drugs do not display characteristic effects of I^{131} by their goiters. This, in fact, has accounted for an additional number of "failures" on I^{131} therapy and re-emphasizes the value of the preliminary tracer studies as a control on optimal time for treat-

ment. These studies also afford an added bit of information in guiding the dosage to be given in individual cases for therapy.⁶ Although Werner's results indicate that the behavior of I^{131} in cases of atypical hyperthyroidism is characteristic, we have been impressed with the utility of thyrotoxic uptake studies or excretion studies as diagnostic aids in borderline or early cases of toxic goiter. Current studies, however, promise that the turnover rate of I^{131} protein-bound I^{131} in the blood after a single dose may be made discretely dependent on this purpose; particularly, when the techniques on finger blood are fully developed. This is work in progress at this

time. Complications of I^{131} therapy have proved to be few and mild in character. Only 10 patients in 100 develop myxedema. Of these 10, only one has proved to be permanent in character; that is, one case only requires post- I^{131} therapy of a permanent sort in our hands. That myxedema eventually be entirely avoided seems probable when accuracy of dosage is further improved and as the fractional treatment of patients becomes more utilized.

Neither tenderness of the gland, slight enlargement, and, rarely, slight exacerbation of thyrotoxicosis have been experienced in our series; but no cases have given us cause for concern with the ready use of local anesthetic and the early use of post- I^{131} therapy. We have not encountered leukopenia or anemia; no fever or radiation

sickness has been noted in our more moderate dosage group.

Repeated renal studies over a period of eight years have revealed no evidence of either acute or chronic long time effects upon the kidneys of our subjects. Fertility has not been decreased in our series; we now have 16 babies born to 11 mothers and 3 fathers who have undergone I^{131} treatment for thyrotoxicosis previous to conception. One of these mothers has had 3 separate pregnancies (normal, full term fetuses at birth). None of the 16 babies has shown evidence of cretinism or congenital defects.

There are still a few observers who raise the question as to whether I^{131} treatment of thyrotoxic patients is going to result in cancer of the thyroid as one of the delayed effects of concentrated radiation delivered to the organ during such therapy. Calculations made by Robley D. Evans and reported by Earle M. Chapman at the Brookhaven National Laboratories Conference on Radio-Isotopes in Biology and Medicine (*q.v.*) give valid assurances that this is a minor likelihood. Further reassurance is given from the long term experience in many lands (over a period of thirty years) of the nondevelopment of any significant number of cases of cancer of the thyroid following the more drastic treatment by intensive x-ray treatment over the thyroid gland for this and other conditions of the cervical region.¹⁴

A similar answer can be given to those who object to I^{131} therapy on the basis that the genetics of the race will be altered by this method of treatment. Calculations of the probability of such genetic changes taking place as a result of the minor deposit of I^{131} in the testicles or ovaries of our patients render such objections remote, indeed.¹⁵ Actuality of fertility has been proved repeatedly following I^{131} therapy in our series.

That these therapeutic effects can now be regularly obtained by proper dosage, consideration of the underlying principles of the type of therapy and due care to perform proper standardization of the approach by preliminary tracer studies, becomes more

evident as the method enjoys greater application.^{8-10,13}

There have been excellent accounts of the results obtained by others using I^{130} and I^{131} in treatment: Notably by Werner, Schmidt, and Quimby; and Soley, Chapman, Skanse, Evans and Printzmetal. In essence, these authors and others conclude, as do we, that I^{131} therapy of hyperthyroidism is effective, safe to the patient and to the doctor with proper precautions set out by the Atomic Energy Commission, and that it is free of some of the drawbacks of either the surgical or other medical approaches to the problem.

The contribution of radioactive iodine studies to the field of thyroid physiology, chemistry and pathology continues at a rapid rate.^c Of these we shall plan to report in full detail on some other occasion. At this time we wish to emphasize the importance of fundamental studies on the subject: "How does I^{131} exert its characteristic action on the hyperplastic gland of Graves' disease?" Inherent in this mechanism are the secrets of cellular proliferation, and enzyme action in the cells. The hope of understanding these is closer as applied to the problems of this disease than in many other fields of medicine or biology, because of the accuracy of the measurements that can be applied and because of the clear-cut effects with which we must now deal.⁷

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MY
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Fiedler, in 1888 reported carditis which has since there was pericardium without associated disease. Scott and others reported 2 cases and elevated temperature. Simon and others collected 10 additional cases. Other authors reported individual cases.

Isolated myocarditis denotes a morphological change in the myocardium of a variety and various characteristics than the isolated involvement of a nonspecific lesion. Changes in the myocardium.

It may occur as reported from 10 months commonly between diagnosis of myocarditis made and frequently suspected. The pulse rapid, tachycardia and murmurs may be present. Death frequently of the 13 reported cases the symptoms are out evidence or history.

In a review of the Charity Hospital, conforming to the

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