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USE OF RADIOACTIVE IODINE IN THE DIAGNOSIS, STUDY AND TREATMENT OF DISEASES OF THE THYROID

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General Considerations

THE EARLY STUDIES of Hertz, Roberts, and their associates at Massachusetts General Hospital and Massachusetts Institute of Technology, starting in 1936–1937 and continued to the present, have opened a new era in the study of the physiology, diagnosis and treatment of diseases of the thyroid gland.[1-7] Their preliminary studies on rabbits and man served to introduce the use of the isotopes of radioactive iodine as tracer substances in the study of thyroid physiology. Extensions of these exploratory experiments have been made by the in vitro and in vivo studies of Chaikoff et al.[8] to elucidate the steps whereby inorganic iodides are converted to di-iodotyrosin, to thyroxin and, subsequently, to thyroglobulin.

Clinical studies by Rawson, Keating, Werner and others have substantiated the use of I^{131} in differential diagnosis. Astwood and his coworkers have devised short (4 hour) tests utilizing external gamma ray counting technic over the human thyroid, which method was initially utilized by Hamilton and Soley, and by Hertz, Roberts, Means and Evans for the clinical demonstration of tracer behavior of radioactive iodine following oral administration of carefully standardized doses of $I.^{130}$ Leblond in Canada, and others in the United States have utilized the principle of radio autography first used for localization of the distribution of radioactive materials by Lacassagne. Leblond made a study of the fate of I^{131}, labelled thyroxin and other organic fractions of importance in thyroid biochemistry following intravenous and oral administration, thereby tracing the fate of these materials in the organism.

Study of the action of the thyrotropic factor of the anterior pituitary (T.S.H.), cyanate goiter, cabbage feeding, thiouracil and other goiterogens has led to a fairly clear understanding of the mechanisms of action of these agents as compared with each other and with iodine deficiency goiterogenesis. From careful radioactive iodine studies, there is increasing evidence that there is in the normal and pathologic thyroid gland an enzyme system for the oxidation of iodides to iodine; that, in turn, iodine is taken by a two-stage process thereafter into di-iodotyrosin and then into protein-bound

form for storage in the acinar colloid. It seems clear that the various goiterogens differ in their site of impingement upon this complicated biochemical system.[9] It is growing more clear that both the anterior pituitary as well as the adrenal cortex and medulla exert a regulatory role upon the rate at which these reactions occur in health and disease.

Disorders of the pituitary and adrenal glands have been studied with I^{131} tracer technics, as have various pathologic changes in the thyroid per se, such as malignancy, nodular goiter, cyanate and other "goiterogenic" types of goiter in man. The action of the goiterogens has been analyzed clinically by Astwood[10] by these means with important results. The finding by Leblond of a low level function in the atrophied thyroid following hypophysectomy serves to indicate a system in the thyroid which is not dependent upon the thyrotropic or adrenal factors for regulation.

Chaikoff has considered the level of inorganic iodide in the blood of the rat as the most important factor in regulating the thyroid enzymatic functions via its effect on T.S.H. production by the pituitary. We are unable to agree entirely with this point of view because the clinical experiences which we have had on feeding high amounts of iodide to patients with normal thyroids do not indicate any action in lowering metabolic rate or in influencing the thyroid in any detectable manner by such a procedure. One would expect if Chaikoff were correct, that the high level of inorganic iodide in the blood of subjects who are fed iodide would inhibit T.S.H. in normals yielding myxedema or, at least, in lowering of basal metabolic rate (B.M.R.). Since this does not occur we, on a priori grounds, cannot accept Chaikoff's thesis in this respect.

Astwood[10] has followed the reasoning of the MacKenzies in his exploration of the specific effect of the thiourea type of goiterogens by concluding from his experiments that these agents act by inhibition of thyroxin synthesis. We would expect, if this were true, that normal and overactive thyroids would respond to the goiterogens by the *invariable* development of myxedema following high dosage of these agents over long periods of time. In our experience, development of myxedema is the rare, rather than the usual happening following exhibition of the goiterogens even to thyrotoxic individuals over such long periods of time.

The fact that thiourea goiterogenesis requires the presence of an intact anterior pituitary gland has been regarded as evidence that the T.S.H. mechanism is either increased or augmented by these agents in parallel with an inhibition of thyroxin synthesis.

That thiourea exerts its characteristic inhibition of thyroxin synthesis in vitro seems well established; but there is no direct evidence that T.S.H. increase or augmentation is uniquely responsible for thiourea goiterogenesis.

Hypophysectomy is followed by characteristic alterations in the adrenals and gonads; and, also eliminates the hypothalamic-pituitary pathways to other endocrine organs. It is at least tenable that these other organs play a role in the genesis of thyroid changes. Evidence lately adduced by Reiss and Forsham working in Thorn's laboratory gives strong indications that this is so.

In Addison's disease there is a low uptake of I^{131} by the thyroid which is enhanced above normal by the administration of compound E or lipoadrenal extract. At last, we have a reasonable explanation of the lowered basal metabolic rate of uncomplicated, full-blown Addison's disease cases. Administration of ACTH to cases of panhypopituitary disease with secondary Addison's disease has resulted in activation of the hypofunctioning adrenals and increased thyroid I^{131} uptake, whereas response to adrenalin is nil in these cases. The corticoids of the adrenal cortex may well play an important role in thyroid regulation in both health and disease. That the goiterogens have an action upon the adrenal cortical mechanisms remains an open possibility that requires close analysis.

Practical Clinical Applications of I^{131} Tracer Technic

The clinical applications of the isotope technic to the problems of diagnosis have been primarily based upon the findings of a characteristic uptake by the thyroid gland in its several altered conditions. It has been amply demonstrated that such studies presuppose that the patient or subject studied must be free of all previous iodide or goiterogenic influence due to premedication or unrecognized intake of substances such as iodized salt, or indeed, the ingestion of large quantities of members of the Brassica family of plants, the therapeutic exhibition of cyanate (as in the treatment of hypertension) etc. Tracer studies upon subjects on a low salt intake (rice diet) have shown that such individuals may have a large thyroid uptake of I^{131}, probably related to the fact that low salt diets also are iodide-free diets unless supplemented by iodide medication.

Recent studies on the effect of sulfanilamide upon tubular reabsorption of such electrolytes as sodium suggest that there may also be a renal component to goiterogenesis. Via the mechanism of iodide loss from the body by failure of tubular iodide reabsorption, with consequent relative insufficiency of iodide, normal thyroxin synthesis might be expected to decrease due to the absence of one of the major components for that synthesis, namely iodide. A corresponding explanation has been offered for the markedly decreased basal metabolic rate of patients with lipoid nephrosis. In these instances there is loss of iodide bound to protein of which there is a tremendous loss in the urine in this disorder. This explanation has been

substantiated by demonstration of I^{131} labelled protein fraction in the urine of nephrotic patients following the administration of tracer doses of I^{131}.

Radio Autography Utilizing I^{131}

Although much has been done with radio autography utilizing radioactive iodine, the results of a recently conducted survey of the latter technic has led the author to the conclusion that erroneous data have been collected by many investigators utilizing it. Because of their failure to use adequate controls upon their technics themselves, much of the disagreement which exists between the various authors, each with his own modified technic, is due in part, at least, to the failure of realization that tissue iodide uptake and retention are separate phases of the physiology of iodide in tissue. That there is a loss of inorganic iodide during fixation and dehydration due to the ready solubility of iodide in water and other solvents has not been fully realized. Organic iodide residues in the tissue after such vigorous treatment remain behind in the tissue in greater but variable percentages of the originally deposited material. The rate of synthesis of protein-bound fraction of tissue iodide varies greatly with such factors as time after the administered dose, the type of treatment the patient or animal receives, as well as many other factors to which the experimental subject is exposed. Diet, temperature, pregnancy, sex, age of the animal or patient are pertinent factors. It is evident, therefore, that reliance cannot be had upon such radio autographic data as has been collected by the rather poorly controlled methods of study thus far utilized. Certainly the methods so far used do not allow any standardized statements with regard to the actual behavior, for example, of tumors of the thyroid, etc. Tumors studied in one clinic as compared with those studied in others by entirely different technics and under a multiplicity of attendant circumstances do not allow quantitative comparisons of any moment to be made.

And yet, from the over-all data one gets the impression that in a roughly qualitative way, the radio autographic use of I^{131} reaffirms the demonstrated behavior of I^{131} physiology in tissues as revealed by the crude external Geiger-Mueller counting technics used to date and from total tissue analyses of specific radioactivity.

Utilizing individual technics, and with data obtained on various tissues under roughly similar conditions, it appears that there is greatly variable uptake, fixation, synthesis and loss in dehydration of I^{131} in tissue radio autographic studies. If one realizes this situation, and if one has the proper conception of the dynamic state of iodide metabolism he can assign proper importance to any particular radio autographic study. The radio autograph, then, becomes a point in time and only a brief incident in the entire process being studied. It is clear, therefore, that it is fallacious to accept the various

doctrines which have been propounded upon the basis of purely radio autographic study without associated or correlated study of external Geiger-Mueller counts, inorganic/organic fractionation and turnover rate from inorganic I^{131} to organic I^{131}.

In the absence of analysis of the material lost during dehydration and fixation, the data so far collected remains uncontrolled and therefore lacking in scientific dependability. The author and colleagues are at present working out detailed technics of radio autography bearing these points in mind. It is our hope to be able to initiate a field of quantitative radio autography on a sound basis by the exercise of these proper controls.

Allowing for the shortcomings of the technics utilized in the published studies, it, however, does appear that I^{131} radio autography has established in a rough sort of manner the fact that there is variation in the functional capacity for fixation of iodide by various tumor types. It appears also that there is some correlation between the degree of differentiation present in a tumor and its capacity for storage of iodine. It is also suggested that there is no uniformity of distribution of I^{131}; just as there is no cytologic uniformity from area to area in individual lesions. One has to exclude compensatory hyperplasia as an important factor in radio iodine distribution even in tumor masses; secondary changes such as necrosis, interference with blood supply and calcification also become factors in such distribution studies. It is conceivable that by proper treatment of tissues in a standardized manner the methods of I^{131} radio autography can be so standardized as to become valuable adjuncts to the anatomic and biochemical studies.

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 BNL-C-5. This published material summarizes much of the physiologic and laboratory aspects to that date. The concentration of radioactive iodine by goiters, etc. 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 as well as of academic value in relation to this form of treatment.

Succinctly summarized, the session indicated beyond any question of doubt that *properly assayed dosage and selection of patients with toxic goi for treatment led to entirely satisfactory cures in the great majority of pati treated by means of radioactive iodine.* Various methods of approach we utilized, as for instance the oft repeated and small dose (Soley) as oppos to the excessively large dose of other (Chapman) investigators. Somewhe between the two schools lies the ideal dosage for the treatment of hyp thyroid cases. Methods of measurement of both the administered mater and also the uptake in the thyroid gland being treated are gradually b coming more standardized and improved so that specific dosage for i dividual thyroid cases is becoming more clarified.

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

The treatment of cancer of the thyroid is based primarily on the sam principle as that utilized by Hertz and Roberts in their treatment thyrotoxicosis by means of radioactive iodine. The situation with regard t the locally static case of carcinoma of the thyroid is clear. The patien should have as radical a removal of tissue as is possible and have subsequen dosage of radioactive iodine administered as long as there is any significan retention of radioactive iodine within the body. It is fair to say that th administration of external irradiation should be considered an outmode form of treatment wherever radioactive iodine is available. No patien should be discharged as cured of cancer of the thyroid until he has develope total myxedema and in the absence of any metastatic lesion is placed upo thyroid medication and requires it as a permanent form of substitutio 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 iodin in repeated dosage with either local excision of the tumor or massive dosag destruction of the local normal tissue with subsequent repeated dosages o

dioactive 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 a preliminary treatment of the patient with propylthiouracil for the purpose of promoting increased uptake by lesions which were not originally iodo-receptive.

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. Seidlin[11] 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-ray, remained free of any new lesions. Most of his old ones 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 original prescription of therapy.

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 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 has been utilized without undesirable irreversible changes in the patient. Leukopenia should be watched for and also anemia be corrected before aplastic 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 March, 1949 (6–8 years) may be summarized as in table 1.

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 group has been raised to 24/29. It is fair to

assume with our present knowledge of dosage and confidence in our technic, that the 5 operated cases might well have responded to a second dose of I^{130} 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 I^{130} 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 no recurrence of thyrotoxicosis. No other patient of the series died either during or since treatment. No complications were encountered. No case has developed cancer of the thyroid, anemia, evidence of renal or hepatic

Table 1.—*Follow-up Results in Twenty-nine Patients with Graves' Disease Treated by Radioactive Iodine (1941 to 1943)*

	Case no.	No. of cases
Died of rectal cancer (independent of treatment)	22	1
Treated for persistence or ? recurrence after I^{130} by I^{131}	2, 3, 26	3
Remained well after I^{130}–I^{131} induced remission		17
Treated for recurrence (? one)	3(?)	0
Developed myxedema after long latent period	12	1
Ophthalmopathic (controlled on medical measures) slowly improving on iodide and thyroid	4	1
Operated—myxedema and hypothyroidism	1, 5, 10, 14, 16, 19	6
Total of series		29

damage. No instance of malignant exophthalmos, tetany, or vocal damage has been encountered in this series or in any other case known to us to the present time.

Chapman and Evans reported in some detail in 1946[12] on the use of higher doses of I^{130}–I^{131} as the sole agent, i.e., no additional iodide therapy during the radiational period. Between May, 1943 and March, 1945 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 two doses and 5 required three 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 3 to 4 days after the radioactive

dose are sufficiently great to warrant the adoption of this routine as standard, providing that such full iodinization does not modify the thyroid retention of radioactive isotope in any serious manner.

Freedberg, et al.[13] under our supervision, reported that such modification of the retention of I^{131} in the thyroid after a therapeutic dose does not occur if the iodinization is accomplished after the third day following the I^{131} therapeutic dose. These authors pointed out that a small peak in urinary excretion of I^{131} does occur following iodinization in this manner, but that this is at the expense of extrathyroidal or total body distributed I^{131}. It is likely that this is an additional advantage to post-I^{131} iodinization rather than a deterrent to the therapy. From the results, now, in the treatment of over 350 cases treated by ourselves and by Drs. R. H. Williams, Werner and Quinby, and Soley it becomes quite evident that the procedure of iodinipation does in no way interfere with the desired radiational effects of I^{131}, and that it lends safety to the clinical care of the severely toxic and desperately 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 and multiple antecedent operations, drug sensitivities to iodide, propylthiouracil, etc., as well as patients with severe infections have responded favorably to I^{131} therapy followed by routine iodinization. Detailed reports of these subsequent series of patients will be available soon. In no instance was it thought that iodinization contributed negatively to the cure of the patients in such instances in which iodinization was not carried out prior to the 72 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 iodinization during the first 48 hours following I^{131}, by adjustment of the dosage upwards it is permissible to carry out full iodinization relatively early in order to bring the patient's disease under as rapid control as 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 experience of analyzing the few 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 schema calls for 200 to 250 μc./gram of estimated thyroid weight. By clinical practice it is possible to calibrate one's palpation of thyroid, as has Soley, to a fair accuracy in such estimation of thyroid weight. Werner's models are also helpful adjuvants in such self education in this important aspect of thyroid examination. Unless the thyroid is of inordinate size, i.e., over 7–10 times normal, it is unlikely that over 12–15 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 90–100 Gm. 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 μc. and determinations of both the thyroid uptake and urinary excretions over a period of 48–72 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 iodinized salt, kelp or cough mixtures prior to presentation for I^{131} treatment. Early studies in both animal and man[1, 6] indicated the importance of having the systems free of extraneous iodide ingestion prior to therapeutic uptake of I^{131}. In one case three doses of I^{131} had been administered at another clinic without tracer or excretion studies. This patient responded very little to these 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 unreceptive 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 iodinized 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 other antithyroidal agents, such as thiouracil and propylthiouracil, alone without iodides offer less of a problem than those previously on iodide medication from the above point of view. It is, however, imperative that the goiterogen be stopped for at least three days prior to the tracer or therapeutic dose as patients who are under the influence of these drugs do not display characteristic uptakes of I^{131} by their goiters. This, in part, has accounted for an additional number of "failures" on I^{131} therapy and re-emphasizes the value of the preliminary tracer study as a control on optimal time for treatment.

Tracer studies also afford an added bit of information in guiding the dosage to be used in individual cases for therapy. Although Werner's results indicate that the tracer behavior of I^{131} in cases of typical hyperthyroidism is characteristic, we have not been impressed with the utility of

thyroid uptake studies or excretion studies as diagnostic aids in borderline or early cases of toxic goiter. Current studies, however, give promise that the turnover rate of I^{131} into protein-bound I^{131} in the blood after a tracer dose may be made discretely dependable for this purpose; particularly when micro technics on finger blood are fully developed. This is work in progress at this time.

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

Minor tenderness of the gland, slight cough and, rarely, slight exacerbation of thyrotoxicosis have been experienced in our group; but no case has given us cause for concern with the ready use of local measures and the early use of post-I^{131} iodinization. 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 Dr. Earle M. Chapman at the Brookhaven National Laboratories Conference on Radio-Isotopes in Biology and Medicine (q.v.) give valid assurance that this is a minor likelihood. Further reassurance is given from the long term experience in many lands (over a period of 30 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 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, etc., becomes more evident as the method enjoys greater application.

There have been excellent accounts of the results obtained by others using I^{130} and I^{131} in treatment: notably by Werner, Schmidt and Quinby,[16] Soley[17] and Chapman, Skanse and Evans.[18] 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 A. E. C. 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. Of these we shall plan to report in full detail at 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, enzyme action in the cells, etc. 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 may now deal.[7]

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