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The Use of radioactive iodine in the treatment of hyperthyroidism

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THE USE OF RADIOACTIVE IODINE IN THE TREATMENT OF HYPERTHYROIDISM

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INTRODUCTION

Since the advent of the atomic pile with the resultant availability of pile produced radioactive iodine, investigation of thyroid metabolism has progressed rapidly. Concomitant with this speedy extension of knowledge has been the change in attitude toward therapy of hyperthyroidism, a better understanding of the expected results from such therapy and the introduction of new modes of treatment. Since the etiology of hyperthyroidism is not well understood, the therapeutic approach is directed against the main target organ of the disease, the thyroid, rather than the specific cause. This thesis deals with the therapeutic approach to hyperthyroidism inasmuch as it is concerned with radioactive iodine.

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IODINE AND THYROID METABOLISM

Since radioiodine is so closely tied to thyroid metabolism in diagnostic value, it seems proper to introduce the subject of this paper with a brief survey of iodine and thyroid metabolism.

In thyroid hormone manufacture, the preliminary step involved is the transferral of serum iodine to thyroidal iodide and its transformation into iodine for synthesis into thyroxin. Since many tissues have been shown to have the ability to manufacture thyroid hormone if sufficient iodine is present, then that which sets the thyroid aside from other tissues, is its ability to concentrate iodine.

The next step to be accomplished is to transform the iodide taken up by the thyroid gland to iodine for its introduction into the tyrosine molecule. This is thought to take place under the influence of an oxidative process and an oxidative process has been described by Dempsey (8) in 1944, although some take exception to this view. Once di-iodotyrosine is formed, two molecules of it combine to form thyroxine through an oxidative coupling with the elimination of one side chain. From here, thyroxin is transferred to the colloid of the gland in the form of thyroglobulin for

storage or it is secreted directly into the blood stream. Thyroxin is released from thyroglobulin by a process of proteolysis under the influence of thyrotropic hormone.

When drugs of the thiourea group such as thiouracil or propylthiouracil are introduced, the manufacture of thyroid hormone is interrupted. The essential feature of this effect is the blocking of the organic binding of iodine to tyrosine. The exact mechanism is not known, but it may be that the thiurea acts to inhibit oxidation, possibly of a peroxidase system, if this is actually the system for iodide conversion. Organic binding resumes within a matter of a few hours after the administration of a single dose of the drug. If the drug administration is continued long enough so as to induce a decrease in the circulating thyroid hormone, the pituitary will be stimulated to produce more thyrotropin. This will, in turn, stimulate the thyroid gland to gross hyperplasia and will increase its ability to concentrate iodine. However, this iodine is in an inorganic form and cannot be utilized to form thyroid hormone.

The means by which the rate of thyroid hormone manufacture is controlled is obscure, but it seems likely to be mediated by the pituitary. That the fundamental control of the thyrotropin hormone output may

rest in the hypothalamus is suggested by the observations of Jensen and Clark (18) that thyrotoxin labelled with radioiodine can be localized there. Recent experiments, notably by Greer (9), indicate that the pituitary may secrete two factors, a growth factor which is able to increase thyroid cell size, and a metabolic factor which controls iodine metabolism. The growth factor is dependent on direct contiguity with the hypothalamus for its secretion, while the metabolic factor appears to be independent of hypothalamic connection.

The explanation of the well-known effect of iodine in pharmacological amounts, in certain cases of hyperthyroidism, is not well understood although its effect is mediated through interruption of organic binding of iodine to tyrosine as does thiouracil. It is apparently related to the amount of iodine contained in the thyroid gland and not the amount circulating in the blood stream. It has long been observed that iodine has an involuting effect upon the hyperactive thyroid gland, and it is further postulated that iodine may interfere with the action of thyrotropin on the thyroid gland.

The exact mechanism by which thyroxine exerts its effect on tissues is not known although it is apparent that tissue metabolism is controlled through

regulation of enzymatic activity. It has been suggested that its activity could be exerted either as a sort of co-enzyme or indirectly through the release of some metabolically active substance. Because of the small amounts of thyroxin available to the various tissues, some have felt it unlikely that thyroxin acts directly with each of several enzyme systems. However, some recent experimental work by Gemill in 1952 shows a direct participation by thyroxin in two enzymatic mechanisms and suggests that it may act as a mediator between substrates or co-enzymes and cytochrome C, aiding not only oxidation but phosphorylation as well.

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HISTORY

Roentgen treatment has been used for hyperthyroidism for many years. In 1923, Means and Holmes (19) pointed out that in this type of treatment, about one-third of the patients are cured, another one-third improved, and the other third not effected. Since 1923, ordinary iodine by mouth has been used as a preoperative method by quieting the hyperactive thyroid in preparation for surgery. Under iodine alone, occasionally the patient and the doctor alike have been agreeably surprised to find that the symptoms and signs of hyperthyroidism have disappeared, and a permanent remission was apparently effected. That X-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that someday a more effective non-surgical method would be found. Then, the MacKenzies' and Astwood (19) discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated and, until now, thiouracil has been found to be most useful in the treatment of thyrotoxicosis.

Induced radioactivity was discovered in 1934 and that same year, Fermi and his co-workers in Italy

prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine rendered radioactive would have a greater radiation effect than that delivered from roentgen rays derived through the skin and overlaying tissues.

The use of radioactive iodine in the study of thyroid physiology was soon undertaken and reported first in 1938 by Hertz, Roberts and Evans (12). Subsequently, these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function, and it was found that in untreated hyperthyroidism, the thyroid may take up to as much as 90 per cent of a small dose (less than two milligrams) of iodide within a few hours after oral administration. This established the basis for therapeutic trials of radioactive iodine.

In 1942, at the annual meeting of the American Society For Clinical Investigation, Hamilton and Lawrence (11) reported that in a series of experiments with radioactive iodine with the collaboration of Doctors Soley and Eichorn in which two dogs and a series of rabbits were given large doses of radioiodine, the net effect was the nearly complete destruction of the thyroid gland and no evident damage to other body tissue.

This was followed by smaller doses of radioiodine given to a series of three hyperthyroid patients. Marked clinical improvement was noted within two months with no adverse effects. Two of the patients had nearly complete remission in four and a half months, and the third required another small dose. At the same time, Hertz and Roberts (12) published a preliminary report of the treatment in this manner of ten patients. In this series, the procedure was to give the radioactive iodine and follow this with ordinary iodine by mouth for a period of several months. However, a revue of these cases of Hertz and Roberts, and an additional eighteen cases of Hertz following this, led to the conclusion that it was difficult to decide whether those patients who improved were responding to ordinary iodine, to radioactive iodine, or to their combination. The dosage given to this series of patients averaged five millicuries in 1941, ten millicuries in 1942, and 14.5 millicuries in 1943. The largest single dose being 21 millicuries.

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PHYSIOLOGICAL AND BIOLOGICAL EFFECTS OF RADIOACTIVE IODINE

The biological effect of radiation, independent of the type of radiation that is used, is the same on all body tissues. Radioisotopes are like radium and X-ray in that it undergoes continuous disintegration with a resultant emission of radiation. There are two important types of radiation emitted. These are beta and gamma rays. Beta radiation consists of high speed electrons of variable digress of energy which are nearly all absorbed within one centimeter of the tissue. Gamma rays resemble high voltage X-rays and, generally speaking, have a much larger range of penetration and biological effect than beta rays. Radioactive iodine 131 emits a feeble beta ray which is entirely absorbed within 1-2 millimeter of tissue, and a gamma ray equivalent to a 370,000 volt X-ray, although the gamma ray makes up only about 15 per cent of its total energy. Radioiodine 131 dissipates half of its energy in about eight days (half-life). The therapeutic action of all radioactive materials results entirely from the radiation emitted and their physiological effect depends upon the selective localization of the isotope within the body of the patient. The conduction of the radioactivity to selected tissues is the only importance of the chemical

agent used. Thus, the biological effect of the emitted radiation will depend upon the assimilating tissue and the dosage given. Suppression of mitosis, reduction of functional activity in the tissue, and even cytocidal disintegration of radiosensitive neoplasm will occur, depending on the dosage of radiation delivered.

Dailey, Lindsay, and Miller (6) have found in a histological examination of the thyroid of twenty-three hyperthyroid patients of which twenty-one received a therapeutic dose and all but two became euthyroid, that seven patients were hyperplastic and no definite radiation effects were noted. Nine of those treated had lesions identical with Hashimotos' thyroiditis. They state that the high incidence of thyroiditis compared with non-irradiated hyperplastic glands is significant and that it suggests that Hashimotos' thyroiditis is one effect of internal radiation with iodine. Four of the patients showed multiple nodules and showed moderate follicular atrophy of the residual gland tissue. This atrophy, it was believed, was the result of irradiation injury. Diffuse follicular atrophy and fibrosis was displayed by three patients. This is considered the classic lesion of irradiation. Vascular lesions in all the cases examined was minimal and seemed to have no relation to the regressive thyroid lesion observed.

Finally, hyperchromatic and pleomorphic alterations of the thyroid epithelial cells observed by these workers in this study, were not believed to be directly related to irradiation.

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DOSAGE DETERMINATION OF RADIOACTIVE IODINE

Werner and his group (30) were among the first to work out an accurate means of determining the dosage requirements for radioiodine 131. Although, at the present time, there is considerable variation from any single mode of calculation, still their work acted as a guide and aid for the practical use of the isotope.

At the start of their work, no adequate method of dosage planning was being used. There was no established standard for the determination of millicurie activity. Various laboratories showed large and varied discrepancies in the activities characterized as "one millicurie". This discrepancy did not stem from any conflict over the physical definition of the millicurie, but to the variation in the practical application of the instruments used and the absence of an authoritative control standardization bureau. L. D. Marinelli did much to improve this situation through the use of the ionization chamber measurement.

Determination of therapeutic dosages involved taking into account glandular uptake and subsequent gradual loss following this, as well as the amount of energy dissipated from the radioactive isotopes. Werner based his calculations on the fact that if a

relatively small organ would assimilate one microcurie in a uniform concentration and the isotope undergo total decay there, then the organ will receive a total radiation dose of 160 equivalent roentgens (e.r.). This dose will be reduced to about 120 e.r. in a toxic gland due to the gradual loss of the isotope. Earlier cases treated with the twelve-hour isotope appear to have received 2000 to 4000 e.r. When radiation is delivered more slowly, as in the eight-day isotope, the same effect can be duplicated only by increasing the total number of roentgens, thus a dose of 3000 to 5000 e.r. was deemed necessary, assuming a 60 gram thyroid, an uptake of 50 per cent of the administered material, and a gradual loss by elimination from the gland, a dose of about four millicuries would be calculated to deliver this radiation. Werner started treatment on all cases at this dosage regardless of gland size with the realization that differences in gland size, radioactive uptake would lead to large variations in the actual radiation received, and thus, an estimation of clinical response to various doses could be made.

Tracer doses were not always given in the earlier cases of advance therapy. However, at the present time, most clinics are using this method to get an idea of uptake and thus, adjust the dose. The radio-

active material was given by mouth, in water solution, the iodine being carrier free. The four millicurie dose contained only about 0.03 micrograms of iodine which is well below the normal daily intake of the element. However, recent investigations by Werner, Hamilton, and Nemith (29) observed the effects of repeated tracer doses on hyperthyroids in the absence of other therapy, have shown that these tracer doses can have a marked effect on the patient. In a series of twenty-nine patients who received diagnostic doses of radioiodine 131, eight of the patients experienced complete remission, three, partial recovery, and eighteen, no improvement. Of the six children used, four received complete remission. The conclusions reached from this study was that diagnostic doses of radioiodine have significant therapeutic effects in some hyperthyroid patients. Thus, the conclusions reached where some other agent or procedure was used in the treatment of hyperthyroidism and followed with tracer doses of radioiodine, must be reevaluated, such as in Boston where Hill, Reiss, Forsham and Thorne (13) used ACTH and cortisone followed with diagnostic doses of radioiodine for the treatment of hyperthyroidism and obtained clinical relief.

This study also emphasized the fact that hyperthyroid children tend to respond fairly consistently to

the lower levels of radioiodine therapy which would afford a simple and psychological non-taumatic method of therapy if the fear of cancer could be overcome. Clinical protection of the epiphysis of the cervical vertebrae would have to be guarded against in this type of treatment however.

Estimating the size of the gland prior to treatment was done by Werner (30) with the aid of plastic models of the thyroid. These ranged in size from twenty-five to one hundred grams. By palpation and comparison with the plastic models, size could be determined with the realization of the lack of accuracy of the method.

The radioiodine uptake of the gland was taken at given intervals by the Geiger counter at a definite distance (fifteen centimeters). By means of these measurements over several weeks, the biological half-life of the iodine in the gland was determined. This is the rate of decrease of radioactivity due to a combination of physical decay and physiological elimination and must be known for dosage calculation.

Urinary excretion was followed for 24 or 48 hours as a check and dosage was calculated by Werner according to the formula:

Equivalent roentgens=

$$\frac{\text{microcuries administered} \times \% \text{ uptake}}{\text{gms thyroid wt}} \times \frac{\text{biological half-life}}{8.0} \times 160$$

Miller and Sheline (22) at the University of California, in an effort to find an acceptable therapeutic dose of radioiodine in hyperthyroidism, used a series of eighty-eight patients where the dose was given as millicuries of orally administered radioiodine per estimated weight of thyroid tissue with no account taken as to the amount of uptake or effective half-life. They concluded that it took at least ninety microcuries per gram of thyroid tissue as an initial dose to obtain a remission, that no patient became hypothyroid with an initial dose of less than 130 microcuries per gram; that in some cases, a permanent remission was obtained between the above levels. Of those patients receiving less than 110 microcuries per gram, 90 per cent required further radioiodine therapy. Thus, in treatment of diffuse toxic goiter, Miller is using an initial dose of 120 microcuries of radioiodine per gram of thyroid tissue.

Hunt (15) found a variation of from 40 to 240 microcuries of radioiodine per gram of thyroid with an average of 120 microcuries per gram of gland. Remission was rarely obtained with less than fifty, and a below-

normal BMR was occasionally obtained with doses over 120 microcuries per gram. Thus, Hunt has standardized the initial dosage in diffuse toxic goiter at about 80 microcuries per gram and about 120 microcuries per gram in toxic nodular goiter.

As previously mentioned, errors in the thyroid uptake of radioiodine may be made by previous treatment with anti-thyroid drugs such as thiouracil, thus, wrong conclusions may be reached concerning thyroid activity with diagnostic doses of radioiodine. It is generally accepted that any anti-thyroid therapy be discontinued ten days or more prior to the isotope therapy in order to allow the dormant pituitary to respond with secretion of thyroid stimulating hormone and reactivate the thyroid.

Special knowledge and instruments are employed in use of radioisotopes in clinical practice. For detection and measurement, the Geiger-Mueller counter is the most common instrument in use. This instrument is not only used for standardization and assay of radioisotopes but also in determining dosage retained or excreted and for the detection of radioactivity of objects in contact with the isotopes.

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CLINICAL DATA ON TREATMENT OF RADIOIODINE WITH RADIOIODINE

H. B. Hunt (16), at the University of Nebraska Hospital, feels that diffuse toxic goiters, recurrent postoperative goiters, and small nodular goiters are best treated by radioiodine. At this clinic, therapeutic dosages are contraindicated in pregnant women because of the assimilation by the fetus, lactating mothers who are breast-feeding because of the secretion containing the isotope and in large, toxic nodular goiters because of the possibility of cancer, the increased amount of radioiodine needed to cause a remission and the slow response to treatment. Thyroids with single nodules, no matter what the size of the gland, should be resected for evaluation and treatment because of the high incidence of cancer.

Through 1950, Hunt (15) has treated sixty patients. Of these, forty-two patients had diffuse toxic goiter. Half of these had clinical remissions with decreased goiter size in two or three months following a single therapeutic dose. Of this group, two patients developed a mild hypothyroidism requiring thyroid extract.

Of the toxic nodular cases, determination of the therapeutic effect of radioiodine is not as clear cut because of associated conditions such as cardiac

conditions. Improvement in these cases require a longer period, up to five months with repeated doses, as a rule. However, significant hypothyroidism has not been seen even in those cases which require several treatments.

The evaluation of the sixty cases treated has shown no serious complications. A transient thyrotoxicosis may occur during the first few weeks following therapy. Irradiation breaking down the thyroid hormone released during treatment is the explanation of this. Anti-thyroid therapy of propylthiouracil following radioiodine treatment tends to relieve this. Hypothyroidism, as shown above, is a complication in a small percentage of the cases. These cases have all been treated effectively with thyroid extract. An increase in the severity of exopthalamus is no more frequent than those cases treated surgically.

Since 1950, the University of Nebraska clinic has treated thirty additional thyroid patients (excluding those who for some reason or other, no clinical evaluation could be made; such as death due to accidents, etc.). Seven of them were men and twenty-three, women. Four were from seventeen to twenty-one years of age, nineteen from twenty-one to fifty years of age, and seven, above fifty years of age. Of these patients,

thirteen had toxic nodular goiter and seventeen had diffuse toxic goiter. Clinical remission was noted in fifteen of the diffuse goiter cases. One patient with a psychic overlay is showing slow response and one patient showed remission, but failed to show improvement in an exopthalamus. The therapeutic response of the nodular goiters showed twelve of the thirteen patients with clinical remission. The remaining patient had received prior anti-thyroid medication with a consequent 60 per cent uptake of radioiodine and only one dose. One patient developed signs of hypothyroidism but is asymptomatic now with thyroid extract.

Werner (28) in collaboration with Quimby and Smith have reviewed their results in Presbyterian Hospital from 1946 to 1951 with the following results:

During the first two-year period, the patients received one or two doses within a three to four millicurie range. Of this group, two-thirds were in remission following one treatment, and about four-fifths following a second. No permanent hypothyroidism was noted.

A widened dosage range was used during 1948-49, and up to three therapeutic doses used as needed. Remission was noted in 90 per cent of the patients treated. However, about 7 per cent of the patients developed permanent hypothyroidism.

Currently, Werner has been using a dosage range of from two to twenty millicuries and, after three therapeutic doses, 70 per cent had clinical remission. Permanent hypothyroidism developed in 6 per cent. Many of the last-named group received anti-thyroid therapy to establish transient control during the latent period before the radioiodine therapy took effect. The lower remission percentage was felt due to the increased number of toxic nodular goiters treated.

The results suggested that a single dose of radioiodine 131 may be somewhat more effective than when followed immediately by such agents.

Werner has avoided, for the most part, the treatment of toxic nodular goiter because of the unreliability of response to the isotope, larger total dosage, and the possibility of substernal extension. He believes the possibility of missing a malignancy in the gland should not be given serious consideration as a contraindication in the use of radioiodine for it is statistically no greater than in toxic diffuse goiter (1 per cent in either case). The possibility of malignant change following euthyroidism due to the internal radiation, is a threat which Werner is taking into consideration, especially in lieu of the fact that larger therapeutic doses are necessary in this group.

In his treatment of thyrotoxicosis, Werner states that due to idiosyncrasies in individual patients it has been necessary to limit the dosage for the first and sometimes the second dose. Resistant glands are then treated with doses up to twenty millicuries of radioiodine.

Complications included 6 per cent hypothyroids, all of which obtained clinical relief with thyroid extract. Advancing eye signs were occasionally seen in treatment of malignant exopthalamus. Werner's group advise the use of small repeated doses, undue risk to the eyes can be avoided. They also found that heart failure may occur in a border-line compensation and, occasionally, a flare-up in toxicity may result.

Muscle cramps, acute thyroiditis, and psychotic changes are lesser changes which may occur following therapy.

Biopsies up to five years following treatment reveal cell destruction followed by fibrosis. No malignant changes have been noted.

Contraindications for the therapeutic use of radioiodine other than nodular goiter, according to Werner, are after the second month of pregnancy and the breast-feeding mother.

Chapman, Maloof and co-workers at the thyroid

clinic at Massachusetts General Hospital have published their results with the treatment of radioiodine for the last twelve years, the first two years of which patients were treated with the twelve-hour isotope, and the last ten years, with radioiodine 131. Since the early years, the age barrier has been somewhat less restricted due to the lessening of fear of a carcinogenic effect. Chapman in contrast to Hunt and Werner, will treat pregnant women up till the fourth month. However, Chapman does not feel the radioiodine 131 should be used therapeutically in the treatment of simple or multiple nodular goiter because of the high incidence of cancer in single nodules and the fact that multinodular goiter may diminish little in size following treatment and may also harbor a carcinoma.

This clinic advocates an initial dosage figure of 160 microcuries per gram of thyroid. This is based on an assumed average 48-hour retention of 70 per cent of the previous tracer dose. Six to twelve months are allowed before a second dose is administered which is usually as great or greater than the initial dose.

During the ten-year period, Chapman treated 400 patients, 305 of which responded to one dose and 50 responded to two to four doses. Nineteen of the patients still had toxic symptoms six months following

treatment; five were operated on after failure to respond; and twenty-one died of other causes.

In this group, myxadema developed in an average time of four to nine months following treatment in 8 per cent of the patients.

The Chapman group concluded that radioiodine 131 therapy is a slow biological response and the patient's ability to respond may occur over several months' span. They have found myxadema to occur many years after therapy. Thyroidal studies following treatment has revealed several patterns. The patient may become myxadematous, euthyroid, or persist in hyperthyroidism with the usual indicies. However, Chapman has found discrepancies in the indicies of function in two groups: First, in several apparently euthyroid patients with tracer doses under 20 per cent, serum PBI levels less than three micra per 100 milliliters and BMR's above negative 20; and secondly, in those patients who are toxic with a high serum PBI level and a high BMR but with a normal thyroidal uptake of radioiodine.

Of this group, forty-four have been studied histologically. Fibrosis and cellular damage resulting in bizarre nuclear forms have been noted; yet, some of the remaining follicles appear hyperplastic. No malignant change were noted.

Clark and Rule (5) treated 384 cases of hyperthyroidism with follow-ups of from six to sixty months. Two hundred and four were diffuse toxic glands and one hundred and eighty had nodular glands.

At the present time, they advocate an initial dose of 150 microcuries per gram of thyroid on patients under forty and approximately 250 microcuries per gram on those over forty with diffusely enlarged glands. Patients with nodular glands receive from 300 to 350 microcuries per gram. Four weeks are allowed before radiation therapy if the patient has been receiving anti-thyroid drugs.

Those patients receiving one or two doses obtained remission in 76 per cent of the cases. The remainder, except for one case, required three to seven doses. Eighty-five per cent of the patients had a satisfactory remission, while over thirteen per cent developed varying degrees of hypothyroidism, although only 1 per cent had permanent myxadema.

Of those treated who had exopthalamus, 19 per cent had complete regression and 58 per cent had varying degrees of improvement. Three cases developed a unilateral exopthalamus following treatment. Hypothyroidism and the above three cases were the only complications observed.

Clark advocates surgery for patients under forty years of age with uncomplicated primary or secondary hyperthyroidism and in those with solitary nodules.

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SUMMARY

1. In evaluation of thyroid activity and for treatment of thyrotoxicosis by radiation, radioiodine is an efficient treatment. Clinical remissions of hyperthyroidism obtained by radioiodine are comparable to those treated by sub-total thyroidectomy; furthermore, treatment can be applied readily to inoperable and recurrent cases.

2. The uptake of radioiodine is high in hyperthyroidism when it is needed and is low enough when thyroid function is normal, so that it is difficult to cause hypothyroidism if a normal gland is treated. The thyroid in Graves disease can concentrate about 10,000 times more radioiodine than any other tissue.

3. Nearly 85 per cent of the radioactivity of radioiodine is in the form of beta rays which travel less than two millimeters, tissue adjacent to the thyroid are not damaged.

4. Tracer doses prior to treatment are of great importance in determining the clinical activity of the thyroid, although previous thyroid treatment with antithyroid drugs may hamper accurate thyroid pick-up determinations.

5. Therapeutically radioiodine works best in

diffuse toxic goiter, postoperative recurrent goiters, inoperable thyrotoxicosis, and toxic multinodular goiter although, the latter requires increased dosages and treatment is generally prolonged over a longer period of time. Malignant exopthalamus proves to be no greater hazard with radioiodine than with surgery.

6. Radioiodine is contraindicated in nontoxic goiters, thyroids with single nodules, and in breast-feeding mothers. It is generally contraindicated in children and during pregnancy; although, some clinicians administer it during the early months.

7. Therapeutic doses of radioiodine cannot always be accurately determined. Patients tend to vary in response to a given dosage. Where one patient may respond with clinical remission to a particular dose, another may show definite signs of hypothyroidism. The final determination must be left up to the clinician.

8. Complications with radioiodine are relatively few, hypothyroidism being the main offender. Most patients developing this entity, however, are not permanent and the administration of thyroid extract usually corrects the condition. Occasionally, patients develop thyroid storm and increasing eye signs. A few patients fail to show any clinical improvement.

9. Histologically, the typical picture is

fibrosis and diffuse follicular atrophy following treatment with radioiodine. Although, occasionally bizarre nuclear forms are seen, no cases of primary malignancy developing from a thyroid treated with radioiodine have been reported.

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CONCLUSIONS

Since radioiodine was first described for its use in treatment of hyperthyroidism, great advances have been made both in the determination of its specific action on the thyroid gland and the diagnostic and therapeutic effect of its use.

Enough time has now elapsed that a fairly accurate clinical assay can be made and conclusions drawn as to its effect on the physical make-up of the individual.

Radioiodine is advantageous in that it is a form of internal radiation which is selectively absorbed by the thyroid gland. Thus, external complications which occasionally occur with external radiation as it passes through the skin and outer structures is considerably reduced.

The fact that the effective rays of the radioiodine are 85 per cent beta rays which have a very localized effect is advantageous in that the surrounding tissues are minimally effected.

It has proved to be an effective agent as an diagnostic aid and as the therapeutic agent in the treatment of diffuse toxic goiter, recurrent goiter, nonoperable thyrotoxicosis, and in many cases of multi-

nodular goiter. In the treatment of the above conditions, there has been no deleterious effects of the radioactivity on other body tissues or has there been any cases of primary cancer traced directly to the action of radioiodine.

Radioiodine has the added advantage of being convenient to the patient in the form of no hospitalization, little discomfort, and the relative cheapness of the treatment.

Radioiodine has several disadvantages which should be mentioned at this time. The effect of the isotope may be blocked by iodine given in various ways prior to therapy, as in iodine medication, in radiopaque materials or, more recently, in iodinated thioureas.

In nodular goiter, up to the present time, two other disadvantages must be considered in this type of treatment. The tendency to slow response even under large doses, and the failure to remove the nodules completely thus leaving the door open for carcinoma.

Even though there is no direct evidence at the present time that malignancy follows radioiodine treatment, still the histiologic response of the cell structure of the gland itself indicates that nuclear

changes are not always inconsistent with that of pre-cancerous changes, thus this form of therapy is still contraindicated in children.

Finally, there may still be difficulty in obtaining the isotope for treatment and its storage requires extreme care and adequate equipment.

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