Symposium on Radioiodine

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recognized then that a three months interval should be allowed to elapse before evaluating a given dose of iodine. Accordingly, he was treated a second time at this short interval. Three months later, his basal metabolism had fallen from +35 to +5% and he was playing semi-professional basketball.

In another three months, the patient's toxicity had obviously returned; but instead of a third course of therapy as would be given now, patient was referred for subtotal thyroidectomy, and has been well since. The long time needed to establish whether remission has been obtained is noteworthy.

SUMMARY OF THE REMARKS OF THE CHAIRMAN

Saul Hertz*

I suppose the privilege of being your chairman at this session was bestowed upon me because it was our original work in rabbits, performed in 1937 with Drs. Arthur Roberts and Robley D. Evans, which demonstrated the possible applications of radioactive iodine as a diagnostic tracer substance and as a therapeutic agent in the human species. I am grateful for the opportunity of taking an active part in these proceedings, and thank your program chairman.

The tracer studies in man, which were the basis for the therapeutic applications which you will hear described to you by our speakers today, were performed by Drs. John Lawrence, Joseph Hamilton and Mayo Soley, as well as by our Boston group, working at Massachusetts General Hospital and M.I.T. during the subsequent years of 1938-39-40. By 1941, we were in a position to embark upon a therapeutic program in patients with hyperthyroidism, since our early studies of the uptake of radioactive iodine by adenocarcinoma gave little encouragement.

The toxic goiter, however, revealed a most remarkable affinity for the radioactive iodine, and gave concentration factors which made therapeutic efficacy a virtual certainty. The safety and the desirability of treatment of patients devolved upon finding the appropriate dosage scheme, the assurance that no undesired effects upon other tissues than the goiter were produced, and the demonstration of no serious long-term effects upon the thyroid. We have come part way along this path. Your speakers are well equipped to detail this progress to us.

Dr. Earle M. Chapman is a former colleague of mine at the Massachusetts General Hospital in Boston. Our first series of patients was started in March 1941. Drs. Lawrence, Hamilton, and Soley treated a second, smaller series of cases in the fall of 1941 without the addition of stable iodine. By the spring meetings of the American Society of Clinical Investigation in 1942, Hertz and Roberts, as well as Hamilton and Lawrence, were able to report upon the successful therapeutic application of radioactive iodine in patients with hyperthyroidism. These experiences have been extended many fold in many places. Dr. Chapman followed our first series

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of cases during my absence from the program, occasioned by my service in the Medical Corps of the U.S. Navy. He also was able to treat an increasing number of patients with radioactive iodine as the sole therapeutic agent. When I^{131} became available from the chain-reacting uranium pile at Oak Ridge, following the war, many centers of activity in the therapeutic program came into being. Dr. Chapman will now tell us of his experiences in the use of both the cyclotron-produced I^{130} and the pile-produced material I^{131} in the treatment of patients with hyperthyroidism... [E.M. Chapman's paper]

Dr. Chapman has described to you, in most exemplary fashion, the satisfactory treatment of patients with radioactive iodine in rather large dosage without the addition of any other medication. This is excellent confirmation of Hertz' and Roberts' earlier therapeutic experiments. Since the M.I.T. cyclotron was built by funds contributed for this and other medical and biologic applications, Drs. Robley Evans and Chapman were able to continue the experiments during the war years. The efficacy of I^{131} has been attested to by several groups, including ours at Beth Israel Hospital in Boston.

We agree that a single dose of I^{131}, administered by mouth, may be effective in over 50% of the cases. The time interval for the full effect is between 6 and 12 weeks. In patients who are very ill, and in instances in which there are cardiac or other severe complications, we still favor the addition of stable iodide therapy after the radioactive dose, to cover this long period during which the hyperthyroidism may persist, in some degree, until the radiation has become fully effective.

Although previous treatment with iodides precludes immediate therapy with I^{131}, therapy with the thiourea derivatives may be followed by I^{131} after a waiting period of 3 to 5 days off the latter medication. It has also been our experience that propylthiouracil may be started 3 to 5 days after the I^{131}, as may iodide therapy, without materially decreasing the therapeutic concentration of I^{131} in the thyroid, as judged by external gamma-ray counting over the gland. Such counts and estimation of the urinary excretion of I^{131} during the period of 72 hours following the therapeutic dose continue to give us information, of an admittedly qualitative type, upon which to base our dosage schemes in relation to the efficacy of the clinical procedure used. We, therefore, have recommended their continued use.

Our next speaker, Dr. Mayo Soley, has come from a great distance to tell us of his group's part in these diagnostic and therapeutic developments. He has a slightly different approach to the problem of titrating the clinical dosage of I^{131}. He has employed fractional small dosage over an extended period of therapy. Dr. Soley will report upon the status of his first series of cases, treated in 1941, and upon a more recent series treated with I^{131}.

Among Dr. Soley's earlier contributions to the field was that of performance of satisfactory radioautographic studies with Drs. Eichorn and Hamilton. Those studies, of signal importance in establishing the anatomic distribution to the various portions of the thyroid, have been found useful in the study of cancer of the thyroid.

It was a comparison of the pattern

of uptake of I^{130} by the thyroid in patients with hyperthyroidism as Soley *et al.* determined with 14 mg carrier iodide, and that obtained by Hertz and Roberts using less than 2 mg carrier iodide, which re-emphasized the importance of limitation of the size of the carrier for both tracer and therapeutic purposes when utilizing radioactive iodine. With the increased availability of I^{131} in a carrier free state, it has been demonstrated that ideal circumstances are provided by the addition of no carrier.

Dr. Soley's studies on the radioactive iodine uptake of a variety of thyroid lesions by external gamma-ray technique have been repeatedly confirmed. The pattern of urinary excretion in these cases has also been abundantly verified.

He performed long-term experiments in animals indicating that doses of radioactive iodine, which were capable of total thyroid destruction and fibrosis, were not associated with toxic effects in other organs... [M.H. Soley's paper]

Dr. Soley's dosage levels take us back, indeed, to the spring of 1941, when we administered doses of 1 to 5 mc of I^{130} with trepidation. When these are compared to present day dosage in hyperthyroid cases, and to the enormous dosages of our speakers dealing with cancer of the thyroid, we are impressed with the acute or immediate safety of our procedure.

Dr. Soley's results indicate that patients can be effectively treated by his dosage schedule. In cases with complications we favor a more rapid dosage schedule, because of the latent period's dangers to the severely ill or complicated case. In young individuals without complications, the use of the minimal effective dose, arrived at by Dr. Soley's method, offers the obvious advantage of reducing any, slight though they be, dangers due to thyroid neoplasia in later life, which might be associated with this type of treatment. (I might mention in this connection that neither Dr. Chapman nor I have observed any thyroid neoplasia in the cases treated from 5 to 7 years ago with effective doses of radioactive iodine.) Dr. Soley's technique also has the advantage of decreasing the incidence of post I^{131} myxedema. Myxedema is the only undesirable sequel we have encountered in utilizing the single larger dosage levels.

As reported by Dr. Chapman, radiation sickness and thyroiditis have not been prominent with the larger or intermediate dosage which we have employed. The necessity of re-treatment becomes greater as the dosage is reduced, but there have been striking exceptions to this statement. In dealing with a biologic system, such as that involved in the radioactive iodine therapy of hyperthyroidism, it is expected of us to encounter these variations. It is unlikely that they ever will be entirely eliminated. However, it may be possible to correlate clinical dosage of I^{131} with careful standardization of tracer studies before the therapeutic dose is administered. It is also apparent that we are dependent, in this connection, upon a general acceptance of an ideally calibrated millicurie for I^{131}.

As brought out by Dr. Soley, the clinical determination of the thyroid size leaves us with a variable which is difficult of quantitative expression. Calculations of dosage on the basis of currently used formulas are, therefore, subject to this rather large error, expressed by Dr. Soley,

on the basis of his careful attempt to calibrate his fingers as calipers of thyroid size.

Our next speaker, Dr. Sydney C. Werner, has worked in collaboration with Dr. Edith Quimby. We heard this morning of their efforts to solve the problem of thyroid size by means of construction of a series of thyroid reference models. Dr. Werner has treated a considerable sized series of patients with I^{131} with dosage intermediate between the Boston and California techniques. Dr. Werner has applied tracer studies in certain diagnostic problem cases and in testing thyroid uptake in a variety of other endocrine conditions. His data are of special interest, but, unfortunately, because of limitation of time, we shall hear from Dr. Werner in concise manner, and shall have to read the details in his published manuscript...[S.C. Werner's paper]

COMMENTS

It is evident from the size and scope of this symposium on radioiodine that a veritable chain reaction was started by the early animal experiments. It is particularly gratifying to have heard of the multiple uses to which radioiodine has been applied in physiology, dynamic anatomy, and biochemistry of the thyroid. These studies serve as prototypes in the application of radioisotopes to other fields of study. Their applications to the study of thyroid cancer have been initiated. The importance of the biological data obtained in the cancer studies outweighs the therapeutic accomplishments.

I wish to re-emphasize the inverse relationship between the avidity of cancer cells and their neoplastic propensities. This, to my mind, is an important biological fact which has been accepted without any great attempt at analysis. The importance of having an accurately and readily obtained measure of the gradation of cells, from the normal state to various degrees of neoplasia, is that it provides a criterion of malignancy, apart from the notoriously inadequate histopathologic ones. The possibility of applying this measuring stick to controlled carcinogenesis experiments in animals impresses us as one of the most important approaches in the cancer field. Since it is possible to induce carcinogenesis of the thyroid by the Bielschowsky technique, we are confronted with an excellent set of experimental factors for analysis of the underlying process. An intimate study of the ways and means of inducing malignant cells to regain their iodine concentrating powers is a step in the direction of reverting those cells to normal. This line of endeavor has been receiving attention with the intent of promoting the uptake of radioiodine for therapeutic purpose. It is my belief that a non-radioactive approach to therapy may be inherent in such studies. The finding of such an anticarcinogenic substance for the thyroid will have a larger significance than radioactive iodine in thyroid cancer therapy.

The biochemical analysis of the fixation of iodide by thyroid cells has proceeded rapidly with the application of I^{131} in tracer experiments. The experiments reported by Dr. B. Skanse indicate a possible dissociation of thyroid stimulating hormone (T.S.H.), and thiourea effect upon this mechanism. Dr. Stanley's results in utilizing I^{131} in analysis of the action of antithyroidal drugs throw light on this aspect of the problem. The divorce between simple iodide uptake and thyroid hormone synthesis,

although suspected previously, may now be considered fairly well established. The existence of an enzyme (thyroxinase) for the elaboration of the thyroid hormone may be safely postulated. We interpret the data to date as being consistent with an excess of this enzyme in hyperthyroidism, and a loss of this enzyme in the malignant cell. Thiourea may be considered as a poison for that enzyme, whereas T.S.H. may be regarded as a catalyst for its action.

We have been disappointed in our attempts to use I^{131} uptakes or urinary excretion studies as aids in the diagnosis of borderline cases of hyperthyroidism. We have failed to correlate a high uptake or low urinary excretion with the borderline degrees of hyperthyroidism. We have seen the existence of high uptakes in certain goiter cases without associated hyperfunction. In this field, it appears to us that the determination of the rate of turnover into protein-bound iodine in the blood, after tracer doses of I^{131}, would be of greater significance in the detection of hypersecretion from the thyroid gland. It does not appeal to us as logical to paralyze this function in order to test its presence in increased degree. Hyperplasia *per se* is not significant of hyperfunction in the sense of increased thyroid hormone production. It is difficult, therefore, to assign any degree of reliance to the suggested tests for borderline hyperthyroidism based upon inorganic iodide uptake by the gland.

Those investigators who reported the use of doses of 100-300 mc of I^{131} to thyroid cancer cases have done great service to us who are using the minute dosage of I^{131}, by comparison, in our cases of hyperthyroidism. Their toxicity studies and organ distribution studies are of the utmost importance in indicating the high degree of safety at our dosage level to organs outside the thyroid. It remains now for us to be certain that our therapy is not productive of thyroid neoplasia over a period of 20 years. The calculations cited by Dr. Chapman and made by Dr. Robley D. Evans are reassuring on this point.

At this time, it would appear that I^{131} therapy is indicated in all complicated cases, in most cases which have failed to respond to thiourea derivatives, to previous operation, or who refuse either surgery or long and careful observation over periods of a year or more without certainty of remission of their disease even after such trials.

Fortunately, in most pregnant patients with hyperthyroidism, it is possible to carry the patient through with medical measures and to administer I^{131} after delivery. Dr. Chapman's data indicate that early in pregnancy, I^{131} treatment can be carried out safely and successfully.

Since we have had normal offspring of both mothers and fathers who have been treated by current doses of I^{130} and I^{131}, it seems unlikely that the grave warnings which have been uttered concerning the effects of radioactivity on fertility or genes are to be regarded seriously in this connection.

We have satisfied ourselves, by tracer studies in male and female, that the uptake by ovary and testis is of such a small magnitude that we have more to fear from the ordinary gastrointestinal X-ray study of the human, than from the use of radioactive iodine in the treatment of hyperthyroidism.

Despite all of this discussion,

we still insist that patients be individualized with respect to choice of therapy for their hyperthyroidism. Each method of therapy continues to teach us something of fundamental importance with regard to the thyroid. None of the methods should replace the other as yet, but we can offer a guess that I^{131} will increase in its application for this purpose, unless a specific corrective of the metabolic disturbance of hyperthyroidism appears which is simpler, more rapid in its effect, or more physiologic in its approach. Since I^{131} is not as yet generally available, and its use requires the technical knowledge and devices for accurate dosimetry, this method of treatment is restricted to institutions equipped to carry it out in a safe manner. The Atomic Energy Commission has been helpful in fostering the project to its present state of development. It can be expected that in the future an efficient method of distribution of I^{131} for therapy of cases of hyperthyroidism will be worked out, as the method proves its safety and superiority in indicated cases. With cooperation of this type, the method can be expected to be effective, economic of patients' time, doctors' energies, and institutional beds, funds, and resources. Its wider application will depend upon the training of personnel such as you at Brookhaven Laboratory and other Atomic Energy Commission installations are providing...