autumn, a single month providing 5 per cent of the infections. Controlling paving roads and runways and ultimately the use of highly refined oil on athletic areas were important dust control measures. This control reduced infection rates from one half to two thirds.

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ABSTRACT OF DISCUSSION
Dr. Russell V. Lee, San Francisco: Dr. Smith and his associates know more about coccidioidomycosis than any one else, and this work with the Army Air Forces and Ground Forces was a most remarkable piece of combined epidemiology and curative medicine. They surveyed every man and every important military area, important because is exactly in the training fields for the Army Air Forces were located within the area where coccidioidomycosis is prevalent. Dr. Smith was of great help in outlining the problems which might be encountered, and one type threatened to be a considerable menace. It was shown in the paper that dust control could remarkably reduce the incidence of the disease in an area where, left alone, in a year or two the incidence of infection would increase remarkably, and after a number of years' residence in the area we practically 100 per cent uninfected with coccidioidomycosis. While the mortality was very low, it was the principal cause of hospitalization in many of the Air Force hospitals in that southwest area, so that anything that can be done to reduce it under such circumstances should be done. The incidence under military conditions, particularly under air conditions, was very high. The airplane propeller picks up a lot of dust; soldiers around camps and marching in physical training, they get a lot of dust, and they have become infected at a terrific rate. There was a hospital at San Benito where about one fourth of the men of one detachment were hospitalized and thus saved from going back to this exceedingly dusty region right in the middle of the season of highest incidence. This has lessons for civilian application. This whole desert area has been outlined now largely by the work of Dr. Smith. He can draw a very accurate line around the endemic area of coccidioidomycosis. It is a much larger area than was ever dreamed of before, and when certain types of activities are going to be carried out in that area certain precautions will have to be adopted to protect against coccidioidomycosis. For instance, we had Negro troops in that area, and the Negro is many times more susceptible to coccidioidomycosis than the white. Negroes should be kept out of that area and the dusty occupations there. It is definitely a hazard for them, judging by the army experience there. In due time there is going to come from Dr. Smith's work the most comprehensive, complete definition of the clinical features as well as the epidemiologic features of coccidioidomycosis. The knowledge of this disease is exactly 50 years old, but in the last five years the whole thing has crystallized. Papers and monographs undoubtedly will appear shortly as a result of this army experience, and this disease is going to be defined with a precision with which it has never been defined before.

Postwar Malaria.—In continental United States civilian malaria in the aggregate is at an all time low; there has been little change in the past five years. Available data show a marked decrease in malaria rates among continental military personnel since 1941, but in these figures is reflected the extensive control programs in military areas. The cyclic upswing predicted for the early forties by some malariologists has not occurred. In the past two decades reported malaria mortality and morbidity have dropped 85 per cent and 70 per cent respectively.—Hollis, Mark D.: Postwar Malaria Control in Continental United States, J. Nat. Malaria Soc., June 1946.

RADIOACTIVE IODINE THERAPY

Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

S. M. Seidlin, M.D.
L. D. Marinelli, M.A.
and
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New York

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocarcinoma of the thyroid, the primary site together with its immediate extensions is conventionally treated by surgery, radiation or both. Distant metastases, if treated, are usually subjected to palliative external irradiation. This paper is a report of successful therapy of a case of metastatic adenocarcinoma of the thyroid treated by the principle of specific internal irradiation with radioactive iodine.

The earliest study of the uptake of radioactive iodine in 2 cases of carcinoma was reported by Hamilton and his associates in 1940. In 1942 he described 2 more cases in which tracer doses of radioactive iodine had been given to the patients prior to the removal of carcinomatous thyroid. Radioautographs of the excised glands showed no significant deposition of the radioactive iodine in malignant areas in any of these cases.

In April 1942, Keston, Ball, Frantz and Palmer reported the first positive evidence of pickup of the radioactive iodine by a metastasis from a carcinoma of the thyroid. In a patient with multiple lesions, Geiger counter measurements showed appreciable uptake of radioactive iodine in only one of the metastases. Subsequently, from the autopsy, these authors reported that "the bulk of the metastatic tissue was undifferentiated. The metastasis which showed consistent uptake of iodine was the only one which grossly resembled thyroid tissue and which, microscopically, showed chiefly well differentiated tumor."

Leiter, Seidlin, Marinelli and Baumann in a report of 2 cases (1 of which is the subject of the present paper) of hyperthyroidism due to adenocarcinoma of the thyroid and to functioning metastases showed that the effect of thiouracil on the basal metabolic rate, plasma cholesterol, blood iodine and excretion of radioactive iodine in these patients was in every respect...

From the Medical Division and Department of Medical Physics of the Montefiore Hospital and the Physics Department of the Memorial Hospital.

A preliminary report of this work was presented at the Clinical Research Meeting of the New York Academy of Medicine on May 16, 1943.

Aided by grants from the Dazian Foundation for Medical Research and from the Lederle Laboratories to Dr. S. M. Seidlin at Montefiore Hospital.

The cooperation of the staffs of the Massachusetts Institute of Technology and Washington University cyclotrons and of Dr. R. D. Evans made this work possible.

Dr. Louis Leiter, Chief of the Medical Division of Montefiore Hospital, gave valuable assistance throughout this work, as did Dr. David Marine and Dr. S. H. Rosen in the field of thyroid pathology and Dr. E. J. Baumann in iodine chemistry. Dr. Solomon Fineman reviewed the routine programs. Valuable technical assistance was rendered by Elizabeth E. Poct, Ruth Hill, Gertrude Ross, Luella Tuill and Dr. A. A. Yalow.


Dr. A. A. Yalow.


Dr. A. A. Yalow.
similar to the response already described in the literature on ordinary thyrotoxicosis or hyperthyroidism. This indicates that thiouracil suppresses hormone production by functioning metabolites from adenocarcinoma of the thyroid as readily as it inhibits this process in the hyperplastic thyroid of ordinary hyperthyroidism.

Since physiologically the thyroid cell, normal or malignant, cannot distinguish between inert and radioactive iodine, we are utilizing the normal affinity of this cell for iodine as a method of "selective irradiation" of a type of carcinoma of the thyroid. We now report the results of three years' study of the therapeutic effect of radioactive iodine in 1 case of metastatic carcinoma of the thyroid, in which all demonstrable metastases were shown to pick up radioactive iodine.

Radioactive iodine, as used in this and similar studies, consists of a mixture, in varying proportions, of two isotopes, I\(^{131}\), half life 126.6 hours, and I\(^{131}\), half life 8.0 days, prepared in a cyclotron by the bombardment of tellurium with deuterons. These two isotopes are chemically identical with stable iodine and cannot be separated by ordinary chemical or physiologic methods and processes. Both I\(^{131}\) and I\(^{131}\) emit beta rays (high speed electrons) which cause intense ionization within a few millimeters of tissue, as well as gamma rays which cause a negligible amount of ionization within the body and are sufficiently penetrating to be detected readily by an external Geiger counter.

**REPORT OF CASE**

**Observations Prior to Radioactive Iodine Therapy.**—Thyroidectomy: B. B., a man aged 81, had in 1923, at the age of 39, undergone a thyroidectomy because of substernal goiter. There was no history of relieved pain and pressure symptoms on the trachea. He had no thyrotoxicosis. The histologic diagnosis was "malignant adenoma."

Pathologic Report: The pathologic report gave a gross description of three pieces of tissue received. The first one measured 5 by 5 by 3 cm. It was firm in consistency, and the cut section showed a fairly dense central core of connective tissue. No cystic or hemorrhagic areas were observed. The outer portion of the section disclosed a brownish yellow semipurulent material. The remaining two pieces of tissue were relatively the same in general structure but averaged about 2.5 cm. in thickness.

On microscopic examination, sections of the goiter showed no normal structures. Sections of tissue revealed definite fibrous change and there was an abundant pinkish hyaline-like stroma manifesting cell formation. There was a definite, highly atypical epithelial overgrowth which showed abundant growth and a tendency toward cord formation. In these areas no acini resembling the normal were seen. The nuclei of the cells took a rich blue stain. The growth showed no definite capsule surrounding it. Areas showing cartilage formation were present. No hemorrhage or infection was observed.

Recurrence and Laminectomy: Postoperatively there were few symptoms of hypothyroidism. The patient was in apparent good health for fifteen years. Then he developed palpitation, nervousness, loss of weight and signs typical of hyperthyroidism. In addition, severe pains developed in the lower back and radiated down the legs. On examination at another hospital in October 1939, a small pulsating tumor was found in the midline of the back at the level of the twelfth thoracic vertebra. Visualization by injection of diodrast showed the tumor to be extratral and extraosseous. Roentgenograms of the skeleton revealed no osseous lesions. The basal metabolic rate was +40 per cent. A larnectomy was performed in November 1939. The tumor proved to be a metastatic carcinoma of the thyroid (fig. 1).

The histologic report revealed that the slide showed several large ragged fragments of tissue, one of which contained suspicious nodules of bone and consisted of irregular cellular areas formed by broad hyalinized stroma bands. The general pattern was the same in all portions and consisted of irregular, often elongated, closely packed follicles with infoldings of the lining epithelium which varied from cuboidal to low columnar. There was no well formed stroma. Traces of glandular colloid-like material were present in some follicles. In some areas the follicles appeared to have atrophied leaving the hyalinized-like bands previously mentioned. There were large areas of necrosis and some foci of hemorrhage. No mitosis was seen.

The nuclei were fairly regular, dark and vesicular. The diagnosis was metastatic adenocarcinoma of the thyroid.

**Treatment and Course:** A thyroid crisis developed postoperatively. A few weeks later an exploratory operation was performed in the region of the thyroid and no thyroid tissue, normal or malignant, was found. Because of continuing pain, physiotherapy was given to the patient. In the next two years the symptoms and signs of hyperthyroidism increased. In December 1941 the basal metabolic rate was +45 per cent. In addition, roentgen ray films of the lungs revealed "numerous circular deposits in the lower lobe on the left side and in the cardiohepatic angle on the right side, strongly suspicions of metastatic lesions." There was also radiographic evidence of destruction of the right upper femur (1.0 by 2.0 cm.) and the second rib on the left side. A gastrointestinal roentgenologic series was negative. A film of the pelvis taken at this time was reported negative for metastases, but our subsequent review (1946) of the plate revealed a small area (0.6 by 1.8 cm.) of early destructive changes in the inner border of the left ilium, above the acetabulum, just below the inframes isthidiaca major.

From December 1941 to February 1942 high voltage

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7. Courtesy of H. L. Jaffe, Hospital for Joint Diseases.

8. The slide was reviewed by Dr. David Marine.
Radioactive Iodine Therapy.—Observations at Hospitalization and Administration to Montefiore Hospital on April 20, 1942, the patient still had symptoms of pain in the lower part of the spine, in addition to the previously mentioned symptoms of hyperthyroidism.

The physical examination showed a rather small, emaciated, poorly developed man, aged 48, weight 38 Kg and height 146 cm; he was hypometabolic, his blood pressure was 126 mm. of mercury systolic and 50 diastolic; his pulse rate was 100 to 110. There were no eye signs. There was a thyroidectomy scar in the neck, and no thyroid tissue was palpable. The heart was normal except for tachycardia. The lungs were clear. There was a laminitomy scar and tenderness over the dorsolumbar spine. The eye grounds were normal. The skin was warm, and there was a coarse tremor of the hands. The basal metabolic rate on May 7, 1942 was +36 per cent. The plasma cholesterol about this time was 114 mg. per hundred cubic centimeters and the blood iodine soon thereafter was 11.9 micrograms per hundred cubic centimeters.

Other laboratory examinations revealed nothing of special significance. The blood chemistry tests showed calcium, 10.3 mg., and phosphorus, 3.9 mg. per hundred cubic centimeters; phosphatase (alkaline) 12.2 Bodansky units; total serum protein, 6.7 Gm.; serum albumin, 3.2 Gm.; serum globulin, 3.5 Gm., and uric acid, 3.9 mg. per hundred cubic centimeters. The Wassermann and Kahn tests were negative; the blood count was within normal limits. Urinalysis was negative. The Ewald test showed free hydrochloric acid, none; combined acid 20 per cent.

A roentgenologic examination of the chest on April 25, 1942 revealed several rounded shadows suggestive of metastases in the lower lobe of the left lung; an extensive destructive lesion (5 cm. long) which involved the lateral and posterior aspect of the second rib on the left side; a circumscribed shadow (3.2 by 1.1 cm.) in the left intracavicular region, which seemingly arose from the involved rib and represented a soft tissue mass. A picture of the dorsolumbar spine on Nov. 10, 1942 disclosed evidence of laminectomy; the spinous processes of the eleventh and twelfth thoracic vertebrae and the first lumbar vertebra were missing, and osteoporosis involved all the vertebrae. The pelvis was slightly deformed; the area of bone absorption (0.6 by 2.3 cm.) along the medial aspect of the left ilium above the acetabulum. The femurs on Oct. 29, 1942 presented a small area (larger than in films of December 1941) of bone absorption in the cortex of the right femur just below the lesser trochanter.

In view of the evident hyperthyroidism, iodine as Lugol's solution was administered every day in doses varying from 1 to 6 cc., from June 13, 1942 to March 8, 1943.

As shown in figure 2, a mild remission in the hyperthyroidism occurred in response to the iodine therapy. By January 1943, iodine given as Lugol's solution in doses of 3 to 4 cc. a day lost its effectiveness even in regard to the hyperthyroidism itself, and its continued administration produced little further improvement.

The lesions of the bone continued to grow, and pain persisted. Another course of roentgen therapy was instituted as follows: right upper femur, 5,200 r; through two fields, and left pelvis, 1,955 r; through two fields. There was no relief of pain.

Administration of Radioactive Iodine: In March 1943 a tracer dose of radioactive iodine was given intravenously in the form of sodium iodide in water. This method of administration has been used for all doses. Geiger counter measurements revealed iodine retention by all the known lesions plus two previously unsuspected ones (fig. 3); one in the skull and one, not evident in the roentgenograms, located in the region of the ischium. During the taking of Geiger counter measurements, the patient asked that the counter be placed on the right parietal part of his head, for, he stated, there is a pain there which is "not a headache." Surprisingly, the counter registered the uptake of radioactive iodine. A subsequent roentgenogram (May 18, 1943) of the skull was reported as disclosing a fairly sharply circumscribed area of bone rarefaction (3.7 by 3.5 cm.) in the right posterior parietal region. At this time, the study of radioactive iodine uptake in the neck was made, and no evidence of residual functioning thyroid tissue could be established (see later comment). Due to technical difficulties, no attempt was made to study the radioactive iodine content of the lung metastases reported by the roentgen ray diagnostic department.

Measurements on urine after several tracer doses revealed that the patient excreted a relatively small amount (30 per cent to 40 per cent) of the tracer dose over a seventy-two to ninety-six hour period. The first course of radioactive iodine therapy, a total of 102 millicuries of the 12.6 hour isotope (118) and 20.5 millicuries of the 8 day isotope (123I), was administered between May and August, 1943 (see the accompanying table). The estimated radiation dose to the tumors was 10,000 equivalent r, whereas that for the bone was 70 equivalent r.

Since this course was administered in fractions of varying potency, it was possible to determine the effect of the different radiation doses on the leukocyte count. The 123I had no

9. Radiation dosages in this paper refer to tumor doses exclusively. Tumors were determined from roentgenograms; data used here were obtained from Roth, R. and Raider, L.: Radiation Therapy of Carcinoma of the Thyroid, Radiology 44: 516-514 (June) 1945 and a personal communication from Dr. Roth.


11. This dose and the following therapeutic doses are calculated on the basis of an effective tumor volume of 312 cc. (vole infra) and on the basis of 1 r (1 r refers to radioactive iodine without specifying the isotope) retained; that is, that administered minus that excreted in the urine. The possible change in the effective tumor volume with time has been neglected. It would have been preferable, and is planned in the future to estimate tumor dose by actual measurement with radioactive isotopes, Am. J. Roentgenol. 47: 210-216 (Feb.) 1942.

12. Equivalent roentgens as used herein are defined and discussed in Maue, J. D.; Dosage Determinations with Radioactive Isotopes, Am. J. Roentgenol. 44: 516-514 (June) 1945.
significant effect while the $1^{131}$ had a considerable, though temporary, depressing influence (fig. 2). The expanded curve, figure 4, shows that after one dose of 40 millicuries of $1^{131}$ the white blood cell count dropped from 5,150 to 2,900 in one week. The blood count returned to normal in ten days even though another dose of 35 millicuries of $1^{131}$ was given while the count was low.

The resulting improvement in the patient's clinical picture was definite in the course of the next few months. By November 1943 the pains diminished, the basal metabolic rate dropped from an average level of above $+35$ per cent to about $+20$ per cent, the patient gained about 7 Kg. in weight and roentgenographically there was no demonstrable growth of the metastases.

Biopsy: On Nov. 6, 1943, a dissection biopsy of the metastasis in the second rib on the left side was performed by Dr. A. H. Avenues. In order to obtain a radioautograph of this lesion and to ascertain the radioactive iodine concentration in the tumor tissue, a large tracer dose of $1^{131}$ (5 millicuries) was administered eight days before the operation. To remove the tumor in general on the second rib on the left side it was necessary to perform a scapula-mobilizing incision, with

From these figures and from the total urinary excretion up to the time of the biopsy it is possible to calculate the apparent tumor weight in the patient, assuming that the iodine concentration is uniform throughout the metastases and that no appreciable radioactive iodine is present in nontumorous tissues. This value is 312 Gm. It is interesting to note at this point that an independent calculation of the tumor volume based on the contour of the metastases in the roentgen ray film agrees with the above value.

A comparison of the biopsy tissue (figs. 5 and 9) with a section of the tissue removed on laminectomy in October 1939 (fig. 1) revealed close similarity.

Pathologic Report: The pathologic report was as follows: On macroscopic examination the fresh specimen was an oval mass measuring 7.5 by 4.3 by 2.5 cm. and weighing 41.9 Gm. It was enclosed in a grayish white capsule about 0.5 cm. thick on the surface of which there were, in places, some fibrofatty tissue and muscle. Attached to the capsule on one surface there was a piece of rib measuring 3.5 cm. in length to which was attached some fragments of muscle and fascia. The mass was moderately soft, rather rubbery in consistency. On section, the tissue presented a mottled appearance, predomi-

Complete Tabulation of $I^{131}$ Administered

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<th>Date</th>
<th>Week</th>
<th>Carrier (mg)</th>
<th>Radioactive Iodine (mc)</th>
<th>Isotope</th>
<th>Excretion, per Cent. p. c. at Hours</th>
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* $I^{131}$ refers to radioactive iodine without specifying the isotope.  
1. Tr. indicates a tracer dose.

icision through the muscles of the posterior chest wall. The postoperative course was uneventful, and the patient made an excellent recovery.

Several radioautographs of the biopsy specimen were obtained by following in this technic already described by Hamilton. Figure 6 shows a representative radioautograph and figure 7 is the cosin and hematoxylin stained section from which it was made. A superimposition of these two photographs is shown in figure 8. A detailed comparison between radioautographs and photomicrographs shows specific localization of the radioactive iodine within the regions of viable thyroid tumor cells.

The total iodine content per gram of dry tissue of the biopsy specimen was 0.192 mg. with a thyroxin fraction of 17.4 per cent.

The radioactive iodine content of the tumor tissue at the time of the biopsy was determined on four separate fresh specimens, weighing 0.28, 0.17, 1.49 and 2.05 Gm., respectively. The results were 0.18, 0.16, 0.19 and 0.20 per cent of the administered dose per gram of wet tissue. 

13. This composite photograph was made by John M. Walke of the Physics Department of Memorial Hospital.
14. Dr. Albert Keaton made an independent determination on two of the specimens.

Incidentally pale brownish with small and larger irregular dark red areas of congestion and hemorrhage, small translucent gray and yellowish foci and a few small, opaque, yellowish areas, probably of necrosis. Some thin grayish white strands of fibrous tissue could be seen running through the mass. The portion of rib attached to the mass was invaded on its adherent surface by tumor similar to and continuous with that of the mass, and fine bony spicules could be palpated in the latter for a distance of 1 cm. or more from the rib.

Microscopic examination revealed that the specimen consisted of sections of the tumor fixed in solution of formaldehyde and in Orth's solution and of decalcified portions of the tumor which included invaded rib. The tumor was surrounded by a thick capsule of dense fibrous tissue covered by fibrofatty tissue containing striated muscle fibers as well as some nerves and thickened arteries. The muscle fibers showed considerable atrophy and degeneration. Occasional focal infiltrations of small round cells were seen. The rather extensive hemorrhage in the capsule and surrounding tissue was probably largely traumatic. There was slight invasion of the capsule by tumor in a few places. In all sections the central two thirds or more of the tumor showed
were empty or contained some red blood corpuscles and fibrin-like material, a considerable number contained a homogeneous colloid-like material which took a pale pink stain. In some areas the follicles were closely packed and separated only by narrow strands of connective tissue which contained many thin-walled sinusoidal-like vascular channels, frequently engorged. In other areas the connective tissue septums were widened by edema and hemorrhage so that the follicles became widely separated. In still other areas there was appreciable fibrosis with atrophy of follicles; the fibrous tissue was cellular in some foci and partly hyalinized in others. Numerous hematoidin crystals were present in areas of recent hemorrhage. A few spicules of bone, some of them necrotic, were seen deep within the tumor.

Sections taken through rib and adjacent tumor showed invasion of the bone by tumor with replacement of the narrow by a loose connective tissue. There was active formation of new bone, usually by apposition on old trabeculae, together with a lesser degree of osseous destruction. Spicules of bone

were seen deep within the tumor itself; some of them were new bone arising from connective tissue septums. Similar new bone formation from connective tissue was seen in one place in the capsule.

The diagnosis was metastatic thyroid adenocarcinoma of the differentiated small follicle type.15

Subsequent Treatment and Course: From Jan. 23 to Feb. 21, 1944, the patient was submitted to a course of treatment with thiouracil. This was done to check further on the functional nature of the metastases. The thiouracil therapy produced a striking remission of the hyperthyroidism, which, however, promptly recurred after the treatment was discontinued. The effect of thiouracil on the objective criteria of hyperthyroidism is shown in figure 2.

By the end of April 1944 the patient's condition had reached what might be called a state of equilibrium. His weight remained unchanged for two months at the level of 48 Kg., with basal metabolic rate at about +10 per cent and the

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15. Dr. S. H. Rosen and Dr. David Marine.
plasma cholesterol level between 200 and 214 mg. per hundred cubic centimeters. The blood iodine on March 24 was 9.4 micrograms per hundred cubic centimeters. Roentgenograms taken on April 21, 1944, showed no detectable changes in the various metastases. The second therapeutic dose of radioactive iodine, 55.4 millicuries of the eight day isotope, was administered on April 28, 1944. Twenty-seven per cent of this dose (13.8 millicuries) was extracted from a twenty-one hour urine collection and readministered on April 29. A second fraction from urine was obtained later (6.3 millicuries) and readministered on April 30. Thus a total of 75.5 millicuries was administered within three days, giving a radiation dose of 15,200 equivalent r to the tumor and 64 equivalent r to the blood. The white blood cell count showed only a slight temporary fall from 6,000 to 4,500, which, in our opinion, was not significant. The basal metabolic rate dropped to zero in about three weeks and remained at about this level until March 1945. The plasma cholesterol fluctuated from a level of about 200 mg. per hundred cubic centimeters to a somewhat higher level. The blood iodine level dropped to 6.5 micrograms on June 10, 1944, to 4.7 micrograms on Oct. 7, 1944 and to 5.1 micrograms per hundred cubic centimeters on Feb. 8, 1945. The patient's weight began to rise about three weeks after the administration of the therapeutic dose of radioactive iodine and continued to rise steadily from 48 Kg. in April 1944 to 53 Kg. in January 1945. Shortly after this second therapeutic dose of radioactive iodine a temporary sharply circumscribed alopecia appeared over the area corresponding to the skull metastasis. The patient's general well-being improved, his pains diminished, his locomotion improved, and he complained of getting fat. Roentgenograms on Aug. 19, 1944 and Feb. 6, 1945 showed no change.

Fig. 6.—Roentgenograph of an entire unstained section of metastatic tumor in second rib on the left side with magnification slightly reduced from 8 times, showing distribution of radioactive iodine in the viable tissue.

Fig. 7.—Photomicrograph of section used for figure 6 stained with eosin and hematoxylin, same magnification. Note viable (dark) and necrotic (light) areas.

Fig. 8.—Photograph of figures 6 and 7 superimposed, showing coincidence of radioactive iodine distribution with the viable tumor.

From Feb. 8 to 25, 1945, the patient was given intramuscular injections of thyrotropic factor (Armour's: Rowlands-Parkers' units per cubic centimeter). The injections were given in divided doses every one or two days for a total of 33 cc. in eighteen days. During this interval of treatment there was no rise in the basal metabolic rate, no significant change in plasma cholesterol and a slight fall in blood iodine (from

COMMENT

Adenocarcinoma of the thyroid is generally considered highly radioresistant. H. F. Hare\textsuperscript{19} specifically stated that alveolar carcinoma of the thyroid is not changed histologically by 6,000 r (x-ray). For a successfully treated patient (his case 2) Hare gives the dimensions of the tumor and the interstitial radon dose employed. Calculations show the gamma ray dose to be close to 20,000 r, a value well beyond the reach of external radiation.

\textsuperscript{16} Dr. F. J. Baumann, Chemistry Department, Montefiore Hospital, developed a procedure for extracting iodine from urine so that it could be fed to the patient in the form of sodium iodide. This technique was utilized whenever the amount of I\textsuperscript{131} involved warranted it. The efficiency of recovery was consistently high, 80 to 95 per cent.

\textsuperscript{17} Determinations were made on young guinea pigs weighing 200 Gm., using total weight of thyroid gland and degree of hyperplasia as criteria. Extraction of thyrotropic hormone from the urine followed the method described by Jones, M. S.: Study of Thyrotrophic Hormone in Clinical States. Endocrinology 24: 655-651 (May) 1939.


\textsuperscript{19} Hare, H. F.: Radiation Treatment of Carcinoma of the Thyroid. Am. J. Roentgenol. 40: 451-453 (Oct.) 1941.
Since 1 microcurie of 8 day iodine destroyed per gram of tissue gives approximately 150 equivalent r,\textsuperscript{29} to achieve comparable dosage we must concentrate at least 133 microcuries in each cubic centimeter of tumor, if turnover is assumed to be zero. For our patient, with approximately 300 cc. of tumor tissue, such a dose would require that 40 millicuries of I\textsuperscript{131} be fixed in the tumors. The actual amount to be fed, however, may be several times this amount, because of the loss of iodine by excretion and by deposition in other tissues, especially if normal thyroid tissue is present.

In addition to these rough quantitative considerations, criteria of a biologic nature, such as the time factor and lack of irradiation of the tumor bed beyond a few millimeters, must be considered in comparing the results of 8 day iodine beta ray therapy with those of 3.82 day radon gamma ray therapy. These remain to be assessed on the basis of additional experience.

Over a period of three years, our patient has received nearly 40,000 equivalent r to each of his tumors. In spite of the remarkable clinical improvement, it cannot be concluded that the functioning tumors have been completely destroyed because recent tracer studies, although showing a marked increase in excretion, still show localization of radioactive iodine in the lesions. Further therapy is indicated and is being planned, the limiting factor being the availability of the isotope in sufficient quantity. The criterion for completion of I\textsuperscript{*} therapy will be the lack of radioactive iodine pickup by any of the known metastases, although the possibility remains that the tumors, even in the absence of any uptake, will not be completely destroyed.

All available roentgenograms taken of this patient since July 1939 were reviewed recently in order to evaluate as precisely as possible the progress of the various skeletal lesions. Between July and October of 1939, films were made of the spine, pelvis, skull, arms, legs and left femur. At this time all the regions were negative for metastases. In November 1939, the extra-osseous metastatic tumor in the back was removed. By 1941 there were early lesions in the right femur, right ileum and chest as described in the case history. These lesions increased in size, and the one in the skull was discovered in 1943. Frequent plates were taken of all these regions from 1942 until the present, and they show that there was no increase in the area of bone destruction in any region after the first therapeutic dose of I\textsuperscript{*} was administered in 1943. Representative films showing the progress of three of the lesions are shown in figures 10, 11 and 12.

The urinary excretion of radioactive iodine was followed after almost every dose, tracer or therapeutic; on several occasions the collection period was longer than a month. As an illustration, the data obtained after the dose of Aug. 5, 1943, is shown in figure 13. Plotted on semilogarithmic paper, the curve shows two distinct, consecutive rates of change in daily excretion, the break occurring three days after administration. In the same figure a second curve is shown which represents the daily excretion of radioactive iodine by this patient soon after the cessation of thioauracil therapy. The data as a whole seem consistent with the hypothesis that in both instances the excretion of radioactive iodine within three days of administration is governed by a mechanism different from the one which governs its excretion thereafter.

The concentration of radioactive iodine in the blood as a function of time was studied in order to gain information of physiologic and radiologic significance. Shown in figure 14 is a composite curve obtained after the administration of the last two therapeutic doses of radioactive iodine (April 28, 1944; March 3, 1945). The individual determinations pertaining to each study are shown in detail. The data of Frantz and her associates\textsuperscript{*} are also shown for comparison. From the curve it is seen that the level of I\textsuperscript{*} in the blood

\textsuperscript{29} A complete description of experimental methods and calculations will be given in a companion paper now in preparation.
remains essentially constant for a considerable period after the first day. An analysis of the detailed data obtained on this particular patient indicates that the curve represents three different phases: a rapid initial turnover (about twenty-four hours) which is succeeded by a stabilized level of one week's duration, and finally, a slow but steady decline.

Many authors have reported significant drops in the white blood count after the administration of radioactive isotopes other than iodine. Our experience with large doses of radioactive iodine shows that with this element the effects on the white blood cells are not pronounced and are short-lived. A drop in total leukocytes with no significant variation in the differential was observed after the administration of large amounts of I\textsuperscript{125} but not after the use of I\textsuperscript{131}, although the total blood dosages were comparable in magnitude. However, since radiation from the 12.6 hour isotope is delivered almost entirely within two days, whereas from the 8 day isotope nearly the same proportion is delivered within thirty-two days, we must infer that the time factor is mainly responsible for the previously stated results. This is analogous to many other radiobiologic phenomena such as erythema production with single and fractional roentgen therapy, in which time is an important factor.

It is logical to assume that the effect of this factor on tumor tissue will be in the same direction as it is on the blood. Therefore, consideration of the time blood dose as the 8 day isotope before there could be a question about the advisability of the use of I\textsuperscript{131} in preference to I\textsuperscript{125}. This remains to be determined.

In earlier studies\textsuperscript{22} of thyroid–iodine metabolism by the use of I\textsuperscript{131} it was shown that irrespective of the total amount of iodine administered, the hyperactive gland initially retains more I\textsuperscript{131} than the normal gland but loses it faster. The rate of loss seems to increase with larger amounts of carrier iodine.

With this in mind as well as with the purpose of determining ultimately the actual radiation dose deliv-

\textsuperscript{21} Calculated on the basis of the experimental curve of concentration of the \textsuperscript{131}I in the blood and a net tumor elimination rate of 0.5 per cent per day.

eled to the tumors, the I* turnover in the lesions was studied by means of suitable Geiger-Mueller counters under reproducible geometric conditions. This was done several times between May and August 1943, as well as ten months and one year after the third therapeutic dose. Unfortunately, the 1943 measurements—due to circumstances partially beyond our control—cannot be interpreted without making some assumptions. The only thing that can be said is that several days after the administration of a tracer dose of I* the activity of all the lesions, when corrected for decay of 8 day iodine, disclosed the elimination of about 0.5 per cent of the dose per day. This observation per se cannot be interpreted as a demonstration that the tumor tissue metabolized I* at the rate of normal thyroid tissue, although this was our impression. The latest data (1946), figures 15 and 16, taken much more accurately, show a rapid loss of I* in the two lesions studied when 40 micrograms of carrier iodine was administered. With the larger amount of carrier iodine, the rate of loss was not as great, in study. The readings over the thyroid region were two to three times the readings taken over the lateral surface, of the right calf but consistently less than readings obtained over the apex of the right lung, although both regions were free from metastases. A comparison with 2 nonthyroidecetized patients under similar conditions of dosage and excretion showed that iodine pickup in this patient’s thyroid region was only 4 per cent and 6 per cent, respectively, of the iodine pickup in the thyroid regions of the other 2 patients.

While the evidence presented herein shows clearly that there was little activity over the thyroid region, it might be argued that since this activity was greater than that obtained over the calf, the existence of some residual thyroid tissue cannot be ruled out. However, the presence of functioning metastases in the neighborhood of the thyroid region will cause some scattered gamma radiation to enter the instrument. No similar condition exists in the region of the calf, which was first used as a control. But when, with this in mind, we chose as a control region the apex of the right lung—analogously situated with respect to the neighboring functioning metastases, but containing none—we obtained readings even greater than those in the thyroid region by 15 to 30 per cent.

The foregoing, in our opinion, is presumptive evidence that there is no functioning thyroid tissue in proportion. We are unable to interpret these data in the light of published works on the turnover of I* in the thyroid itself.

Owing to the unusual nature of this case, that is, hyperthyroidism despite total thyroidecotomy, the procedure and results of our studies of radioactivity over the region of the original thyroid as well as over the metastases may be of interest.

The experimental setup and the theoretic considerations will be described in detail in another paper. It suffices to state here that the Geiger counter is shielded with a 3/4 inch (1.91 cm.) thickness of lead and provided with a suitable window. The activity of any lesion or region is obtained by taking the difference between readings with the window open and those with the window plugged with a 3/4 inch (1.91 cm.) thickness of lead. This method greatly facilitates the localization of radioactive iodine in contiguous lesions.

The counter readings over the thyroid area were on the average only 5 per cent of the readings obtained over the metastasis of the skull. This percentage did not change materially throughout the course of the the neck and confirms the previous surgical observations.

It is pertinent to mention that 4 cases of metastatic carcinoma of the thyroid without clinical hyperthyroidism have been studied with radioactive iodine and have shown selective localization in the lesions. Two of these are now under treatment with I*.
SUMMARY

A case of metastatic adenocarcinoma of the thyroid is reported in which treatment by means of radioactive iodine has been successful. The patient was completely thyroidec tomized for "malignant adenoma" in 1923, with neither thyrotoxicosis then nor hypothyroidism postoperatively; fifteen years later there developed classic symptoms of hyperthyroidism and severe pain in the lower back. In October 1939 a pulsating tumor removed from the level of the twelfth thoracic vertebra proved to be metastatic thyroid adenocarcinoma (histologically well differentiated, with small follicles and colloid). In the next two years hyperthyroidism increased and roentgenograms revealed new metastases in the lungs, upper part of the right femur, second rib on the left side, left ileum and skull. Roentgeno logic irradiation of the metastases proved ineffectual.

In March 1943 a tracer dose of radioactive iodine revealed iodine retention by all the known lesions and no evidence of residual thyroid tissue in the neck. Therapeutic amounts of radioactive iodine were adminis tered orally between May and October 1943. Definite and lasting clinical improvement followed. In April 1944 and March 1945 additional 1* was administered with a resultant disappearance of pain, increase in weight and progressive change in all clinical criteria in the direction of hypothyroidism. Roentgenographic evidence pointed to an arrest if not a regression of the disease. No untoward effects followed this therapy.

Radioactive iodine seems to be an effective therapeutic agent in the control of this type of tumor.

Fundamental Research and the Rh Factor.—The fundamental basis for the recognition of the Rh factor was laid in 1900 when three important discoveries were made. First, the mendelian laws of heredity, published thirty-five years previously, were independently rediscovered by Correns, Thetemak and de Vries. Second, in the same year Landsteiner discovered the phenomenon of normal isoagglutination as the basis of the four blood groups, and in the next year he mentioned their significance in the selection of donors for transfusion. Third, and of more immediate importance, Ehrlich and Morgenroth discovered the phenomenon of isoimmunization, which they demonstrated in goat blood and which other workers later demonstrated in many species.—Levine, Philip, M.D.: The Present Status of the Rh Factor, Am. J. Clin. Path. October 1946.

TREATMENT OF EARLY SYphilIS WITH CALCIUM PENICILLIN-OIL-BEEsWAX

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The early development and progress in the production of a suspension of calcium penicillin in beeswax and peanut oil has already been reported. The initial successful clinical results in the treatment of gonorrhea by a single injection of this mixture suggested its use for the treatment of syphilis. It should be emphasized that the primary purpose of this paper is to illustrate an ambulatory method of therapy whereby the patient receives one injection of penicillin instead of the usual eight injections a day.

This study was initiated in August 1944. Since then 75 patients with early syphilis have been treated, of whom 22 were men and 3 women. The ages varied from 18 to 44. There were 37 white and 38 Negro patients. Fifty-six had primary syphilis, of whom only 6 were seronegative, while the remaining 19 had secondary syphilis. All patients were subjected to serologic examination prior to institution of treatment. Dark field examinations gave positive results in 73 patients. The remaining 2 gave a history of having had a penile lesion followed by the development of a generalized eruption and had persistent strongly positive serologic reactions for syphilis, but dark field examinations were not made. Before treatment 31 patients with primary syphilis and 16 with secondary syphilis had an examination of the spinal fluid, which included cell count, Kolmer complement fixation, total protein, globulin and colloidal gold tests. The 31 patients with primary syphilis had normal spinal fluids, while 4 of the 16 with secondary syphilis had abnormal spinal fluids.

The treatment consisted of the daily intramuscular (buttock, deltoid or triceps) administration of 300,000 units of calcium penicillin in beeswax and peanut oil for eight days. Of the first 14 patients treated, 2 received 100,000 units three times a day, 2 received 150,000 units twice a day and 10 received 300,000 units in 2 or 3 cc. once a day. The remaining 61 patients received 300,000 units in 1 cc. The total number of Oxford units for all patients was 2,400,000 which is comparable to the...