BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 22 1952

THE INDICATIONS FOR RADIO-IODINE TREATMENT OF THYROID CARCINOMA

BY

E. E. POCHIN, M.D., F.R.C.P.
N. B. MYANT, D.M.

GWEN HILTON, M.B., B.S., F.F.R.
A. J. HONOUR

AND

B. D. CORBETT, B.A.

(From the Department of Clinical Research, University College Hospital Medical School, London)

Bases of Selection

Certain thyroid carcinomata resemble normal thyroid tissue in having the capacity to concentrate iodine. Since radioactive iodine is chemically indistinguishable from normal iodine, such tumours will selectively concentrate radio-iodine. They may therefore be selectively irradiated by the intense local beta radiation which is emitted from radio-iodine. If the local concentration and retention of radio-iodine in the tumour is high enough relative to that in other body tissues, the local radiation within the tumour may be great enough to cause its destruction, without causing fatal or toxic effects in the body as a whole. In principle, therefore, the selection of cases for such treatment is simple. Complete surgical excision remains, of course, the treatment of choice if ever it is possible (Dobyns, 1951); otherwise, radio-iodine should be used to treat any thyroid carcinoma which can be shown, or can be induced, to take up radio-iodine sufficiently.

In practice, this criterion is complicated by several considerations. First, the detection of radio-iodine uptake, and the judgment of its adequacy, may be difficult, particularly if the tumour is adjacent to normal thyroid tissue and if repeated biopsies cannot conveniently be made. Secondly, uptake may be demonstrable after total thyroidectomy in a tumour in which no uptake could be detected before the thyroid was removed. It may therefore be necessary to select for thyroid ablation* those cases in which uptake cannot be shown but is likely to be demonstrable after thyroidectomy. This decision will be based on such indirect evidence as the histological differentiation of the tumour and perhaps its rate of growth. In such cases tests for uptake are repeated after thyroid ablation, and radio-iodine treatment is started if adequate retention can be demonstrated.

The most direct evidence of radio-iodine uptake in a tumour is obtained by examination of biopsy material, using methods which are discussed later. These biopsy methods, however, are often inadequate for the selection of cases for radio-iodine therapy, since repeated tests may be required for the uptake in one or in various metastases, and following thyroidectomy or other pro-

cedures designed to reveal or stimulate uptake, or during the course of treatment. Since frequent biopsies of carcinomatous tissue are rarely desirable, and even single biopsies of some metastases—for example, in lung or bone—may be impracticable, the study of radio-iodine uptake will commonly depend on methods of external counting, by which the localization of radio-iodine is detected with a counter external to the body.

In the following account the detection of radio-iodine uptake in thyroid tumours by biopsy and by external counting is illustrated; and the criteria used in selecting cases for thyroid ablation and for radio-iodine treatment are then discussed.

Radioactivity of Biopsy Material

If a test dose of radio-iodine is given, and tumour tissue is removed several days later, the selective concentration of radio-iodine by the tumour may be inferred by comparing the radioactivity per gramme of its tissue with that per gramme of, say, plasma removed at the same time. The radioactivities are readily compared by placing the samples at a known distance from a gamma-radiation counter, or, if greater sensitivity is required, by "liquid counting" of tissue extracts (Dobyns and Maloof, 1951). The ratio is useful as indicating whether the metastasis examined has any capacity to concentrate and retain radio-iodine. It does not estimate the relative doses of radiation that tumour and plasma would receive during radio-iodine therapy, since the plasma will usually receive its heaviest irradiation during the first day after the radio-iodine dose, which is then circulating as iodide; whereas the iodine-concentrating tumour will receive most of its irradiation in later days, from organically combined radio-iodine.

If the tumour radio-iodine concentration at, say, four days after the dose is many times the low value to be expected in the plasma, the tumour can be regarded as retaining iodine and as possibly suitable for radio-iodine treatment. If, however, the tumour concentration is about equal to that in plasma the tumour either does not concentrate iodine and is unsuitable for treatment or, possibly, as in a case discussed below, the tumour may concentrate but not retain the iodine. The latter type of case, which might be suitable for radio-iodine therapy, could be missed if the biopsy was made after an interval which was optimal in most other cases.

*"Thyroid ablation" is used to cover the destruction of all normal thyroid tissue either surgically or by therapeutic doses of radio-iodine.

In this respect daily external counts may therefore be more valuable than observations at biopsy on a particular day.

If tumour tissue is removed from the thyroid gland or from an adjacent area radio-iodine may be present in the material examined owing to inclusion of small remnants of normal thyroid tissue (Dobyns and Maloof, 1951) and be misinterpreted as indicating uptake in the tumour.

In a case of "Hashimoto's thyroiditis" the large, hard, and bulky gland had led to a tentative diagnosis of carcinoma. Four days after a test dose of radio-iodine a sample of tissue regarded as carcinomatous lymph node was removed from the posterior triangle of the neck and was found to be considerably more radioactive than a sample of muscle removed at the same time. Autoradiograms from this tissue, however, showed the radio-iodine to be present in islets of normal thyroid tissue displaced into the lateral cervical region by the growth of lymphadenoid tissue.

An autoradiogram is therefore likely to give more reliable information than simple radioactivity determinations on tissue removed from the neck. It will also give evidence of the homogeneity of any radio-iodine uptake, and so of the uniformity of radiation to be expected.

Autoradiograms on Biopsy Material

The autoradiograms obtained from thyroid carcinomata have been discussed in detail by several authors (Dobyns and Lennon, 1948; Fitzgerald and Foote, 1949; Marinelli *et al.*, 1947; Rawson, Skanse, *et al.*, 1948), who have shown that iodine concentration occurs most commonly in well-differentiated tumours and particularly if colloid-filled follicles are present, or in those areas of an adenopapillomatous carcinoma in which such follicles occur. It has, however, been emphasized repeatedly that uptake is not always correlated with these or other histological structures. An autoradiogram may therefore be valuable in demonstrating the uptake that sometimes occurs in undifferentiated tumours of the thyroid. It can give direct evidence that a tumour, or at least the metastasis examined, may be suitable for radio-iodine treatment, although it will give no exact basis for calculating the radiation dose to be expected.

A negative autoradiogram should not be taken to exclude good prospects from treatment unless an adequately large test dose has been given, and the following calculation suggests that several millicuries may be required.

Radio-iodine treatment would certainly be worth giving for any tumour which would receive 5,000 r of beta radiation from a 100-mc. oral dose. But a radio-iodine autoradiogram would normally become positive only if the tumour retained an average of about 1 $\mu\text{c.}$ per ml.; and tissue retaining 1 $\mu\text{c.}$ of I^{131} per ml. will receive a total of about 150 r of beta radiation. But all tumours which will receive 150 r or more, and therefore give a positive autoradiogram, from a 3-mc. test dose should, on a proportionate basis, receive 5,000 r or more from a 100-mc. therapy dose. This calculation is inexact in several ways. It suggests, however, that a tumour which may respond to radio-iodine therapy will not necessarily give a positive autoradiogram after a test dose of only 1 or 2 mc.

The corresponding test dose could be very much smaller if the metastasis were remote from the thyroid, so that it was unnecessary to use an autoradiogram to show that any uptake observed was in the tumour and not in normal thyroid tissue contained within the biopsy material. With a test dose of only 150 $\mu\text{c.}$, 1 g. of a tumour removed at biopsy and of the activity considered above would contain 0.05 $\mu\text{c.}$, which could be readily measured by a gamma counter. Liquid counting of an extract from this weight of tissue would determine accurately a content of 0.004 $\mu\text{c.}$, which would be achieved with an even smaller test dose of 12 $\mu\text{c.}$

It is evident that autoradiography will give valuable evidence in the selection of cases for radio-iodine treatment, provided that an adequate test dose of several millicuries is

given; and much smaller test doses can be used if an autoradiogram is unnecessary. In many cases, however, this direct evidence may be unobtainable because of difficulties in biopsy or serial biopsy, or possibly because of rapid discharge of iodine from the tumour; and selection of cases may then depend upon external counting methods. These methods have great practical value throughout the investigation of thyroid carcinomata and are always essential in the control of treatment.

External Counting

Since its gamma radiations penetrate body tissues freely, radio-iodine within the body can be detected by a counter external to the body; and its localization within the body can be examined if the counter is suitably shielded so as to receive radiations from certain known directions only.

Two such types of shielding are found to be useful. If the counter is surrounded by a cylindrical lead shield which is open at one end only (Fig. 1), this open end can be placed on or over the body surface at any point, and the counter used to determine the amount of radio-isotope underlying the surface at that point (Corbett and Honour, 1951).

In this way a chart may be constructed showing the distribution of radio-iodine in any body region (Pochin, 1950; Coliez *et al.*, 1951). This method, which may be described as "local counting," has been widely used in exploring the body for iodine-concentrating metastases (Frantz *et al.*, 1944; Dobyns and Lennon, 1948; Seidlin *et al.*, 1949; Pochin, 1950; Green *et al.*, 1951).

FIG. 1.—Counter shielding applicable to "local counting."

FIG. 2.—"Profile counter" arrangement, indicating profile distribution observed in a case of thyroid carcinoma, with peaks of uptake corresponding to bladder, stomach, carcinoma tissue in the neck, and salivary glands. Case 17.

Alternatively, the counter may be shielded by lead plates on each side of it and used to estimate the distribution of radio-iodine along the length of the body. By making counts with such a counter at different positions down the anterior midline of the body (Fig. 2) a diagram can be constructed showing the radio-iodine content of the tissues at each level examined. The diagram gives a "profile" of radio-iodine distribution down the body which may be of considerable value in detecting and following uptake in metastases (Pochin, 1950; Dobyns and Maloof, 1951).

The procedures of "local counting" and "profile counting" have somewhat different uses. An iodine-concentrating area in the body will often be detected with greater sensitivity and efficiency by the profile method, and the affected tissue or organ then be identified by local counting over the suspected area and, if necessary, with a larger test dose. Subsequent variations in the radio-iodine content of the tissue so localized will, however, often be more accurately measured by the further use of profiles than by local counting, since the counting rates measured with any highly directional local counter depend critically on the exact position and orientation of the counter relative to the body, which are less easily controlled than with a profile counter.

Metastases Remote from any Iodine-concentrating Tissues

When a metastasis is remote from the thyroid or from any other tissue in which iodine is normally concentrated, either counting procedure is likely to give clear evidence of uptake in any tumour in which the uptake is adequate to allow effective radio-iodine treatment. Thus, a metastasis comprising only 2 g. of tumour tissue with enough uptake to receive 5,000 r from a 100-mc. dose would be readily detected by a gamma-radiation counter 20 cm. from it after a test dose of 1 mc., if it was remote from other iodine-concentrating tissue. The problem in external counting is, in fact, usually one of *discrimination* rather than of *detection* of sites of radio-iodine concentration. Difficulty may, however, arise with very small metastases or in detecting weak uptake which is insufficient to allow immediate treatment yet might indicate the value of further treatment designed to increase such uptake.

Usually in such cases the concentration of radio-iodine may be identified by comparing counts over the tumour with those at surrounding points or on the opposite side of the body. Over a large metastasis in the femoral neck from a thyroid carcinoma, however, we have observed counts between 1.7 and 3 times those over adjacent areas or over the opposite femur. Since other metastases in this patient (Case 18) showed no radio-iodine concentration at biopsy, however, it seemed likely that the slightly raised counts over the femur were due to the increased size and perhaps vascularity produced in the thigh by the metastasis.

Metastases Adjacent to Iodine-concentrating Tissue

Greater difficulties arise when the tumour lies near tissue which normally concentrates iodine, and a familiarity with the sites and times of such normal concentration is essential in the diagnosis of uptake in tumours.

When radio-iodine is given as iodide it normally circulates in the blood stream for two or three days, its concentration decreasing as it is progressively removed by the thyroid and kidneys. In myxoedema or in renal failure this initial phase of circulating radio-iodide may be demonstrable for up to six days, whereas in thyrotoxicosis it is usually completed within 12 hours. During this phase the kidneys and bladder will contain radioactive urine, and the bladder content of radio-iodine is regularly demonstrable by suitable counting methods. Since the gastric juice and saliva contain iodide in high concentration relative to the plasma, the stomach and salivary glands are also radioactive. The gastric concentration is commonly demonstrable during this iodide phase, even after an intravenous dose. The radio-iodine in salivary glands is usually detectable at the same period only in myxoedema, since otherwise the radio-iodine in the adjacent thyroid prevents the weaker salivary uptake from being discriminated. The radio-iodine content of the milk of a lactating breast would also usually be detectable.

Within a few days of an oral or intravenous dose almost all the administered radio-iodine will have entered the thyroid or been excreted in the urine. After this time, renal, gastric, or salivary

uptake continues only at a very much lower rate, depending upon the recirculation of small quantities of radio-iodine that have completed the metabolic iodine cycle. These small amounts are not usually detectable, but might give difficulty in cases with rapid iodine recirculation. Normally, however, by a few days after the dose radio-iodine can be detected only in thyroid tissue or in such thyroid tumours as concentrate and retain iodine. As, however, at this stage thyroxine containing radioactive iodine is being released by the thyroid, any site of high thyroxine concentration may become detectable by external counting. The liver appears to be readily detectable in this way (Pochin, 1950) provided that the blood radiothyroxine content is high enough. This occurs commonly after a few days in hyperthyroid subjects, but we have rarely seen it in normal subjects with present methods of examination, and then only a week or more after the dose. It is possible, however, that in patients with functioning thyroid tumours the liver radiothyroxine content may be detectable by external counting and be mistaken for uptake in pulmonary or other metastases at this level. The radio-iodine content of the liver may also be conspicuous during destruction of the thyroid gland by radio-iodine, when organically bound radio-iodine is being discharged rapidly into the circulation.

In tumours adjacent to the bladder, kidneys, stomach, or salivary glands, therefore, any radio-iodine uptake that occurs may be difficult to detect in the first few days after the dose but will usually be evident thereafter. In tumours adjacent to the liver, uncertainty will occur only if organically bound iodine is being discharged rapidly from the thyroid, as may be established by plasma samples. In tumours adjacent to the thyroid, however, the difficulties are always greater, since normal thyroid tissue takes up iodine rapidly and retains it for long periods.

Metastases Close to the Thyroid

In some patients with tumour tissue only in or adjacent to the thyroid, the detection of uptake may prove impracticable by external counting. In such cases local counting may indeed show that the normal uptake of a thyroid lobe invaded by tumour is much reduced, and indicate that the tumour does not concentrate iodine with an efficiency approaching that of thyroid tissue. Slight remaining activity in the lobe may, however, be due to some remaining thyroid tissue or to weak tumour uptake. The distinction between these two possibilities is important in the selection of cases for treatment, yet cannot usually be made by external counting.

Occasionally, however, local counting may be useful in showing that the distribution of radio-iodine in the neck closely follows the outline of tissue masses regarded as being neoplastic. This result may be due simply to generalized expansion of the thyroid—for example, in thyroiditis—but if the masses are shown to be carcinomatous by biopsy it may give a strong indication that they concentrate radio-iodine (Fig. 3). Normally, however, in any tumour adjacent to the thyroid, uptake can be tested adequately only after total thyroid ablation, which is in any case a necessary step if radio-iodine treatment is attempted.

FIG. 3.—Outline of palpable carcinomatous mass in neck (continuous line) and corresponding contours (interrupted lines) indicating underlying concentrations of radio-iodine. Case 3.

FIG. 4.—Areas of radio-iodine concentration in the neck: February, 1952, before thyroid ablation, indicating uptake in both thyroid lobes, but not in metastasized lymph nodes; April, 1952, after thyroid ablation, uptake in glands now being apparent. Case 8.

FIG. 5.—Areas of radio-iodine concentration in the neck: November, 1950, before thyroid ablation, suggesting uptake in remaining left thyroid lobe but not in right-sided mass deep to sternomastoid; April, 1952, after thyroid ablation, uptake now evident in right-sided mass and probably also in mediastinal glands. Case 5.

Effects of Thyroid Ablation

As has been mentioned, radio-iodine uptake in a thyroid carcinoma may only become demonstrable after all normal thyroid tissue is removed from the body. This might be due to any of several causes:

(1) The amount of isotope concentrated by the tumour will be greater when it is competing for radio-iodine against the kidneys alone, and not against kidneys and the normal thyroid. The uptake will normally be about doubled after thyroid ablation owing to this effect.

(2) The detection of weak uptake is technically simpler if no site of strong uptake such as thyroid tissue is adjacent. This is a most important consideration with metastases in the neck, and, except with heavily shielded counters, may sometimes apply in the case of mediastinal or pulmonary metastases.

(3) In certain cases the capacity of the tumour to concentrate iodine seemed to develop only after thyroid ablation; or in other cases to have increased under these circumstances (Rawson, Marinelli, *et al.*, 1948; Rawson *et al.*, 1949; Dobyns and Maloof, 1951).

Thyroid ablation has been of value in revealing or inducing iodine uptake for the first time in five of our cases of thyroid carcinoma. In three, uptake then became demonstrable in metastasized glands at the angle of the jaw (Cases 8 (Fig. 4) and 9) or below the sternomastoid (Case 5, Fig. 5); while in two other patients uptake could be detected in mediastinal (Case 6, Fig. 6) or pulmonary (Case 4, Fig. 7) metastases.

The cases are quoted to show the practical necessity for thyroid ablation in detecting cases which may be suitable for radio-iodine treatment.

They do not prove that uptake in the tumour was induced or increased, rather than simply revealed, by thyroidectomy. This important distinction may be made when, after thyroid ablation, the tumour uptake increases progressively (Rawson, Marinelli, *et al.*, 1948). It could be systematically examined if the plasma radio-iodide clearance rate of the tumour or of a metastasis is measured before and after a thyroid ablation, and this has not been reported. Some estimate, can, however, be made, if the renal clearance for

FIG. 6.—Profiles showing: before thyroid ablation (crosses), uptake in thyroid region only; after radio-iodine ablation (dots), clear uptake corresponding in position to mediastinal mass. Case 6.

FIG. 7.—Profiles showing: before thyroid ablation (open circles), uptake in thyroid region only; after thyroidectomy (dots), clear uptake corresponding to pulmonary metastases as well as to remaining thyroid tissue in neck. Case 4.

iodide is assumed to be unchanged, or is estimated, before and after ablation; and if the tumour uptake is compared with the proportion of the dose initially excreted in the urine (Dobyns and Maloof, 1951).

Frequency of Demonstrable Uptake

The frequency of radio-iodine uptake may be illustrated by the findings in 27 patients examined by these methods in the last four years (Table I). Only those cases are

TABLE I.—Radio-iodine Uptake in Tumour Demonstrated Before and After Thyroid Ablation

Histological Type	Case No.	Before Ablation	Thyroid Ablation Effected by	After Ablation	Plasma Conc'n.† %/l.
Adenocarcinoma	1	Clear	Surgery	Clear	2.2
Papillary adenocarcinoma	2	None	Not attempted	—	0.3
	3	Probable	Radio-iodine	None	—
	4	None	"	Clear	—
	5	"	"	Probable	0.3
	6	"	"	Clear	0.7
	7	"	Not attempted	—	—
	8	"*	Radio-iodine	Clear	0.5
Adenocarcinoma becoming anaplastic	9	"	"	"	0.8
	10	"	Not completed	—	0.03
	11	"	Not attempted	—	—
	12	"*	Not completed	—	—
Papillary carcinoma, some follicles	13	Clear	Surgery	Clear	0.05
	14	None	Radio-iodine	None	0.1
	15	"	"	"	0.1
	16	Probable	"	Probable	0.6
Anaplastic, some follicles	17	Probable	Radio-iodine	Probable	0.5
	18	None	"	None	0.06
	19	"	Not attempted	—	0.6
Anaplastic	20	"	"	—	—
	21	"	"	—	—
	22	Probable	Seen too late	—	—
	23	None	Radio-iodine	None	—
	24	"	"	—	—
	25	Not seen	Surgery	Probable	0.02
	26	None	Not attempted	—	—
	27	"	Seen too late	—	0.05

* Metastasized cervical glands became tender and reduced in size following the ablation dose of radio-iodine.

† The plasma concentration indicates the maximum or limiting concentration of protein-bound radio-iodine, in % of the dose per litre, reached after doses given early in the treatment. With effective treatment the concentrations so attained fall progressively with successive doses.

included in which the tumour structure has been examined histologically from the primary or at least one metastasis, and has indicated malignant disease consistent with a thyroid carcinoma. All patients so diagnosed have been included except two who have been seen only recently. Table I indicates the histological type of carcinoma, the type of any thyroid ablation performed, and whether radio-iodine uptake was observed in the tumour by external counting methods either before or after ablation.

It will be seen that in the 26 cases examined before thyroid ablation radio-iodine uptake was clearly demonstrable in two and was probable but not certain in four more. In the remaining 20 no uptake could be demonstrated at this stage, although in seven there were metastases remote from the thyroid. The thyroid was then ablated, surgically or by radio-iodine, in five of the patients in whom uptake had been proved or suspected, and in 10 of those without demonstrable uptake; and it had already been removed before the first examination of a further case. After ablation in these 16 patients, or during subsequent radio-iodine therapy, conclusive evidence of uptake was obtained by counting methods in a total of six cases, with probable uptake in four more; uptake was indicated in one further case (No. 12) by considerable tenderness and reduction in size of enlarged submental glands during radio-iodine ablation; and in at least one other case the absence of uptake after ablation was associated with a diminution in the tumour mass and may have been due to tumour destruction.

Radio-iodine uptake has thus occurred in at least a quarter of all patients and probably in over one-third. Of patients with mainly differentiated tumours examined

after ablation, uptake has been demonstrable in over one-half with certainty and probably in about three-quarters (Table II).

TABLE II

Group	Radio-iodine Uptake				Proved or Probable
	Proved	Probable	Not Shown	Total	
All tumours seen	7	6	14	27	48%
All differentiated tumours	7	3	6	16	62%
All differentiated tumours after ablation	6	2	3	11	73%

These frequencies cannot be taken as representative of all thyroid carcinomata, since many of our patients were sent for investigation on the understanding that histologically differentiated tumours were most suitable for treatment; and uptake has been demonstrated less frequently in other series of cases (Frantz *et al.*, 1948; Dargent *et al.*, 1950; Paterson, 1950; Dobyns and Maloof, 1951; Green *et al.*, 1951; Rawson *et al.*, 1951—but see Marinelli *et al.*, 1947; Seidlin *et al.*, 1949; Coliez *et al.*, 1951). On the other hand, several patients with differentiated tumours might have shown uptake if examined after thyroid ablation.

It seems clear that a significant proportion, at least of differentiated thyroid carcinomata, can be shown to concentrate radio-iodine to a useful degree, and particularly if normal thyroid tissue is first ablated.

Evidence of Tumour Function from Plasma Radio-iodine Concentration

Thyroid carcinomata rarely liberate enough thyroxine to cause clinically evident thyrotoxicosis. In one of our patients (Case 1) the large and multiple pulmonary metastases of highly functional tissue did cause a typical thyrotoxicosis, which was abolished after radio-iodine destruction of tumour tissue (Pochin, 1950). This degree of activity is, however, too unusual to be of value in diagnosing iodine uptake in a tumour. A more sensitive test may be based upon the rate with which protein-bound radio-iodine accumulates in the plasma after a dose of radio-iodine. Its concentration usually rises during the first few days to a "plateau" value of which the height probably indicates the rate of thyroxine production in the body (Pochin, 1950). Seidlin *et al.* (1951) observe that in cases of thyroid carcinoma the value attained has some correlation with function in the tumour. This relationship is evident from Table I, the three highest values occurring in patients with iodine-concentrating tumours. The correlation, however, is not exact, since at least one of our cases with clear although probably transient uptake, and a good response to treatment, has shown a low plateau value (Case 13). It seems probable, however, that useful indications of the presence of functioning tumour tissue would often be obtained if this test was made under standard conditions—for example, by measuring the protein-bound radio-iodine six days after a 1-mc. test dose given after thyroid ablation in a patient who was not receiving thyroxine.

Evidence of Tumour Function from Urinary Radio-iodine Excretion

The urinary excretion of a test dose of radio-iodine gives indirect and approximate evidence of the presence of iodine-retaining tissues in the body. Thus if any greater proportion than about 10% of the dose remains unexcreted after, say, four days, it is likely that thyroid or functioning tumour tissue is still present. More direct and valuable information could, however, always be obtained by examining the localization of this retained radio-iodine by profile measurements, except possibly if tumour tissue were widely disseminated. The urinary excretion is also useful in estimating the radiation dosage that the body as a whole will receive.

Some basis for this estimate may be derived as follows. Most of the whole body radiation will be received while the radio-iodine is circulating as iodide rather than as thyroxine, except when much functioning tissue is present. As a rough approximation, the dose (d) of radio-iodine may be regarded as causing a plasma concentration which then falls exponentially with a half-period inversely proportional to the sum of the renal iodide clearance (r) and the total iodide clearance (G) of thyroid and tumour tissue (Pochin, 1950). The plasma beta radiation from circulating radio-iodide will therefore be proportional to $\frac{d}{G+r}$; and the proportion of the dose initially excreted in the urine will be given by $\frac{r}{G+r}$. For a given radio-iodine dose (d) and with a normal renal clearance (r), the body radiation will therefore be approximately proportional to the urinary excretion of the dose, whatever the value of G. Since, however, the value of G rarely exceeds that of r, the body radiation per millicurie is unlikely to change by a factor of more than two even after the thyroid has been totally ablated.

The urinary excretion may therefore be informative when a large tumour of poor uptake is being treated, since whole body radiation will be a limiting factor in treatment and it is important that the ratio of tumour to body radiation shall be high for every dose; and if the dose is largely excreted in the urine little will remain in and irradiate the tumour. For a tumour which is not decreasing in size, therefore, therapy should be avoided if the tumour uptake of iodine is low and the urinary excretion high. If, however, the tumour retains good uptake but is decreasing in size, the remaining tumour tissue can be irradiated with little loss of efficiency even though the urinary excretion is high.

Other Indications of Radio-iodine Uptake

In two patients a therapeutic dose of radio-iodine has caused clear and severe tenderness in metastasized lymph nodes, although it had not been possible to demonstrate uptake in these nodes by counting methods during a preceding test dose or after the therapy dose. Similar tenderness is normally observed during the week following the dose in the thyroid gland during radio-iodine ablation if doses of 60 to 100 mc. are used; and is presumably due to irradiation injury. When it occurs in neoplastic tissue it may therefore be taken as evidence of radio-iodine uptake. This interpretation was supported by a considerable reduction in size of the lymph nodes concerned in both cases and by other evidence of uptake: in one case by external counting eight weeks after ablation, when the remaining palpable metastasized glands concentrated well; and in the other by histological evidence of tumour destruction in the glands concerned. In each case normal thyroid tissue was still present in the neck and adjacent to the glands concerned, which may account for detection of uptake by tenderness and not by counting. Such tenderness may thus give the first indication that uptake is occurring. Oedema may also develop at the site of the tumour during radio-iodine therapy. We have observed this in one case with metastases in glands of the posterior triangle and in another patient with pulmonary metastases involving the pleura who developed a moderately extensive although transient pleural effusion on the side of the lesion within five days of the first therapeutic dose.

It seems likely, therefore, that the occurrence of local pain or oedema during the week after a therapeutic dose may support or extend the evidence of uptake; and that in some cases these events may provide a more sensitive, although less objective, indication of such uptake than measurements over the tumour.

Procedure in the Investigation of Thyroid Carcinoma

Since none of our patients have been under radio-iodine treatment for longer than three and a half years, no general statement can be made on its efficacy. It is, however, clear from the response of certain of our patients (Pochin, 1950) and of cases previously described (Howes and Foote, 1949; Horn and Ravdin, 1951; Sorrentino *et al.*, 1951) that the treatment can be valuable, and probably curative in some patients (Seidlin *et al.*, 1951) even when metastasis has occurred before radio-iodine is given. It is also clear that

it can be effective in a significant proportion of all thyroid carcinomata, and not only in occasional cases. Finally, it seems that treatment may be valuable for a tumour which cannot by the usual counting methods be shown to concentrate radio-iodine before thyroid ablation.

When a thyroid carcinoma is diagnosed, therefore, it is usually necessary to decide, without evidence that the tumour concentrates iodine, whether the normal thyroid tissue should be removed. This decision will normally be based on the histology of the tumour, since it has been shown that the most differentiated tumours, and particularly those with abundant colloid, are likely to concentrate iodine, although the correlation between uptake and histological differentiation is not exact. This is supported by the results in our cases (Table I).

We therefore suggest the following procedure in the management of thyroid carcinomata:

1. Biopsy, if this seems surgically justifiable, for evidence both of the thyroid origin of the neoplasm and of its degree of differentiation; with
2. Radical excision if ever this course appears likely to be successful. If such excision is attempted and is found to be impracticable, and if biopsy has revealed a differentiated tumour, as much normal thyroid tissue as possible should be removed at this operation instead.
3. Inoperable tumours that are undifferentiated and seem likely to be radio-sensitive should be treated by radiotherapy if sufficiently localized and unless they have been shown to take up radio-iodine.
4. For inoperable but histologically well-differentiated tumours, and certainly for those with colloid-filled follicles throughout their structure, thyroid ablation should be effected: (a) by surgical total thyroidectomy if possible, or (b) by radio-iodine in therapeutic (for example, 80 mc.) dosage. For completely anaplastic and rapidly growing tumours thyroid ablation is unlikely to be justifiable.
5. After thyroid ablation radio-iodine treatment should be instituted if adequate uptake can be detected in the tumour or induced, for example by use of thiouracil (Rawson *et al.*, 1951; Rall *et al.*, 1951). Therapy is continued until profile counting after a test dose reveals no abnormal site of radio-iodine retention, if this can be achieved without the development of radiation anaemia.

This scheme is clearly oversimplified in several respects, and the problems involved have been fully discussed by several authors (for example, Dobyns, 1951; Mitchell, 1951; Rawson *et al.*, 1951). It appears to afford a useful basis, however, for the initial selection of cases. In particular, it may have practical value in hospitals which are not at present using radio-iodine, since the most important steps in selection of cases for this treatment are independent of the use of isotopes. In patients with metastases remote from the thyroid, radio-iodine tests may be usefully made at any stage, but in tumours with colloid-filled vesicles these would in any case need to be repeated after ablation. In the absence of metastases remote from the thyroid, radio-iodine tests are rarely profitable before thyroidectomy, except sometimes when the tumour is extensive and thyroiditis can be excluded. For most patients, therefore, no information is lost, and valuable time may be gained, if a biopsy is performed immediately upon a presumptive diagnosis of thyroid carcinoma, and followed by total thyroidectomy if the tumour proves to be highly differentiated, the patient then being sent for radio-iodine investigation of residual areas of iodine uptake by profile counting. If thyroidectomy is impracticable, such a patient is sent for radio-iodine destruction of the thyroid, followed by treatment of any areas of abnormal concentration that are subsequently detected.

Finally, it should be emphasized that this procedure is suggested at an early stage in a form of treatment which will certainly develop considerably. Throughout this paper we have discussed methods of diagnosing tumours which concentrate and retain radio-iodine. A thyroid carcinoma might, however, concentrate radio-iodine in the tumour cells and convert it into organic combination but discharge it again rapidly, as would be likely to occur in the absence of

follicles. It should then show high initial uptake of radio-iodine for the first hours or day after the dose, which might allow its treatment by special methods. But it would have lost its radio-iodine by the second or third day, at which time autoradiograms and external counting tests of uptake are normally made. This might conceivably be the reason why most "undifferentiated" tumours—namely, those lacking follicles and colloid—are found to contain no radio-iodine when tested by normal methods several days after the dose. They may possess the biochemical cellular mechanisms and the capacity for uptake of iodine, even though they are shown not to have the follicular mechanism and capacity for its retention.

Dobyns and Maloof (1951) mention such behaviour in a metastasis in one case. We have had one patient (Case 13) in whom this mechanism of uptake and rapid discharge seemed to occur, and who has shown an unequivocal radiological response to treatment. The counting rate over the tumours, which were at the right lung base on the antero-

FIG. 8.—Profiles at intervals after radio-iodine in case of thyroid carcinoma with pulmonary metastases, showing initial uptake but rapid discharge in position corresponding to site of metastases. Case 13.

lateral aspect of the chest, rose to a high value on the day following the dose. In the next two days the value fell progressively, and was almost zero after three days although normal thyroid tissue, remaining after thyroidectomy, had taken up radio-iodine progressively during these days (Fig. 8). This is the behaviour to be expected on mathematical grounds if the

iodine storage time in the tumour is short, the mean time of stay having been only 2.3 days in this case. The estimation of the tumour uptake and discharge of radio-iodine, however, involves careful differentiation

FIG. 9.—Measurements round circumference of chest in Case 13, showing uptake anteriorly and to the right, in position of metastases.

between activity ascribed to the tumour and that ascribed to viscera such as the stomach, the radio-iodide content of which is considerable soon after the dose. The distinction could not be made adequately by profile counting, since the levels of tumour and stomach did not differ widely.

Measurements round the circumference of the trunk, however (Fig. 9), showed the highest counts to be opposite the site of the metastases and remote from that of the stomach. The evidence from this case is not conclusive, but it strongly suggests that a therapeutically useful degree of radio-iodine concentration in undifferentiated tumours may be unnoticed unless accurate and early profile examinations are made. It is clearly important that evidence of any such early uptake should be sought in this way in cases

of undifferentiated thyroid carcinoma which have metastases remote from the bladder, stomach, or salivary glands. If uptake is found at this stage, and suitable treatment can be based on this finding, the criteria for selecting cases for thyroid ablation will clearly require revision, and the scope of radio-iodine treatment for thyroid carcinoma will increase.

Already, however, it appears essential that, with any inoperable thyroid carcinoma in which copious colloid is demonstrable microscopically, radio-iodine uptake should be investigated after total thyroid ablation. If this is not done it seems clear that a substantial proportion of these patients will be inadequately treated.

Summary

In at least one-quarter, and probably in over one-third of a series of patients with thyroid carcinoma, the tumour could be shown by external counting to take up radio-iodine. These methods, particularly by profile counting, are valuable in detecting and following the degree of such uptake, which may become apparent only after thyroid ablation.

It seems likely that all patients in whom biopsy reveals a well-differentiated thyroid carcinoma which cannot be removed surgically should be investigated with radio-iodine, preferably after thyroid ablation. In a substantial proportion of such patients radio-iodine may be useful in treatment even though the tumour has already metastasized.

We are greatly indebted to the many clinicians who have sent us these patients, to Dr. R. C. F. Poynton for his help in their care, and to Miss M. Adams, Miss J. Forshaw, and Miss E. Ryan for assistance in their investigation.

REFERENCES

- Collez, R., Tubiana, M., Dutreix, J., and Gueiff, J. (1951). *Radiol. Électrol.*, 32, 881.
 Corbett, B. D., and Honour, A. J. (1951). *Nucleonics*, 9, 43.
 Dargent, M., Berger, M., Moret, R., and Guinet, P. (1950). *Presse méd.*, 58, 1016.
 Dobyns, B. M. (1951). *Surg. Gynec. Obstet.*, 93, 415.
 — and Lennon, B. (1948). *J. clin. Endocr.*, 8, 732.
 — and Maloof, F. (1951). *Ibid.*, 11, 1323.
 Fitzgerald, P. J., and Foote, F. W., Jun. (1949). *Ibid.*, 9, 1153.
 Frantz, V. K., Ball, R. P., Keston, A. S., and Palmer, W. W. (1944). *Ann. Surg.*, 119, 668.
 Quimby, E. H., and Evans, T. C. (1948). *Radiology*, 51, 532.
 Green, G. F., Tait, J. F., and Worsnop, R. (1951). *Brit. J. Radiol.*, 24, 148.
 Horn, R. C., Jun., and Ravdin, I. S. (1951). *J. clin. Endocr.*, 11, 1166.
 Howes, W. E., and Foote, M. N. (1949). *Radiology*, 52, 541.
 Marinelli, L. D., Foote, F. W., Hill, R. F., and Hocker, A. F. (1947). *Amer. J. Roentgenol.*, 58, 17.
 Mitchell, J. S. (1951). *British Medical Journal*, 2, 747.
 Paterson, J. R. (1950). *Ibid.*, 1, 839.
 Pochin, E. E. (1950). *Lancet*, 2, 41, 84.
 Rall, J. E., Miller, W. N., Foster, C. G., Peacock, W. C., and Rawson, R. W. (1951). *J. clin. Endocr.*, 11, 1273.
 Rawson, R. W., Dobyns, B. M., Hill, R., and Fluharty, R. G. (1949). *Acta Un. Int. Cancr.*, 6, 831.
 — Marinelli, L. D., Skanse, B. N., Trunnell, J., and Fluharty, R. G. (1948). *J. clin. Endocr.*, 8, 826.
 — Skanse, B. N., Fluharty, R. G., and Marinelli, L. D. (1948). *Cancer Res.*, 8, 382.
 — Rall, J. E., and Peacock, W. (1951). *J. clin. Endocr.*, 11, 1128.
 Seidlin, S. M., Rossman, I., Oshry, E., and Siegel, E. (1949). *Ibid.*, 9, 1122.
 — Yalow, A. A., and Siegel, E. (1951). *Proc. Soc. exp. Biol., N.Y.*, 76, 711.
 Sorrentino, J., Roswit, B., and Yalow, R. (1951). *Radiology*, 57, 729.

Six films dealing with accessible cancers have been made by the Ministry of Health. They are intended for general practitioners and other professional audiences. They do not stress any particular method of treatment, but emphasize the added years of normal useful life which may result from early diagnosis and treatment. The regions covered are the skin; lip, tongue, and mouth; larynx; breast; cervix and uterus; and rectum. The Ministry has also revised the leaflets "Health" and "Medicine and Surgery," describing the films available on these topics and the terms on which they may be hired or purchased. All the films are available from the Central Film Library, Bromyard Avenue, London, W.3, or from 16-17, Woodside Terrace, Glasgow, C.3, or 48, Park Place, Cardiff.