THE TREATMENT OF THYROID CARCINOMA

By VICTOR RIDDELL, F.R.C.S.

Surgeon, St. George's Hospital

FIG. 1.—*Diffuse carcinoma*. Short history. No previous goitre (Type 1).

Clinical Types

Cancer of the thyroid is not common nor is it as uncommon as was at one time supposed. It forms approximately 1 per cent. of all cancers, being three times more common in women than men. The histological interpretation of the different types of malignant disease of the thyroid is notoriously difficult. There is no uniform agreement amongst pathologists on the classification of the various types of cancer in this situation and there is frequently disagreement on the interpretation of the same section. Confusion has been added to the study of an already complex subject by the hyperplastic effects upon the gland of thiouracil which may produce a picture closely simulating malignant disease. It is possible that this tendency on the part of the anti-thyroid agents to confuse the issue is responsible for some of the high incidence figures for cancer reported in some

FIG. 2.—*Diffuse carcinoma*. Previous multi-nodular goitre for 20 years. History of recent increase in size (Type 2).

clinics. There is, however, a measure of agreement about the different *clinical* forms in which cancer of the thyroid may be present. The malignant process can arise *de novo* or in a previously present goitre. Five different types can be recognized, two bilateral and three unilateral (initially).

Type 1. *Diffuse carcinoma* (bilateral; *de novo*) (Fig. 1). In this variety the cancer arises *de novo* in a previously normal gland and is diffuse throughout both lobes. It is usually of bad prognosis.

Type 2. *Diffuse carcinoma* (bilateral; pre-existing multi-nodular goitre) (Fig. 2). In this variety the cancer arises in a previously present multi-nodular goitre. It is in connection with the frequency with which cancer arises as a secondary change in the multi-nodular goitre that there is some difference of opinion. It seems probable that

FIG. 3.—*Occult carcinoma* with impalpable primary in the thyroid (diagrammatic).

while the possibility of malignant change in multi-nodular goitres is unquestioned, the liability is less than 5 per cent. A balanced evaluation of the position by surgeons is of the greatest practical importance since if the tendency to malignant change is interpreted too radically it might lead to a 'prophylactic' thyroidectomy in many patients who showed little more than an unevenness of the surface of the thyroid.

In practice it would seem reasonable to leave alone those patients with small multi-nodular goitres who are symptom free *provided* the goitre appears to be quiescent as shown by the absence of any history of recent increase in size and provided that the patient is warned to report immediately, any alteration in consistency or increase in size which should subsequently be noticed.

Type 3. Occult carcinoma (unilateral). The most fascinating and the rarest type is occult carcinoma of the thyroid. It is exactly comparable to occult carcinoma of the breast. In this variety the primary in the thyroid is too minute to be palpable; the condition draws attention to itself by virtue of the enlarged cervical lymph nodes which on biopsy are found to contain typical thyroid metastases. Until the presence of the primary in the

FIG. 4.—*Malignant adenoma*. Previous unilateral goitre for 18 years. History of recent increase in size (Type 4).

thyroid was demonstrated to be a feature of these cases, the glandular swelling in the neck used to be referred to as carcinoma of a lateral aberrant thyroid. A lobectomy on the side on which the glands are enlarged together with a dissection of the palpable cervical glands on that side is probably the best treatment, if such a rarity should ever come one's way.

Type 4. Malignant adenoma (unilateral; pre-existing unilateral goitre). In this variety—the malignant adenoma—the cancer arises in a previously present unilateral goitre. Malignant change occurs more commonly in the solitary 'adenoma' than in the multi-nodular goitre, and its frequency in this country in Types 4 and 5 together is probably of the order of 7 per cent., although American writers have quoted a figure as high as 14.4 per cent. (Hermanson *et al.*, 1952).

Type 5. Symptomless solitary swelling (unilateral; *de novo*). This variety, which is the commonest of all, is also the most favourable and the one most liable to be left alone for the reason that it is usually a *symptomless* solitary swelling of recent origin and *indistinguishable* clinically from the innocent simple adenoma. It often occurs in young women, and is usually of the papilliferous type. A solitary swelling in the thyroid must be

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regarded in quite a different light to the multinodular swelling. It should be treated just as we treat a solitary swelling in the breast, by removal and presentation to the pathologist, who *alone* can say for certain that such a tumour is innocent. It should be excised not because it may become malignant, but because it may already *be* malignant. The majority of unilateral goitres present with symptoms, and symptoms sufficiently striking to induce their removal—for example because of pressure, haemorrhage or toxicity. It is only the few that are symptomless, and it is these swellings which are so tempting to leave alone. It cannot be too strongly urged that these solitary symptomless swellings should be regarded as malignant until proved otherwise. In advising patients to have these removed it is important to bear in mind that the operation for their removal is hemithyroidectomy, a minor procedure compared with the subtotal operation, a small premium to pay for a high rate of insurance, for the results are amongst the best in cancer surgery.

Radioactive Iodine

One of the most significant advances of modern times has been the development and use of radioactive iodine in the investigation and treatment of diseases of the thyroid gland. The use of this isotope has now passed the experimental stage and, as it seems likely to be going to play an increasingly important role in this field, it may not be out of place here briefly to review the history of its development.

Introduction. Although all atoms of an element (e.g. iodine) behave in the same way chemically, they do not necessarily have the same physical properties, in particular the masses of the atoms may be different. Because the atoms of one element behave the same chemically they all occupy the 'same place' in the periodic table of the elements, and are therefore called 'isotopes'

($\begin{smallmatrix} 21 \\ \iota \sigma \omicron \varsigma \end{smallmatrix}$: same
 $\begin{smallmatrix} \tau \acute{o} \pi \omicron \varsigma \end{smallmatrix}$: place) Some, but not all isotopes have an unstable nucleus to the atom, and in reaching a more stable state they spontaneously emit energy in the form of alpha particles (the nuclei of helium atoms), beta particles (high speed electrons), or gamma rays (similar to X-rays), or some combination of these. The time taken for the activity of an isotope in a living creature to fall to half its initial value is known as the biological half life, and will be less than the physical half life, as biological excretion is added to physical decay.

Iodine occurring in nature has an atomic weight of 127 (written I^{127}), but many radioactive forms of other atomic weight have been prepared. The first application of radioactive iodine to the study of thyroid function was that of Hertz *et al.* in 1938,

FIG. 5.—'Symptomless solitary swelling.' Carcinoma unsuspected clinically. Age 28 (Type 5).

who worked on animals. They used I^{128} which had a half life of only 25 minutes and this made any prolonged investigation impossible as the material rapidly decayed below a detectable level of activity. The first clinical studies in humans were by Hamilton and Soley (1939, 1940) who used I^{131} of half life eight days in their classical investigations of thyroid metabolism. Hamilton *et al.* (1940) were also the first to use radio-iodine to study cancer of the thyroid. The first demonstration of metastatic carcinomatous tissue taking up radioactive iodine was made by Keston *et al.* (1942). The extensive use of I^{131} in thyroid investigation is due in no small measure to the avidity with which the thyroid takes up iodine, the concentration in the thyroid sometimes reaching 10,000 times that of the average throughout the body.

Dosage. The isotope of iodine most commonly used at present is, as is implied above, I^{131} . It is manufactured at the Atomic Energy Research Station at Harwell by irradiating tellurium of atomic weight 130 with neutrons in an atomic pile. It is supplied by Harwell in solution as iodide ion together with a little sodium and sodium sulphate. It is not inexpensive; at the time of writing 100 millicuries cost £27 5s. and 250 millicuries cost £39 15s. I^{131} has a half life of eight days and

emits both beta particles and gamma rays. The beta particles—which are the tissue destroying particles—only travel about 2 mm. in tissue and cannot, therefore, be detected outside the body. The gamma rays are much more penetrating and are readily detected external to the body using a suitable counter.

For tracer investigations quantities of I^{131} up to about 50 μc . (1 μc . = 1 microcurie = 1/1,000 millicurie) are usually employed, but for the destruction of normal thyroid function about 70 millicuries might be used (i.e. over 1,000 times the quantity used for diagnostic purposes), and for the treatment of a thyroid carcinoma as much as 250 mc. has been taken in a single 'drink,' comparable quantities being administered in subsequent treatments of the same patient if these become necessary.

Administration. The isotope used is administered in solution by mouth, being given in a small and harmless dose for diagnostic (tracer) purposes and in a larger dose for therapy. It is rapidly absorbed from the intestinal tract into the blood stream, being detectable in the thyroid area within 20 minutes. It is largely removed by the thyroid and kidneys but small amounts are concentrated in the salivary glands and gastric mucous membrane. The isotope is excreted in the urine at a rate dependant upon the function of the kidneys and the thyroid condition present. In a normal person approximately 50 per cent. will be excreted in the first 48 hours and up to 90 per cent. by the end of four days. In myxoedema the radio-iodine uptake by the thyroid is small and a correspondingly larger amount will be excreted in the urine in a shorter time, and in hyperthyroidism the opposite will be the case. In cancer of the thyroid the excretion rate will depend upon whether or not the tumour is iodine concentrating.

Methods of detection. The great value of radioactive isotopes in clinical investigation is consequent upon the extreme sensitivity of the physical methods of detecting them. Isotopes may be administered in quantities insufficient to cause biological disturbance and their subsequent fate may be detected by (i) a Geiger counter, (ii) a scintillation counter or (iii) autoradiographs on photographic emulsions.

(i) **Geiger counter.** This instrument, which is capable of detecting the disintegration of a single atom, was developed by Geiger while working under the late Lord Rutherford at the Cavendish Laboratory in Cambridge in the early part of this century. It was further developed by Müller in the 1920's, and today exists in several forms. A common type consists of a copper gauze cylinder 4 in. long and 1 in. diameter with a fine wire running along its axis, the whole being enclosed in

a glass tube filled with a mixture of alcohol vapour and argon to about one-sixth of atmospheric pressure. A steady voltage of about 1,000 volts is maintained between the copper cylinder and the central wire. If a gamma ray falls on the counter an electrical discharge will be initiated between the cylinder and the wire. This discharge is amplified and recorded electrically. It is important that the counter should be suitably shielded so as to receive radiations from known directions only. Such an improved counter has been described by Pochin *et al.* (1952) for local counting, and an adaptation of this counter has been devised to determine the distribution of radio-iodine throughout the length of the body for 'profile' counting.

(ii) **Scintillation counter.** Some materials fluoresce when alpha, beta or gamma rays fall upon them. The minute scintillation due to a single beta or gamma ray can be detected by a special light sensitive cell called a photomultiplier, and can be recorded electrically. The scintillation counter is so sensitive that only a very small dose of radio-iodine is required for tracer work. For this and other reasons the scintillation counter is likely to be used more and more in the future.

(iii) **Autoradiographs.** The third method of observing radioactive isotopes in biological material, is to cut a thin histological section of a biopsy specimen and place it in intimate contact with a photographic emulsion. Any particles emitted by the radioactive material cause a blackening of the emulsion (after normal development), the blackening being greatest in regions of highest concentration of radioactive material. The histological section and autoradiograph may be compared to determine the exact location of radioactive material in the specimen.

Precautions in the use of radioactive isotopes. The radiation from radioactive isotopes is a potential hazard to the investigator, to the patient and, after disposal, to the general public. The supply of radioactive materials for use on humans must be sanctioned by the Medical Research Council. The precautions to be observed in their handling and disposal have been set out in a document prepared for the M.R.C. by the Atomic Energy Research Establishment.

TREATMENT

Thyroid cancer is best treated by complete *surgical excision*. If excision is not possible thyroid cancer should be treated with radioactive iodine, provided the carcinoma can be shown to take up the radioactive iodine sufficiently. If excision is impossible and the gland cannot be induced to take up radioactive iodine it will be necessary to resort to the third of the available methods of treatment—deep X-ray therapy.

Radioiodine uptake. Before deciding upon treatment with radioactive iodine it is necessary to demonstrate that the tumour concerned is capable of concentrating radioiodine. Unfortunately all thyroid carcinomata do not take up radioiodine but it is now believed that more do so than was previously thought. The detection of radioiodine uptake by a tumour is not always as straightforward an investigation as might be supposed and is particularly liable to be complicated if there is normal thyroid tissue nearby. Recently it has been shown that certain thyroid tumours, both primary and metastatic, which by external counting methods showed no initial evidence of radioiodine uptake, were found to take up iodine *after removal* or destruction of the contralateral lobe and all remaining normal thyroid tissue. This is an important development and has substantially increased the number of thyroid carcinomata and their metastases which can hopefully be submitted to treatment by radioactive iodine. Take up is particularly likely to occur if the tumour is well differentiated.

The explanation of the behaviour of such thyroid tumours may be that the concentration of isotope by the tumour is greater when it is competing for radioiodine against the kidneys alone and not against kidneys and normal thyroid. In addition the detection of weak uptake is technically simpler if there is no site of strong uptake such as thyroid tissue adjacent. Thus it may be that uptake in a thyroid tumour or metastases is *revealed* rather than induced by removal of normal thyroid tissue. (Pochin *et al.*, 1952).

Metastases. Metastases distant from the thyroid gland are most readily discovered by 'profile' counting. Metastases lying close to the kidneys or bladder and those near to the stomach or salivary glands may all contain radioactive iodine and so may be difficult to detect if searched for too soon after the dose of radioiodine has been taken. If metastases are present, examination after a few days is likely to be more successful as by this time almost all the administered radioiodine will have been excreted in the urine. Paradoxically the presence of metastases in thyroid carcinoma would appear to afford no contraindication to radical surgery upon the primary growth provided that the secondary deposits can be shown to concentrate radioiodine and so render themselves liable to self destruction.

Operability

In arriving at a decision as to the best course of treatment to pursue it is wise first to determine the local operability of the particular case under review.

Assessment of operability. It is not always possible by clinical methods alone to determine whether any given case is operable or not and resort to actual operation may alone decide this point. At the same time fixation of the gland due to transcapsular spread with limitation of its excursion on swallowing is a suspicious sign as also is paralysis of a vocal cord which may not always be associated with a hoarse voice and may therefore not be suspected unless the cords are *routinely examined by laryngoscopy*. Confusion in diagnosis sometimes arises between malignancy and chronic thyroiditis—which can only be settled by biopsy; occasionally a calcified nodule in the thyroid will be deceiving but its true nature will usually be revealed by a straight X-ray.

Limitations in treatment. The following plan of treatment is an attempt to provide a practical guide in the light of our present knowledge, but it should not be interpreted too rigidly in so constantly changing a sphere of therapy. It must also be borne in mind that no single surgeon has had so wide an experience of thyroid cancer that he can be dogmatic about treatment. Further, it must be admitted that great as the potentialities of radioiodine are in this field it has not so far always fulfilled our hopes. Success has been limited and disappointments numerous, so that too much must not be expected of it.

For a further account of the present position the reader will be well advised to study the comprehensive paper by Pochin, Hilton, Myant and Honour (1952), frequently and gratefully referred to in this contribution.

Operable

Operable cases should be treated by thyroidectomy—inoperable cases by radioiodine or radiotherapy according to the degree of differentiation present as revealed by preliminary biopsy. In operable cases it seems doubtful whether preliminary biopsy is worth while or justifiable as material for examination will be supplied by the operation specimen, and in bulk, which will allow a more comprehensive examination by the pathologist. Only when the diagnosis is in doubt should a biopsy be done—as for example if chronic thyroiditis is a possible alternative diagnosis.

Unilateral. Unilateral operable thyroid cancer may present in two forms (excluding occult carcinoma) the *suspected* (malignant adenoma) and the *unsuspected* (solitary symptomless 'adenoma').

Malignant adenoma (Type 4). If the diagnosis is certain the treatment is total unilateral lobectomy, which should include all thyroid tissue on the affected side together with any enlarged glands and the isthmus and the pyramidal lobe, so that the trachea is left bare anteriorly. In an operable

case of this kind there is no clear indication that there is any advantage in removing the contralateral normal lobe unless it is known that malignant tissue has been left behind or metastases are suspected of being present which might thereby be revealed and induced to take up iodine. In the absence of such special circumstances the normal lobe should be left undisturbed.

Unsuspected carcinoma (Type 5). Carcinoma occurring in the solitary symptomless swelling is usually discovered 'accidentally' when the 'adenoma' is cut across in the theatre after the operation (Fig. 6). As a rule the operation for its removal has been a hemithyroidectomy, that is to say a partial lobectomy on the side affected, leaving a strip of thyroid tissue posteriorly. Fortunately these carcinomata are usually well encapsulated, and it has not been my practice to carry out any further surgical procedure in this particular group of cases.

Bilateral. In diffuse operable thyroid cancer affecting both lobes, total thyroidectomy should be the surgical aim. The operation, in the writer's opinion, should be confined to the removal of the thyroid gland and associated enlarged lymphatic glands. It is questionable whether a standard block dissection with bilateral removal of the sternomastoid and infrahyoid muscles is any longer justifiable or beneficial in view of the availability of radioiodine. If transcapsular spread has already occurred and the growth is involving the muscles, the condition must surely be regarded as inoperable.

Following thyroidectomy the patient should be sent for radioactive iodine investigation by profile counting of any remaining areas of iodine uptake in the body.

Inoperable

In inoperable thyroid cancer a *preliminary biopsy* should be carried out with the object of determining the degree of differentiation of the tumour (and incidentally its thyroid origin and malignant nature), as the subsequent treatment will be much influenced by the histological picture. In hospitals which are not yet equipped with radioactive iodine facilities for investigation, the preliminary biopsy may form the basis of selection of cases for treatment.

Unilateral. If the biopsy shows *well differentiated* tissue the remaining normal thyroid tissue should be removed by operation (or if this is not feasible it should be destroyed by radioactive iodine in therapeutic dosage). Following the removal of all normal thyroid tissue the tumour should be tested for radioactive iodine uptake and if this can be demonstrated radioiodine treatment should be instituted.

FIG. 6.—Papilliferous carcinoma revealed on section of 'adenoma' removed from patient illustrated in Fig. 5.

Bilateral. If the biopsy shows well differentiated tissue the remaining normal thyroid tissue scattered throughout both lobes should be destroyed by radioactive iodine in therapeutic dosage. The gland should then be tested for any residual areas concentrating radioactive iodine, and if any can be demonstrated radioiodine treatment should be instituted.

Inoperable tumours—unilateral or bilateral— which are *undifferentiated* should be treated with radioiodine if they can be shown to take it up, but this is uncommon. In most cases in this category such uptake will not be demonstrable and treatment should be with *radiotherapy*.

Tracheostomy. Tracheostomy is sometimes necessary when respiratory obstruction is present. In these circumstances it is essential to use a rubber tube if the area is being or is to be irradiated.

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