THE PLACE OF RADIOACTIVE IODINE IN THE TREATMENT OF THYROID DISEASE*

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Since all isotopes of any element have identical chemical behaviour, the radioactive isotopes of iodine are metabolised in the same way as normal iodine, and become highly concentrated in normal or over-active thyroid tissue and, in some circumstances, in thyroid cancer tissue. It may consequently be possible to destroy part or all of such tissues by the effects of the intense local beta radiation emitted by the radioiodine which becomes concentrated in them, and to do so without causing undue radiation damage to other parts of the body, in which the radioiodine is only weakly or transiently concentrated. Normal or over-active thyroid tissue can readily be destroyed in this way without hazardous radiation of bone marrow, gonads or other organs, since iodine is highly concentrated and well retained in such tissues. In thyroid carcinoma, on the other hand, where iodine is less efficiently concentrated and is poorly retained, much larger doses are required and the progress of treatment is often limited by the need to avoid undue marrow depression.

Radioiodine Treatment of Thyroid Carcinoma

Radioactive iodine has considerable value in the treatment of many cancers of the thyroid^{4, 7, 10, 11, 12, 13, 15} and the indications for its use in this disease depend upon a number of factors which are now becoming clearly established.

1. The radical removal by surgery of all tumour tissue, where this is practicable, must always be regarded as preferable to radioiodine therapy.

2. Anaplastic thyroid carcinomata are unlikely ever to concentrate radioiodine, whereas a substantial majority of all differentiated tumours, including those of mainly papillary structure, are likely to concentrate radioiodine under suitable conditions of stimulation and may, therefore, become suitable for treatment by this means.

3. Even the histologically differentiated tumours do not usually concentrate radioiodine until the function of all normal thyroid tissue has been abolished, the uptake in the tumour commonly only developing with the advent of myxoedema two or three months after thyroid ablation.

4. The extent to which tumour tissue will be destroyed by the radiations from any radioiodine that is selectively concentrated in it will depend, not only on the efficiency and on the duration of such radioiodine concentration, but also on the radiosensitivity of the tumour. Good clinical results may, therefore, be obtained despite poor concentration, while tumours with good concentration may sometimes only respond slowly, if at all.

5. When the series of large doses is given, which is usually necessary to ensure tumour destruction, bone marrow depression appears to occur commonly in patients with multiple secondary deposits in bone, but rarely in those without such metastases.

SELECTION OF PATIENTS FOR THYROID ABLATION

It will be seen that patients cannot be selected as suitable for radioiodine treatment by the simple test of whether their tumour concentrates radioiodine, since it is unlikely to do so until after thyroid ablation in any case. It is necessary, therefore, to select for thyroid ablation those patients whose tumours will probably concentrate radioiodine well after normal thyroid function has been abolished. The histological character of the tumour as found by biopsy is almost certainly the best basis for this choice. Patients with anaplastic or undifferentiated tumours should normally not be subjected to thyroid ablation, and are likely to prove more suitable for treatment by external radiotherapy. In many such patients the rapid growth of these tumours would in any case cause death before the development of myxoedema after thyroid ablation, and so before any useful test for radioiodine uptake could be made.

Patients with differentiated tumours which are surgically inoperable by reason of their local or

*Work undertaken on behalf of the Medical Research Council.

remote spread should, however, in the opinion of many clinics, undergo thyroid ablation and subsequent tests for radioiodine uptake in the tumour, since it appears likely that radioiodine treatment is of greater value than external radiotherapy in the majority of these patients. In some cases with purely or largely papillary tumours, repeated surgical resection of local recurrences may offer adequate treatment for prolonged periods. In most patients with disseminated and well differentiated thyroid carcinomata, however, ablation should be undertaken as soon as it is clear that radical removal is impossible by surgery, or if it seems probable that some tumour tissue has been left in the body after attempted radical resection.

METHOD OF THYROID ABLATION

In patients selected for thyroid ablation, the function of the normal thyroid gland can be abolished, either by total thyroidectomy, or by an initial therapeutic dose of radioiodine. Thyroidectomy will usually be preferable in the following circumstances.

1. Whenever it seems possible that total resection of all tumours tissue may be practicable.
2. When a substantial mass of tumour tissue can be removed at the same time as the thyroidectomy.
3. When the trachea is seriously compressed or invaded, or when continued growth of the tumour during the ensuing few months seems likely to threaten the airway. In some cases it may be valuable to establish a tracheotomy at the time of this operation.
4. Where the histology of a tumour is in doubt, it may be useful to examine frozen sections of tumour tissue removed and proceed to a total thyroidectomy if the tumour is of well differentiated character. More commonly, however, it appears preferable to obtain tissue by biopsy and plan the necessary operation as soon as this tissue has been fully examined.

Thyroid ablation by radioiodine, using a dose of about 80 mc., will commonly be preferable to thyroidectomy in the following conditions.

1. When previous biopsies or local resections are likely to have so distorted the neck structures that thyroidectomy is unlikely to be complete or achieved without hazard to parathyroids or recurrent laryngeal nerves. The difficulties of total thyroidectomy may be increased by the effects of previous radiotherapy to the neck, or by the presence of active and vascular tumour tissue.
2. When one vocal cord is already paralysed as a result of tumour growth or previous operations, or if there is any history of parathyroid disturbance following earlier surgery.

SELECTION OF PATIENTS FOLLOWING THYROID ABLATION

In differentiated thyroid carcinomata, radioiodine uptake is occasionally demonstrable before thyroid ablation and is sometimes evident immediately after this procedure. More commonly, however, it only develops with the onset of full myxoedema at about twelve to sixteen weeks after thyroid ablation. The efficiency of radioiodine concentration in the tumour tissue often then increases during the following month or more.

It is therefore necessary to test for tumour uptake for some months after thyroid ablation, and we normally make tests of this sort at about 14 and 21 weeks from the time of the thyroidectomy or ablation dose. If clear uptake is demonstrable in tumour tissue at any of these times, radioiodine treatment is started. If, on the other hand, little or no uptake is demonstrable with the onset of myxoedema, tests should be continued for one or two months before the possibility of radioiodine treatment is abandoned. In practice, several questions arise at this stage.

1. If radioiodine is detectable in the thyroid region, it will be difficult to know whether this represents uptake in remaining normal thyroid tissue or in the primary tumour. This distinction is not, however, of importance, since a therapeutic dose should be given in either case, whether to complete the thyroid ablation or to start the treatment of an iodine-concentrating tumour.

2. How much radioiodine uptake is needed in tumour tissue to justify the initiation of radioiodine treatment? The opinion in different clinics varies on this point, and some would only undertake treatment if a large proportion of the test dose was retained in tumour tissue. No reliable figure can, however, be given since the amount of active tumour tissue is rarely known and since the radioiodine sensitivity of the tumour is in any case unpredictable. It is not, in fact, important to establish a figure for the amount of uptake which would justify treatment, since the response of the tumour to a first therapeutic dose is probably the most reliable and direct indication as to whether further treatment should be undertaken. It appears reasonable, therefore, that if uptake at sites of tumour tissue can be clearly demonstrated by external counting methods or otherwise, an initial therapeutic dose of radioiodine should be given and further doses should be given subsequently if evidence of a response is obtained and while radioiodine uptake persists.

3. If little or no uptake is demonstrable at tumour sites with the onset of myxoedema, most clinics would allow the myxoedema to persist and would repeat the tests for uptake after one or two months. Some would attempt to improve the

degree or likelihood of uptake by the administration of antithyroid drugs of the thiouracil group, testing for tumour uptake a few days after withdrawal of such drugs. It does not seem clear when, or in what circumstances, the administration of these derivatives, or of thyrotropic hormone preparations, induces a more efficient tumour uptake than results from the persistence of myxoedema alone, but these methods may be tried if no adequate uptake is demonstrable in a tumour of differentiated histology.

CONDUCT OF TREATMENT

Most clinics would agree on the need for repeated dosage in the treatment of thyroid carcinoma, but the size of dose and interval at which doses are given vary widely, as do also the criteria for stopping treatment. Our own practice^{7, 10, 13} is to give doses of 150 mc. at intervals initially of six to eight weeks, but later of six months or a year, as evidence is obtained of a decrease in the remaining amount of functioning tumour tissue. The patient is given thyroxine or thyroid extract from 48 hours after each dose until four weeks before the next dose. A progressive reduction of tumour tissue may be demonstrable clinically by measurement of neck metastases, radiologically for lung, mediastinal, pleural and sometimes bone deposits, or indirectly by the relief of symptoms, particularly from involvement of the spinal cord. Useful indirect evidence as to the amount of remaining functioning tumour tissue may also be obtained by measurements of the percentage of each radioiodine dose which becomes concentrated at tumour sites, since it seems likely that in many patients, the uptake per gram of such tissue remains about constant during treatment, and therefore that the total uptake gives an indication of the remaining tumour mass. It is normally found that during a treatment which can be shown on other grounds to be causing a progressive destruction of tumour tissue, the percentage of each successive dose which is concentrated at tumour sites falls correspondingly.

If curative treatment is being attempted, radioiodine doses should be continued until iodine uptake is no longer demonstrable at tumour sites. In a group of 10 patients in whom the total tumour uptake has been reduced in this way to a value of less than 0.01 per cent. of the dose given, the necessary course of treatment has involved an average of about seven doses given at widening intervals over a period of two to three years and involving an average total administration of about 1,100 millicuries. Such patients in whom tumour uptake of radioiodine is no longer detectable are then given annual test doses to confirm that no

recurrence of iodine-concentrating tissue is occurring.

In some cases the estimation of tumour uptake by gamma counting methods may prove difficult because of the wide dissemination of small deposits throughout the body, or because of the proximity of some of these deposits to organs in which iodine is normally concentrated. In these patients, and provided that ablation of normal thyroid tissue is complete, it is possible to detect the persistence of functioning tumour tissue by two other and simpler methods^{12, 14}. Firstly, if the plasma is examined, say at six days after the dose, and found to contain radioiodine in proteinbound form, it is likely that the persistence of functioning tumour tissue is responsible for the synthesis of this hormonal material. Secondly, if the course of urinary excretion is followed and the excretion of some radioiodine is found to be delayed later than the normal rapid and complete excretion that occurs in the athyroid subject, it is again a reasonable assumption that this delay has been due to retention of the radioiodine in functioning tumour tissue. These methods seem likely to give a useful guide as to the need for continuing or stopping radioiodine dosage when curative treatment is being attempted.

A purely palliative treatment with radioiodine may appear preferable in patients whose tumours are very extensive, or are responding only slowly to successive doses, so that an unduly large total dose would be needed to abolish all signs of functioning tumour tissue, and marrow aplasia might result from the extensive radiation involved in such a course. It appears also that patients with multiple bone metastases are unduly likely to develop such marrow aplasia and that radioiodine treatment, which is often of considerable value for about a year in these patients, may subsequently prove hazardous owing to the development of blood changes. In both these groups of patients, therefore, if radioiodine does not appear to be achieving a rapid and complete tumour destruction, doses may subsequently be given only on the recurrence of symptoms or to avoid undue spread of the disease. In all other patients, however, the risk of marrow aplasia, even with high total dosage, appears to us to be considerably less than the alternative risk of allowing active tumour tissue to remain untreated in the body, if this can be prevented by repeated administration of radioiodine.

Radioiodine Treatment of Hyperthyroidism

Radioactive iodine offers a simple, although rather inaccurate and possibly hazardous, method of treating the hyperthyroid gland^{1, 2, 6, 12}. The simplicity of this treatment is very evident to the

patient, since a single dose is often sufficient to restore the metabolism to normal and more than three doses are rarely needed. The inaccuracy is probably no greater than that of subtotal thyroidectomy, since the frequency of subsequent myxoedema is about equal, and the chance of recurrent hyperthyroidism, at least after two or three doses if these are required, is probably less than that after surgical treatment. Injury to the recurrent laryngeal nerves or to the parathyroids does not of course occur.

The widespread use of radioiodine in the treatment of hyperthyroidism is, at present, restricted in most clinics because it is not yet clear that there is no hazard of a late development of malignant changes in the thyroid, or in the immediately adjacent tissues. This uncertainty applies to all new radiation treatments for benign conditions, since a follow-up of perhaps 20 years is necessary before it can be known how frequently, if at all, any malignant changes may occur. Since no radioiodine-treated patients have been followed for longer than 16 years^{8, 9} and few for over 12 years, the risks of subsequent malignancy must remain entirely speculative for some years longer, and no information from animal experiments can indicate whether the treatment in man carries, for example, a 5 per cent. hazard and so should rarely be used, or a 0.05 per cent. hazard and so should usually be employed.

At present, therefore, few clinics would use radioiodine as the treatment of choice in young patients unless the alternative forms of therapy were contra-indicated; but many would so use it in patients over 45 or 50 when the normal expectation of life is shorter than the probable latency of any likely carcinogenic effect. It is probably the right treatment for most elderly thyrocardiac patients, and for younger patients with severe toxicity which recurs after thyroidectomy. Radioiodine should not be used therapeutically in pregnancy, in view of its concentration in the foetal thyroid, or in childhood, since thyroid cancer may be readily induced by radiation in children^{3, 5, 16}. It should clearly not be used in preference to surgery if a toxic nodular gland is suspected of malignancy, and it is said to be less effective, and sometimes to require large doses, in patients with toxic nodular goitre in general.

In patients selected for treatment, a test dose of radioiodine is normally given, in order that the uptake and time of retention of radioiodine by the gland can be estimated, and in order to determine the size of therapeutic dose needed to administer the required amount of radiation to the gland. An attempt is also made to estimate the gland size by palpation, or by mapping the distribution of radioiodine in the neck. A radiation dose of 8,000 to

9,000 rads. to the thyroid is usually required to restore a typically overactive gland to normal function. There is, however, considerable individual variation in the amount of radiation needed, and a radiation dose which may leave one gland overactive, may cause myxoedema in another patient. For this reason, the clinical results obtained when the size of dose is calculated simply upon the basis of gland size, are usually little worse than those observed when the dose is based upon an accurate determination of radioiodine metabolism by means of a test dose. In each case the amount of radiation given will depend somewhat upon the urgency of obtaining effective treatment by a single dose, and on the acceptability of some risk of myxoedema, and doses between 5,000 and 10,000 rads. are commonly used.

The immediate effects of a therapeutic dose are usually limited to some tenderness of the gland and occasional symptoms of increased toxicity during the following week, during which it can be shown chemically that the blood protein-bound iodine is raised. For this reason, patients who are severely toxic or who have cardiac complications, are normally treated in hospital for the week following the dose, although the practice of different clinics varies considerably in this respect. The full effects of each dose in controlling thyroid activity are only reached after two or three months from their administration. In severely toxic patients, therefore, further treatment may be required in control of symptoms during this interval, Lugol's iodine or, less commonly, antithyroid drugs, usually being used for this purpose. The need for further radioiodine treatment can be assessed after three months, or will be evident if a patient is still clearly thyrotoxic after, say, six weeks from the dose. In patients in whom myxoedema develops, this complication may arise at any time up to several years from therapy, but more commonly occurs after a few months and is then often transient, requiring thyroid administration for a period of a few months only.

If a patient remains thyrotoxic after radioiodine treatment and further dosage is required, a test dose is usually omitted and the size of dose estimated on the basis of the size and effects of the first dose.

Other Therapeutic Uses of Radioiodine for Thyroid Disease

Radioiodine has occasionally been used in an attempt to induce atrophy of either lingual or retrosternal thyroid tissue which cannot be treated surgically. Both these applications have the disadvantage that it is likely to be necessary to induce myxoedema before full atrophy of the ectopic tissue can be achieved, although some decrease in

size or vascularity may be more easily obtained. The treatment by these means of a retrosternal goitre which is already causing pressure symptoms, involves the careful use of repeated small doses of radioiodine to avoid the risk of oedema of the irradiated tissue in the days following the dose, and an increase in obstruction. For these reasons, radioiodine has only a limited use in reducing the size of ectopic thyroid deposits but may occasionally be of value.

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