HYPERTHYROIDISM, RESULTS OF TREATMENT —
AN APPRAISAL*

by

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"WHENEVER you find that for a particular disease there are many remedies, you may know that there is something doubtful about the action of these remedies, and that none is particularly efficacious."

INTRODUCTION

We have come a long way since Mackenzie wrote these words in 1905, and yet in one sense they are still true. It is not that the modern modes of treatment are of doubtful value; all are effective, but the ideal treatment for hyperthyroidism still eludes us. Neither do we have reliable methods of selecting the best treatment for the individual patient. This could be arranged more rationally if it was possible to predict which patients would undergo spontaneous remission without therapy and which would suffer protracted and serious illness.

The aim of treatment is to reduce the secretion of the thyroid gland to a level which supports normal metabolic processes, to prevent complications and to correct those already present. Specific measures which reduce the secretion of the toxic gland effectively are antithyroid drugs, subtotal thyroidectomy and radioactive iodine. Opinions differ about their relative merits and no well-controlled comparisons of the three methods appear to have been made.

The purpose of this paper is to report the experience gained in the Metabolic Unit of the Royal Victoria Hospital in treating patients with hyperthyroidism and to make an appraisal of their advantages and disadvantages. Table I shows how some of our patients have been managed over the last 14 years. All these have been subject to special analysis and study. Some have had more than one form of treatment. Antithyroid drugs and surgery have, of course, been continued since 1967, although not analysed for the purpose of this presentation.

ANTITHYROID DRUG TREATMENT

Many different forms of medical treatment have been used over the years to treat thyrotoxicosis but all have been superceded by the use of modern definitive antithyroid drugs and beta-adrenoceptor blockade.

* Based in part on a lecture delivered at the Royal College of Surgeons in London in 1970 and revised.
Table I

Treatment of Hyperthyroidism and Methods Employed 1960–1973

Metabolic Unit, Royal Victoria Hospital, Belfast

| Medical—antithyroid drugs | Surgical | RAI—conventional dosage | RAI—small dosage with propranolol | Propranolol alone |
|---------------------------|----------|-------------------------|---------------------------------|------------------|
| 1960–67                   | 153      | —                       | —                               | —                |
| 1961–66                   | —        | —                       | 254                             | —                |
| 1968–73                   | —        | —                       | 247                             | 25               |
| 1970–71                   | —        | —                       | —                               | —                |

Antithyroid Drugs

These are of two types: (1) those which interfere with the synthesis of thyroid hormones (methyl and propyl thiouracil, methimazole and carbimazole, and (2) those which inhibit the trapping of iodide by the thyroid gland ( perchlorate). Definitive treatment of hyperthyroidism with antithyroid drugs is undertaken in the hope that the disease will undergo spontaneous remission, or that the gland will alter in such a way that the hyperthyroidism will not recur when therapy is stopped. Earlier writers on the thyroid (see Wilson 1966) claimed remission in nearly a third of their patients. Recent knowledge of the natural course of thyrotoxicosis is unknown since few patients are permitted to go untreated. Perhaps the easiest way of studying the natural history of the disease is to block its peripheral manifestations with propranolol. Results achieved using this method (see later) confirm the view that remissions of the order of 30 to 40 per cent probably occur naturally. On the other hand, in a study of 50 untreated patients (in terms of specific antithyroid therapy) with fully developed exophthalmic goitre, Kessel and his colleagues (1923) found only one patient in full remission at the end of a year’s observation, although many had improved with non-specific measures. It must be accepted then that, for the present, we do not know how antithyroid drugs “cure” the patient in whom a remission has been obtained. A possibility is that antithyroid drugs induce remissions by virtue of reducing the level of thyroid hormone which, in turn, may have an effect on the production of LATS and LATS protector. In other words, the return of the euthyroid state may reduce the tendency of the body to synthesize antibody directed against the thyroid gland (McKenzie 1967). Others (Alexander et al 1965; Harden et al 1966) have shown that depletion of the body’s store of iodine increases the likelihood of achieving a remission. However, the remission rates achieved by us with antithyroid drugs and propranolol alone (see below) are not much better than the chance of obtaining a natural remission. This must make us ask: Are these drugs doing anything more than making the patient comfortable while a natural remission takes place?

The response of a series of 153 patients treated with carbimazole is shown in Table II. All had continuous treatment for at least 18 months and more than half had had it continued for over two years. The results show that only 43 per cent achieved a remission and that 51 per cent relapsed and required other therapy.
Indeed, a remission rate of 43 per cent may be optimistic because a few patients were observed for less than 12 months after the withdrawal of treatment. Since the majority of relapses occur within a year of this the relapse rate might have been higher if all had been observed for a minimum period of a year.

The reported remission rate achieved by other workers in the field (Astwood 1967) is shown in Table III. Such reports are difficult to compare with each other. However, if one takes a crude average, the overall rate of remission is over 50 per cent. This is probably too high and the best that can be expected for medical treat-

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**TABLE II**

*Antithyroid Treatment (Carbimazole) for Hyperthyroidism (153 patients) 1960–67*

| Clinical status                      | Number | Percentage |
|--------------------------------------|--------|------------|
| Euthyroid (follow-up ½–8 years)      | 64     | 43         |
| Remaining on therapy at time of review| 6      | 4          |
| Untraced                             | 4      | 2          |
| Relapsed—treated surgically          | 75     | 49         |
| Relapsed—treated with RAI            | 4      | 2          |
| **Total**                            | **153**| **100**    |

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**TABLE III**

*Incidence of Remission achieved with Antithyroid Drug Treatment (from Astwood, E. B. 1967)*

| Authors                  | No. of patients | Years after treatment | Remission (percentage) |
|--------------------------|-----------------|------------------------|------------------------|
| Solomon et al            | 101             | 4–10                   | 55–70                  |
| McCullagh and Cassidy    | 60              | 4–6                    | 66                     |
| Douglas and McKenzie     | 187             | ?–5                    | 45                     |
| Manson                   | 70              | >1                     | 71                     |
| Goodwin et al            | 94              | ½–1                    | 41                     |
| Aspenstrom               | 120             | >1                     | 70                     |
| Trotter                  | 157             | 10                     | 45                     |
| Wilcox                   | 152             | 1–12                   | 72                     |
| Revens and Rosenbaum     | 167             | 4–19                   | 57                     |
| Hershman et al           | 176             | 6–20                   | 54                     |
| Metabolic Unit, R.V.H.   | 153             | ½–8                    | 43                     |
| **Total**                | **1,437**       |                        | **56**                 |

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ment will be between 40 and 50 per cent. This means that definitive treatment with antithyroid drugs will often be ineffective, unless the patient and doctor are prepared to continue treatment for an almost indefinite period.

Recently it has been fashionable to try and forecast those patients who are likely to respond to a course of medical treatment from those who will not. Empirical criteria include a small smooth gland, young patient, short history and a reduction in the size of the goitre during treatment, but none are very reliable. Another method involves the identification of patients in whom thyroid suppressibility returns during treatment (Alexander et al 1966). The test is useful in distinguishing between hyperthyroid patients and euthyroid patients with a high $^{131}$I neck uptake. Failure of the radioactive iodine uptake (RAIU) by the thyroid to be suppressed by thyroid hormones (eg, triiodothyronine 100 mg daily for seven days) is characteristic of hyperthyroidism (Werner et al 1952; Werner 1955). A positive response (suppressibility) is defined as a fall of 50 per cent or more of the pre-treatment RAIU or a 20-minute uptake of less than 8 per cent (Alexander et al 1967). The test has been used to try and separate patients who will obtain a prolonged remission with antithyroid drugs from those who will not. Lack of suppressibility is said to be followed by relapse and the return of thyroid suppression during treatment means that a remission will follow the withdrawal of the drug. Proponents of this view (Alexander et al 1967) believe that if thyroid function remains unsuppressible at the end of six months' medical therapy it should be abandoned in favour of subtotal thyroidectomy or radioactive iodine treatment. Unfortunately, the test has not proved to be sufficiently reliable upon which to base a programme of treatment, for it does not indicate clearly those patients who will eventually relapse or remain in remission (Lowry et al 1971; Table IV) and for these reasons it has largely been abandoned. Similar hopes were expressed for the TRH test, which correlates well with the $T_3$ suppression test (Ormston et al 1973), but experience has shown it to be no more reliable.

| Clinical status 2 years after completion of treatment | Suppressed | Non-suppressed |
|--------------------------------------------------------|------------|----------------|
|                                                        | Number     | Percentage     | Number  | Percentage |
| Remission                                              | 35 (55%)   | 20 57.1        | 15      | 42.9       |
| Relapse                                                | 29 (45%)   | 8 27.6         | 21      | 72.4       |
| Total                                                  | 65         | 28 43.8        | 36      | 56.2       |

*Lowry et al (1971)

Despite the drawbacks mentioned, antithyroid drugs play an important part in the overall management of many thyrotoxic patients. They are helpful in the preparation of patients for surgery and have a place in the treatment of hyperthyroidism in special circumstances; for example, in pregnancy, childhood, for those wish-
ing to avoid an operation and for the young patient with mild symptoms and a small smooth gland. Toxic effects of carbimazole are rare and mostly mild and were noted in three of the 153 patients described; an incidence of under 2 per cent. The advantages of antithyroid drug treatment for hyperthyroidism are summarised in Table V.

| TABLE V |
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| **Antithyroid Drug Treatment for Hyperthyroidism** |

**Advantages**

1. No damage is done to the thyroid gland.
2. No irreversible changes are induced.
3. Lasting myxoedema does not occur.
4. Hyperthyroidism can be corrected uniformly in a short time.

**Disadvantages**

1. High incidence of relapse of hyperthyroidism after treatment.
2. Inconvenience of frequent and prolonged (1–2 years) attendance at hospital or health centre.
3. Small incidence of toxic side-effects.
4. Goitre does not diminish in size.
5. Few physicians attain sufficient expertise in their administration.

**Iodine and iodides**

Iodide increases the storage of colloid in the thyrotoxic gland and reduces the height of the epithelial cells. It thus induces the changes characteristic of involution, diminishes the vascularity of the gland and reduces thyroid hormone synthesis and release. The effect is transient, however, so that iodides have no place in the treatment of hyperthyroidism, apart from the preparation of patients for thyroidectomy and in the management of a thyrotoxic crisis (Havard 1974).

**Sympathetic antagonists**

Many of the clinical features of hyperthyroidism resemble the effects of increased activity of the sympathetic nervous system and two types of sympathetic antagonists are helpful in the relief of symptoms and signs. Drugs such as reserpine and guanethidine, which deplete the tissues of their catecholamine content, improve symptoms without affecting the concentration of the circulating thyroid hormones. However, their delayed action and side effects have precluded their general use. More effective in controlling the heart rate and some of the peripheral manifestations of thyrotoxicosis is the beta-adrenoceptor blocking drug propranolol. Since propranolol does not influence thyroid activity (Hadden et al 1969) it can be given in combination with radioactive iodine or as an adjunct to antithyroid medication. It has been used successfully alone or with iodine in preparing patients for thyroidectomy (Vinik et al 1968; Pimstone and Joffe 1970; Lee et al 1973; Michie et al 1974). Propranolol has greatly simplified preoperative management. The peripheral manifestations of the disease are brought under con-
control quickly and the patient's apprehension of operation is rapidly allayed. Those with mild or moderate disease are ready for operation in 10 to 14 days when given iodine and propranolol together, while those with severe hyperthyroidism, given antithyroid drugs simultaneously, are ready in three or four weeks. Propranolol is given orally in a dose of 40 mg six-hourly during the period of preparation and for several days after operation. If it is withdrawn prematurely, at or before surgery, rebound tachycardia or cardiac arrhythmia may develop and be mistaken for a thyroid crisis. Some surgeons (Lee et al 1973; Michie et al 1974) omit iodine pre-operatively and depend solely on propranolol for the preparation of their patients. It remains to be seen whether other thyroid surgeons will follow suit. Iodine is so safe, cheap and effective in reducing the activity of the hyperthyroid that it seems unwise to abandon it altogether.

Propranolol alone in the management of hyperthyroidism

With increasing experience of the successful management of thyrotoxicosis using smaller and smaller doses of RAI and propranolol (see later) it seemed logical to try the effect of propranolol alone in treating the milder cases. Pimstone and others (1969) suggested that this might be an acceptable form of definitive treatment. Accordingly, 25 selected patients have been given 160 mg of propranolol daily for up to one year as the sole method of treatment. The results are shown in Table VI

| Number of patients treated | 25 |
|---------------------------|----|
| Euthyroid at 1 year       | 10  (40%) |
| Remaining thyrotoxic at 1 year and requiring additional treatment (RAI, antithyroid drugs or surgery) | 12  (48%) |
| Withdrawn from trial before 1 year (miscellaneous reasons) | 3  (12%) |
| Total                     | 25 |

(Lowe et al 1975). Those who responded (40 per cent) became euthyroid between two and nine months after commencing treatment. Since propranolol does not affect the intrinsic function of the thyroid it is likely that these are naturally occurring remissions of the disease process to which allusion has been made already. It may or may not be significant that the remission rates for antithyroid drug treatment and propranolol are so close. No difference could be found clinically or biochemically between those who responded to propranolol and those who did not. Ten euthyroid patients have now been followed for up to four years. Two have subsequently relapsed after being euthyroid for three and two years respectively. In the remaining eight patients the TRH test was positive in two and negative (unsuppressible) in six 18 months after they went into remission. Unfortunately,
propranolol alone cannot be recommended as a definitive form of antithyroid treatment because it is impossible to select prospectively patients who are likely to respond; a view supported by McLarty and others (1973).

**Surgical treatment**

Subtotal thyroidectomy has a long and honoured place in the management of hyperthyroidism since the operation was introduced towards the end of last century and perfected by Sir Thomas Dunhill in the first decade of this century. The results achieved in a series of 128 patients treated surgically (1960–67) are shown in Table VI.

| Clinical status | All cases (128) | Subtotal thyroidectomy | Subtotal thyroidectomy--after failed treatment (53) | Subtotal thyroidectomy--after failed medical treatment (75) |
|-----------------|-----------------|------------------------|-----------------------------------------------|------------------------------------------------------|
|                 | Number          | Percentage             | Number                                       | Percentage                                           |
| Euthyroid       | 108             | 84.3                   | 41                                           | 77.3                                                |
| Hypothyroid     | 12              | 9.4                    | 7                                            | 13.3                                                |
| Relapsed        | 8               | 6.3                    | 5                                            | 9.4                                                 |
| Dead            | 0               | 0                      | 0                                            | 0                                                   |

Thyroidectomy was performed as first treatment in 53 patients and as second treatment in a further 75 who had relapsed after antithyroid drug therapy (Table VII). It is of interest that slightly better results appear to have been achieved for those who relapsed after antithyroid drugs than for those whom surgery had been selected as initial treatment. However, the numbers are too small from which to draw valid conclusions. Thyroidectomy is equally successful in Graves’ disease and toxic nodular goitre. Unilateral lobectomy for the solitary toxic adenoma (“hot nodule”) removes the pathological lesion and allows the normal, but suppressed, thyroid tissue to recover.

Complications of surgery in this series are listed in Table VIII. Most are not serious but the morbidity associated with the operation still gives cause for concern. Hypocalcaemia occurs frequently enough for all patients to be screened carefully for three months after thyroidectomy. It has been suggested that “partial” or “latent” hypoparathyroidism may sometimes follow thyroidectomy and cause vague symptoms, which can be relieved by calcium supplements (Fourman 1967). This view has not received general support (Billis and Montgomery 1967; Stowers et al 1967). Deficiency of calcitonin as the result of thyroidectomy does not appear to affect calcium homeostasis to any extent. McIntyre (1969) has suggested that this may be due to extra thyroidal sources of calcitonin. Conversely, hypocalcaemia is not found in the presence of medullary cell carcinomas of the thyroid secreting calcitonin in excess (Montgomery and Welbourn 1975).
TABLE VIII
Complications of Subtotal Thyroidectomy for Hyperthyroidism
(128 cases)

| Complication                                      | Number | Percentage |
|---------------------------------------------------|--------|------------|
| 1. HAEMORRHAGE                                    |        |            |
| (a) Requiring surgery                             | 3      | 2          |
| (b) Extensive bruising                            | 5      | 4          |
| 2. SEROSANGUINEOUS EFFUSION                       |        |            |
| (a) Requiring aspiration                          | 1      | 1          |
| 3. CHEST INFECTION OR PULMONARY COLLAPSE          | 7      | 5          |
| 4. WOUND INFECTION (serious)                      | 4      | 3          |
| 5. RECURRENT LARYNGEAL NERVE PALSY                |        |            |
| (a) Bilateral                                     | 0      | 0          |
| (b) Unilateral – Temporary                         | 10     | 8          |
| (c) Permanent                                     | 0      | 0          |
| 6. TETANY (Hypoparathyroidism)                    |        |            |
| (a) Temporary                                     | 7      | 5          |
| (b) Permanent (requiring continuous therapy)      | 4      | 3          |
| 7. HYPOTHYROIDISM                                  |        |            |
| (a) Temporary                                     | 2      | 2          |
| (b) Permanent (requiring continuous therapy)      | 12     | 9          |
| 8. UNSATISFACTORY SCAR                             |        |            |
| (a) Fibrosis                                      | 0      | 0          |
| (b) Keloid                                        | 3      | 2          |

From these results and essentially similar figures published in several other British surveys (Wade 1960; Riddell 1962, 1970; Green and Wilson 1964; McNeill and Thompson 1968) it may be concluded that subtotal thyroidectomy offers the patient a better than 80 per cent chance of a remission and that the incidence of major surgical complications, such as recurrent laryngeal nerve damage or permanent hypoparathyroidism, while not great, still occur and must continue to challenge thyroid surgeons to produce even better results. The 9 per cent incidence of hypothyroidism might increase with a longer period of observation. On the other hand, we were impressed with the rapidity with which hypothyroidism developed in this group. Most were diagnosed within 12 months of operation. The early onset of hypothyroidism has been confirmed by Olsen et al (1970) and Michie et al (1972). All but one of the latter’s patients who became hypothyroid did so within the year following thyroidectomy. They concluded that if a sufficiently high degree of suspicion of hypothyroidism is maintained during the early postoperative months the late diagnosis of hypothyroidism is rare. In Britain, the incidence of hypothyroidism after thyroidectomy has ranged from 3.3 to 49 per cent (Riddell 1962; Michie et al 1972). In America, for example, a figure quoted for the development
of hypothyroidism following surgery for Graves' disease is 42.8 per cent (Beahrs and Sakulsky 1968) and Olsen and his colleagues (1970) quote an incidence of 25 to 50 per cent.

The causes of postoperative hypothyroidism are not fully understood. Neither the age or sex of the patient, the size of the goitre or the amount and duration of preoperative antithyroid drug therapy appear to be involved (Michie et al 1972). On the other hand, Michie found that the size of the thyroid remnant was the most significant aetiological factor. When a policy of increasing the size of the thyroid remnant was adopted the hypothyroid rate fell although it was not abolished. However, the policy of leaving a larger remnant increases the risk of recurrence of the hyperthyroidism. Wilson (1967) observed that with the removal of a smaller amount of thyroid there is a diminished incidence of hypothyroidism and a higher recurrence rate, while with the more radical excision the reverse holds.

Variations in iodine intake and surgical technique may reflect the differing incidence of postoperative hypothyroidism in certain parts of the world. The level of thyroid antibodies in serum appears to be important and where these are high the incidence may be of the order of 25 per cent or more (Irvine and Stewart 1967; van Welsum et al 1974). The former authors suggest that a high level of circulating thyroid autoantibodies is a relative contraindication of thyroidectomy and that if it is performed the patient should be kept under regular supervision. Possibly in these cases the operation should be less radical than usual. In contrast to surgery, serological tests seem to be of little value in predicting the development of hypothyroidism in patients treated with RAI or of any prognostic value in determining the outcome of the patient's response to antithyroid drug therapy.

**Radioactive iodine treatment (RAIT)**

Radioactive iodine has been in use since 1941 but it was not until the early 1950's that large numbers of patients received this form of therapy. RAIT although much slower in correcting hyperthyroidism (8 to 12 weeks or longer) than subtotal thyroidectomy or antithyroid drugs seemed, at first, to be an ideal method of treatment. For the patient it is the most convenient as it involves only a drink of tasteless water. However, there were some initial difficulties because no satisfactory way of estimating the correct dose of RAI, in relation to size, activity or nodularity of the thyroid gland could be evolved. Too small a dose did not cure the hyperthyroidism, whereas too large a dose caused early and permanent hypothyroidism. The most serious objection to RAIT, however, has become apparent only with the passage of time. In the 1960's, reports of a disturbingly high and progressive incidence of hypothyroidism began to appear from Scandinavia, Great Britain, America and elsewhere. These showed a relentless increase in the incidence of hypothyroidism each year after treatment which reaches a level of about fifty per cent or more at 10 years (Beiling and Eindhorn 1961; Green and Wilson 1964; Nofal et al 1966).

From 1961 to 1966, 254 patients were treated in the Metabolic Unit (Bhatia et al 1968) using conventional doses of RAI (150 μCi/g thyroid tissue). Adequate information about their thyroid function was obtained in over 98 per cent subsequently, and 232 were re-examined in 1967 and 1968 (Table IX). For the group
TABLE IX
Therapeutic Radioactive Iodine 1961–66
Thyroid Status at Review (1967–68)

| Year of first treatment | Mean dose mCi | Number of patients Treated | Number of patients Reviewed | Euthyroid Number | Percentage | Hypothyroid Number | Percentage |
|-------------------------|---------------|-----------------------------|----------------------------|------------------|------------|-------------------|------------|
| 1961                    | 8.2           | 36                          | 31                         | 13               | 42         | 16                | 51         |
| 1962                    | 8.6           | 62                          | 55                         | 24               | 43         | 18                | 33         |
| 1963                    | 8.1           | 40                          | 35                         | 14               | 40         | 16                | 45         |
| 1964                    | 5.1           | 43                          | 39                         | 22               | 56         | 9                 | 23         |
| 1965                    | 4.2           | 48                          | 48                         | 22               | 45         | 7                 | 15         |
| 1966                    | 4.8           | 25                          | 24                         | 14               | 58         | 4                 | 16         |
| Total                   | 254*          | 232                         | 109                        | 47               |            | 30                |            |

* 158 patients had no previous treatment.
81 patients had failed antithyroid treatment.
8 patients had a previous subtotal thyroidectomy.
7 patients had both drug treatment and subtotal thyroidectomy.

As a whole the remission rate, i.e., the achievement of euthyroidism was 47 per cent, while 30 per cent were hypothyroid. However, the longer patients were observed the greater was the incidence of hypothyroidism. For example, 51 per cent of the original 36 patients treated in 1961 were hypothyroid six years later. From 1964 onwards, the dose of RAI was reduced substantially and the incidence of hypothyroidism diminished slightly. Nevertheless, 23 per cent of the 1964 group were hypothyroid in three years. If to this figure is added a yearly cumulative incidence of about 4 per cent of hypothyroidism, which these results suggest, this 23 per cent becomes 35 per cent at six years; an incidence which is still very discouraging.

TABLE X
Effect of Age at First Treatment on Subsequent Incidence of Hypothyroidism

| Age group (years) | Total patients treated 1961–66 | Mean dose of RAI (mCi) | Total percentage hypothyroid at review |
|-------------------|--------------------------------|------------------------|----------------------------------------|
| 40–49             | 89                             | 6.57                   | 38.2                                   |
| 50–59             | 92                             | 6.70                   | 27.1                                   |
| 60+               | 73                             | 6.24                   | 15.1                                   |

The effect of age on the development of hypothyroidism is shown in Table X. The youngest age group had the highest incidence of hypothyroidism regardless of the year of treatment. Differences in the size of the goitre, dosage and turnover rates of RAI do not appear to explain this difference and it is probable that the "younger" the thyroid gland is the more sensitive is it to the effects of ionizing
irradiation. The incidence of hypothyroidism in those who had previously received a course of antithyroid drugs was 26 per cent, less than for the whole group but not statistically significant. For those who had a thyroidectomy previously the rate soared to 62 per cent (five out of eight subjects).

It must be clear to all that the late results of RAIT are most disappointing. Patients require regular follow-up for sooner or later many will require permanent treatment with thyroxine. For these reasons some clinicians felt that such results could not be tolerated and have sought methods that would exploit the advantages of RAIT (using smaller doses) while at the same time diminishing the risk of hypothyroidism. These carry the risk, however, of incomplete control of the disease and usually necessitate the administration of an antithyroid drug as well (Smith and Wilson 1967; Smith et al 1970; Rapoport et al 1973). While these methods reduce substantially the risk of hypothyroidism developing (a reduction from 30 per cent to 8 per cent at two years according to Smith et al 1970), the long period of antithyroid drug treatment makes it less acceptable from the patient's point of view. It can be argued that if RAIT is to be extended over several years using antithyroid drugs, it might be preferable to accept the incidence of hypothyroidism with conventional RAIT alone and administer thyroxine if and when it is needed.

In 1968, we reduced the treatment doses of RAI by about half from that employed earlier, to a level of about 70 μCi/g thyroid tissue. With an average size goitre this meant a therapeutic dose of about 2.5 mCi and this amount was prescribed routinely for all patients. Subsequently the dose was reduced by a further 50 per cent to 1.25 mCi. At the same time 160 mg of propranolol was given daily to control symptoms until the intrinsic thyroid abnormality was brought under control.

Table XI summarises the results obtained with this form of combined therapy in patients given a single dose of RAIT (those given two or more doses have been omitted for the purpose of this presentation). The incidence of hypothyroidism at one year with 2.5 mCi is not far short of that achieved with larger doses but at four years it is much less. For the 1.25 mCi dose the hypothyroid rate is very much less and, although the number of patients achieving euthyroidism at one year is slightly fewer the difference is not pronounced.

The management of patients who have not responded to treatment with a small dose of RAIT at three or four months poses a number of problems. Although a few may become euthyroid over the succeeding months, the majority are likely to

| Dose RAI (mCi) | No. of patients | Euthyroid (%) | Hypothyroid (%) |
|---------------|----------------|---------------|----------------|
| 2.5           | 63             | 41            | 13             |
| 1.25          | 32             | 35            | 0              |

Small Dose RAIT 1968–73
remain hyperthyroid, although protected, to some extent, from the effects of the thyroid toxicity by propranolol. However, adrenergic blockade is unlikely to prevent all the metabolic consequences of protracted hyperthyroidism—for example, the possibility of progressive osteoporosis (McLarty et al 1973). For these reasons, a second dose of 2.5 or 1.25 mCi of RAI is given at three or four months to non-responders. Third or even fourth supplemental doses may be required in an attempt to titrate the amount of RAI required to provide the optimum dose to control thyroid toxicity without inducing hypothyroidism. As might be expected, more (55 per cent) of the 1.25 mCi group than the 2.5 mCi group (38 per cent) required additional doses of RAI to achieve euthyroidism. The long-term effectiveness of this method remains to be worked out fully and will be the subject of a subsequent report but the early results are encouraging. Nevertheless, the criticism levelled at the combined regime of small dose RAIT with antithyroid drugs can be made equally against RAI and propranolol. The only point of difference is that the control of treatment is easier with the latter, for achievement of euthyroidism is specifically related to the RAI, whereas in the former it may be due to either the RAI or antithyroid drug.

**SUMMARY AND CONCLUSIONS**

This review has attempted to show what can be achieved with the available methods of treating hyperthyroidism. None alter the underlying cause of the disease; a possible exception being the removal of a single toxic nodule. Antithyroid drugs and propranolol suppress thyroid hyperfunction or its peripheral manifestations; a lasting cure probably depending on a natural remission which we are powerless to influence. Surgery and radioactive iodine destroy part of the gland and the eventual outcome depends on the balance between the amount of tissue destroyed and the function of the remainder. Until more is known about the fundamental mechanism of hyperthyroidism so that it can be prevented or its causal factors removed, we must apply existing methods in the most efficient way.

Effective treatment can nearly always be provided and the advantages and disadvantages of each method are set forth below:

**Antithyroid drugs**

1. Limited value as definitive treatment.
2. Useful in special circumstances.
3. Morbidity minimal and reversible.
4. Remission in selected cases between 40 and 50 per cent.

**Surgery**

1. Remission rate between 80 and 90 per cent.
2. Hypothyroidism variable but often considerable; high antibody titre significant.
3. Morbidity still important and serious for the patient.

**Radioactive iodine**

1. Remission rate of just under 50 per cent.
2. High cumulative incidence of hypothyroidism.
3. Of value in controlling persistent hyperthyroidism.
All these factors must be considered in relation to the age, clinical findings, nature of the goitre and the patient’s emotional make-up and responsibilities. There are many in whom the choice of treatment is not easy. Problems arise, for instance, when the gland is of moderate size or causing minimal compression of the trachea or when the patient is a few years under the age of 40. A planned policy for treatment must be selected from the start. Where the diagnosis is in doubt, symptomatic

**TABLE XII**

| Type of Goitre and Clinical Features | Treatment recommended |
|-------------------------------------|-----------------------|
| **I. Diffuse Goitre**               |                       |
| 1. Under 40 years                   |                       |
| (a) Small gland and mild or moderate toxicity | Antithyroid drugs |
| (b) Large gland and moderate or severe toxicity | Subtotal thyroidectomy |
| 2. Over 40 years                    |                       |
| **II. Nodular Goitre**              |                       |
| 1. Under 40 years                   | Subtotal thyroidectomy |
| 2. Over 40 years                    |                       |
| (a) Small gland without obstruction | Subtotal thyroidectomy |
| (b) Large gland with obstruction    | Radioactive iodine    |
| **III. Recurrent Thyrotoxicosis**   |                       |
| 1. After antithyroid drugs          |                       |
| (a) Under 40 years                  | Subtotal thyroidectomy |
| (b) Over 40 years                   | Radioactive iodine    |
| 2. After operation                  |                       |
| (a) Under 40 years                  | Antithyroid drugs     |
| (b) Over 40 years                   | Radioactive iodine    |
| (c) Large obstructive goitre at any age | Subtotal thyroidectomy |
| 3. After radioactive iodine          | Radioactive iodine    |
| **IV. Special Circumstances**       |                       |
| 1. Childhood                        | Antithyroid drugs     |
| 2. Pregnancy                        | Antithyroid drugs or subtotal thyroidectomy |
| 3. Neonatal thyrotoxicosis          | Antithyroid drugs     |
| 4. Infirmit (heart failure, old age, intercurrent disease, etc) | Radioactive iodine |
| 5. Hyperophthalmopathic Graves’ disease | Antithyroid drugs until eyes stabilized and special measures |
| 6. Solitary toxic adenoma            | Partial thyroidectomy |
| 7. Thyrotoxic crisis                | Special measures      |

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control of the hyperthyroidism can be achieved with propranolol, while investigation proceeds unhampred by treatment. The best results are achieved by the close collaboration of physicians and surgeons and the provision of a careful follow-up system.

Table XII summarises the general policy for treatment hyperthyroidism in the Metabolic Unit, Royal Victoria Hospital, which has evolved over the last decade.

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BOOK REVIEWS

OBSTETRICS ILLUSTRATED. By M. M. Garry, A. D. T. Govan, C. Hodge and R. Callender. Second Edition. (Pp. 538. Illustrated. £3.75). Edinburgh and London: Churchill Livingstone. 1974.

The second edition of this book, coming only five years after the first (which went to three reprints), must speak of its popularity. The combination of line drawings and simple text produces a method for easy assimilation by the ever-pressed medical student. The rapid changes in many aspects of the specialty have been coped with by extensive rewriting of chapters dealing with fetal monitoring, early diagnosis of immaturity and dysmaturity, induction techniques and planned labour and delivery; the chapter relating to the newborn infant is particularly well presented. The remaining subject matter is covered adequately having sections on physiology and anatomy as well as dealing with the most common, and a good few not so common, pathological states of pregnancy. One obvious error appears on page 186 relating to the estimation of H.S.A.P. The authors rightly point out that this test has now been shown to have little clinical use as it is not sufficiently discriminating; however the estimation of the enzyme is not carried out on a sample of amniotic fluid.

This book (500 pages) is very reasonably priced at £3.75 and I would recommend it to the undergraduate.

W.T.