period of drug treatment required was longer. Hershman *et al.* (1966) found no significant difference in the incidence of remission in the two groups.

The results of treatment with radioiodine were more satisfactory and compared favourably with those reported by Green and Wilson (1964), though the proportion requiring only one dose was less than that reported in other series (MacGregor, 1957; Blomfield *et al.*, 1959; McGirr *et al.*, 1964; Staffurth and Young, 1967). Blomfield *et al.* (1959) found that the response to radioiodine was similar in patients with recurrent thyrotoxicosis and those with primary hyperthyroidism. The incidence of hypothyroidism would appear to be greater, since Greig (1966) reported an incidence of 41% in patients followed up for one to eight years at this clinic. The incidence of hypothyroidism reported in other series is also lower (Beling and Einhorn, 1961; Green and Wilson, 1964; Dunn and Chapman, 1964; McGirr *et al.*, 1964), though Nofal *et al.* (1966) reported an incidence of 51% in patients treated with radioiodine and followed for 1 to 16 years. Dunn and Chapman (1964) found that the incidence of hypothyroidism was significantly greater in those patients who had had a previous thyroidectomy. Sensitivity to radioiodine in patients with recurrent hyperthyroidism may be due in part to increased radiosensitivity and to difficulties in estimating the size of the thyroid remnant (Dunn and Chapman, 1964). Radioiodine would appear to be the treatment of choice in patients who relapse after thyroidectomy provided that adequate follow-up is undertaken. In the present series those who did not receive ^{131}I initially were subjected to prolonged periods of ill-health and fruitless treatment.

It has been shown that in euthyroid patients following thyroidectomy the P.B. ^{131}I may be raised owing to a low intrathyroidal iodine pool, and the thyroidal radioiodine uptake may also be raised owing to a small extrathyroidal iodine pool (Koutras *et al.*, 1961; Roy *et al.*, 1967). When the test results in the present series are compared with those in euthyroid

patients after thyroidectomy (Roy *et al.*, 1967), the P.B. ^{131}I provides poor separation between euthyroid and thyrotoxic patients. Thyroid uptake measurements at five hours and estimation of the serum P.B. ^{127}I are, however, of greater value in diagnosing post-thyroidectomy recurrences.

REFERENCES

- Beling, U., and Einhorn, J. (1961). *Acta Radiologica*, **56**, 275.
 Blomfield, G. W., Eckert, H., Fisher, M., Miller, H., Munro, D. S., and Wilson, G. M. (1959). *British Medical Journal*, **1**, 63.
 Cattell, R. B., Alford, A. W., and Bartels, E. C. (1952). *Journal of Clinical Endocrinology and Metabolism*, **12**, 1389.
 Clark, F., and Horn, D. B. (1965). *Journal of Clinical Endocrinology and Metabolism*, **25**, 39.
 Crooks, J., Buchanan, W. W., and Wayne, E. J. (1960). *British Medical Journal*, **1**, 151.
 Douglas, D., and Kennie, A. T. (1952). *British Medical Journal*, **2**, 1387.
 Dunn, J. T., and Chapman, E. M. (1964). *New England Journal of Medicine*, **271**, 1037.
 Green, M., and Wilson, G. M. (1964). *British Medical Journal*, **1**, 1005.
 Greig, W. R. (1966). *Scottish Medical Journal*, **11**, 307.
 Hayles, A. B., Kennedy, R. L. J., Beahrs, O. H., and Woolner, L. B. (1959). *Journal of Clinical Endocrinology and Metabolism*, **19**, 138.
 Hershman, J. M., Givens, J. R., Cassidy, C. E., and Astwood, E. B. (1966). *Journal of Clinical Endocrinology and Metabolism*, **26**, 803.
 Koutras, D. A., Alexander, W. D., Buchanan, W. W., Crooks, J., and Wayne, E. J. (1961). *Acta Endocrinologica*, **37**, 597.
 McGirr, E. M., Thomson, J. A., and Murray, I. P. C. (1964). *Scottish Medical Journal*, **9**, 505.
 MacGregor, A. G. (1957). *British Medical Journal*, **1**, 492.
 Nofal, M. M., Beierwaltes, W. H., and Patno, M. E. (1966). *Journal of the American Medical Association*, **197**, 605.
 Reveno, W. S., and Rosenbaum, H. (1964). *Annals of Internal Medicine*, **60**, 982.
 Riddell, V. (1965). *British Journal of Surgery*, **52**, 721.
 Roy, A. D., Allan, J., and Harden, R. McG. (1967). *Lancet*, **2**, 684.
 Solomon, D. H., Beck, J. C., VanderLaan, W. P., and Astwood, E. B. (1953). *Journal of the American Medical Association*, **152**, 201.
 Staffurth, J. S., and Young, J. (1967). *Journal of Clinical Endocrinology and Metabolism*, **27**, 1062.
 Taylor, G. W., and Painter, N. S. (1962). *Lancet*, **1**, 287.
 Wayne, E. J. (1960). *British Medical Journal*, **1**, 1, 78.
 Wayne, E. J., Koutras, D. A., and Alexander, W. D. (1964). *Clinical Aspects of Iodine Metabolism*. Oxford, Blackwell Scientific Publications.

Results of Treatment of Thyrotoxicosis following Relapse after Antithyroid Drug Therapy

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British Medical Journal, 1969, **3**, 203–205

Summary: One hundred and thirty patients who relapsed after a full course of treatment with antithyroid drugs have been reviewed. Of 22 patients receiving a second course of antithyroid drugs, 17 (77%) relapsed. In contrast, only 2 out of 44 patients treated by surgery relapsed and seven became hypothyroid. Nevertheless, local complications, in particular parathyroid insufficiency, were especially common in this group. Eighty patients received radioiodine, 11 (14%) requiring more than three doses before finally being rendered euthyroid. Post-radiation hypothyroidism developed in 39 (49%) patients.

Introduction

Since antithyroid drugs were first introduced numerous reports of their effectiveness have been published. Little attention, however, has been paid to the prognosis for those patients in whom thyrotoxicosis recurs after discontinuation of antithyroid drug therapy. In this study 130 thyrotoxic patients who relapsed after treatment with antithyroid drugs have been followed up.

Methods

Patients Studied.—The age and sex of the patients studied is shown in Table I. Of the 130 patients, 102 were treated initially in the Western Infirmary, Glasgow, and 28 in other hospitals. All had received antithyroid drugs for a minimum

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period of one year, 78 for up to 18 months, 25 for 18 to 24 months, and 27 for over 24 months. Eighty-four patients had a diffuse goitre, 18 had a nodular one, 5 had no goitre, and in 23 the nature of the goitre was uncertain. Fifty-three were treated with carbimazole, 47 with potassium perchlorate, and 30 with methylthiouracil. Seventy-five per cent. of the patients had relapsed within one year after discontinuation of therapy and 94% within three years (Fig. 1). Twenty-seven (21%) gave a history of a relative with thyroid disease.

TABLE I.—Age and Sex Distribution of 130 Patients who Relapsed After Treatment with Antithyroid Drugs

		Age in Years						
		10–	20–	30–	40–	50–	60–	70–
Males	..	0	2	12	9	3	2	0
Females	..	7	19	38	27	8	2	1

FIG. 1.—Time of relapse following cessation of antithyroid drug therapy.

¹³¹I Therapy and Surgery.—An empirical dosage prescription procedure as previously described by Crooks *et al.* (1960) was used when radioiodine (¹³¹I) was administered. In those patients who had operative treatment a seven-eighths subtotal thyroidectomy was carried out.

Assessment of Thyroid Status.—Thyroid status was assessed on clinical grounds (Wayne, 1960) and by laboratory tests, including standard radioiodine (¹³¹I) tests with 4- and 48-hour thyroidal uptake and estimation of plasma levels of protein-bound radioiodine (P.B. ¹³¹I) at 48 hours (Wayne, 1960), the two-and-a-half-hour thyroidal radioiodine uptake and clearance and absolute uptake of iodine (Wayne *et al.*, 1964), estimation of the serum P.B. ¹²⁷I, the resin uptake of ¹³¹I-labelled triiodothyronine, and the “free thyroxine” index (Clark and Horn, 1965).

Follow-up.—The patients were followed up at the thyroid clinic of the Western Infirmary until May 1968. Those who had not been followed regularly were requested by letter to attend for review. Ninety-one per cent. of the patients were traced. Eight could not be traced and four had died—three after a myocardial infarction and one after a subdural haematoma.

Results

Treatment with Second Course of Drugs.—Twenty-two of the 130 patients received a second course of antithyroid drugs: 12 were treated with carbimazole, 6 with potassium perchlorate, and 4 with methylthiouracil. Of these 22 patients, 17 (77%) relapsed, 14 within six months. Five have remained euthyroid for an average period of five years. The subsequent management of the 17 patients who relapsed is shown in Fig. 2.

Treatment with Surgery.—Of the 130 patients, 40 had a thyroidectomy following relapse. Thirteen (33%) had post-operative complications. Six (15%) had clinical evidence of parathyroid insufficiency and a serum calcium below the lower limit of normal (9 mg./100 ml.). In all but one the serum calcium concentration returned to normal within one year. Two patients had temporary recurrent laryngeal nerve paralysis, two had glottal oedema, three had haematoma, two had wound infections, and one had progressive exophthalmos. Three of the 13 patients became hypothyroid. Two patients relapsed—one three years after operation and the other five years later. Both were subsequently treated with radioiodine, one being rendered euthyroid with two doses and one with one dose. Seven (18%) developed hypothyroidism—two within three months, one between three and six months, three during the second year after operation, and one during the third post-operative year. Four others had a thyroidectomy following relapse after further courses of antithyroid drugs. The period of follow-up for those treated by surgery ranges from one to seven years, and 16 (55%) have been euthyroid for over three years following thyroidectomy.

Treatment with ¹³¹I.—Sixty-eight of the 130 patients were treated with radioiodine initially following relapse. Of these, 33 (48%) subsequently became hypothyroid. Thirty-nine (57%) were cured with one dose, 18 (27%) with two doses, 2 with three doses, and 9 (13%) with more than three doses. In one case treatment extended over seven years. A further 12 patients received radioiodine following relapse after surgery or antithyroid drugs. The dose in mCi and the incidence of hypothyroidism for all 80 patients are shown in Table II. Forty-six (57%) remitted after one dose and 15 (18%) with three or more doses.

FIG. 2.—Results of treatment following relapse after treatment with antithyroid drugs.

Forty-eight (60%) received 10 mCi or more and 39 (49%) of the total group became hypothyroid. The period of follow-up ranges from 1 to 12 years, and 11 patients have remained euthyroid for over five years after receiving radioiodine.

TABLE II.—Dose of Radioiodine Required in Treatment of Recurrent Hyperthyroidism and Incidence of Hypothyroidism Ensuing

	Dose in mCi									
	<5	5	6	7	8	9	10	11-15	16-20	>20
No. euthyroid	2	4	4	3	4	1	0	11	3	9
No. hypothyroid	0	1	2	3	5	3	1	11	3	10

Discussion

"The major advantages of treatment of thyrotoxicosis with the antithyroid drugs are that no damage is done to the thyroid gland, no irreversible changes are induced, lasting myxoedema does not occur, and hyperthyroidism can be corrected uniformly in a reasonably short time" (Astwood, 1963). The major disadvantage of the use of these drugs, however, is the high incidence of relapse which follows. In the further management of those patients who relapse there are three possible lines of treatment. Firstly, the patient may be given a further course of antithyroid drugs; secondly, a thyroidectomy may be performed; and, thirdly, a therapeutic dose of radioiodine may be administered. Solomon *et al.* (1953) found that the proportion of patients experiencing a prolonged remission diminishes with each successive course of antithyroid drugs. In the present study of 22 patients so treated 17 relapsed; five of these were given a third course and two have so far relapsed. It therefore appears that, though it is reasonable to offer a patient a prolonged course of antithyroid drugs when thyrotoxicosis is first diagnosed, if they subsequently relapse it is less certain that this should be repeated. The measurement of thyroid suppression (Alexander *et al.*, 1967) may help to select those who are likely to be effectively treated with antithyroid drugs.

The incidence of hypothyroidism and recurrent thyrotoxicosis following thyroidectomy in the present series does not differ from the incidence in patients treated in the first instance by thyroidectomy (Painter, 1960; Colcock and King, 1962; Roy *et al.*, 1967; McNeill and Thomson, 1968). Nevertheless, the incidence of local complications, in particular hypoparathyroidism, seems high. This may be related to the larger goitres found in patients relapsing after drug treatment.

The results of treatment with radioiodine are comparable with the results reported in other series, though the proportion

requiring more than three doses (14%) is considerably higher (Cassidy and Astwood, 1959; Volpe *et al.*, 1960-1; Green and Wilson, 1964; Staffurth and Young, 1967). These patients display a noticeable resistance to treatment with radioiodine as well as to treatment with antithyroid drugs, and many years passed before their hyperthyroidism was finally brought under control. The incidence of hypothyroidism is somewhat higher than that previously reported in this clinic by Greig (1966) (49% in comparison with 41%), though the period of follow-up in the present series is longer.

The results of treatment of the patient who relapses after antithyroid drug therapy with radioiodine or surgery are therefore not significantly different from the results of treatment in a newly diagnosed thyrotoxic patient. In contrast, the relapse requiring more than three doses (14%) is considerably higher and antithyroid drugs cannot be recommended for routine treatment in this group of patients unless it proves possible to select those patients likely to respond. Nevertheless, we know of doctors who prefer continued treatment with antithyroid drugs to submitting themselves to surgery or ¹³¹I therapy; this is perhaps a matter of personal preference. Whatever method of treatment is used it is clear that long-term follow-up is essential.

REFERENCES

- Alexander, W. D., Harden, R. McG., Shimmings, J., McLarty, D., and McGill, P. (1967). *Lancet*, 2, 681.
 Astwood, E. B. (1963). *Journal of the American Medical Association*, 186, 585.
 Cassidy, C. E., and Astwood, E. B. (1959). *New England Journal of Medicine*, 261, 53.
 Clark, F., and Horn, D. B. (1965). *Journal of Clinical Endocrinology and Metabolism*, 25, 39.
 Colcock, B. P., and King, M. L. (1962). *Surgery, Gynecology, and Obstetrics*, 114, 131.
 Crooks, J., Buchanan, W. W., and Wayne, E. J. (1960). *British Medical Journal*, 1, 151.
 Green, M., and Wilson, G. M. (1964). *British Medical Journal*, 1, 1005.
 Greig, W. R. (1966). *Scottish Medical Journal*, 11, 307.
 McNeill, A. D., and Thomson, J. A. (1968). *British Medical Journal*, 3, 643.
 Painter, N. S. (1960). *British Journal of Surgery*, 48, 291.
 Roy, A. D., Allan, J., and Harden, R. McG. (1967). *Lancet*, 2, 684.
 Solomon, D. H., Beck, J. C., VanderLaan, W. P., and Astwood, E. B. (1953). *Journal of the American Medical Association*, 152, 201.
 Staffurth, J. S., and Young, J. (1967). *Journal of Clinical Endocrinology and Metabolism*, 27, 1062.
 Volpe, R., *et al.* (1960-1). *Canadian Medical Association Journal*, 83, 1407; 84, 37, 84.
 Wayne, E. J. (1960). *British Medical Journal*, 1, 1, 78.
 Wayne, E. J., Koutras, D. A., and Alexander, W. D. (1964). *Clinical Aspects of Iodine Metabolism*. Oxford, Blackwell Scientific Publications.