

Papers and Originals

Surgical Treatment of Thyrotoxicosis

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Summary: A retrospective study of thyrotoxic patients treated by subtotal thyroidectomy between 2 and 21 years ago in the north-east of Scotland showed that 20% of the patients could not be identified or traced at the time of the survey. The thyroid status of 40% of patients followed up was abnormal.

It is now accepted that radioiodine treatment of thyrotoxicosis is followed by a significant incidence of late onset hypothyroidism, and life-long follow-up is regarded as obligatory. The findings in this study indicate that similar methods of aftercare are required for surgically treated patients and for all patients receiving thyroxine-replacement therapy.

Introduction

The discovery of a cumulative incidence of hypothyroidism after the treatment of thyrotoxicosis with radioiodine led to a period of intensive clinical and radiobiological research to establish the frequency of the complication in various centres (Beling and Einhorn, 1961; Blomfield *et al.*, 1959; Crooks, 1965) and to elucidate the effect of ionizing radiation on the thyroid follicular cell (Greig, 1965; Philp, 1966). In contrast there are few comparable studies of the behaviour of the surgical remnant. Our knowledge of the true long-term effects of surgical treatment of thyrotoxicosis in many centres and the relative importance of the factors which may determine the outcome is still incomplete.

A review of the literature from 1925 to 1968 revealed only 16 out of 66 reports in which the total incidence of hypothyroidism and recurrent hyperthyroidism had been evaluated after surgical treatment for thyrotoxicosis. The wide variation in morbidity in 11 recent reports (Table I) may be due to many factors, including the type of operation, the thoroughness of follow-up, the local environment, the immunological status

TABLE I.—Recently Reported Results of Subtotal Thyroidectomy

Author	% Hypothyroid	% Hyperthyroid	% Total Morbidity
Blackburn (1962)	3.0	—	—
Riddell (1962)	3.3	—	—
Green and Wilson .. (1964)	5.0	8.0	13.0
Reeve (1964)	3.6	1.2	4.8
Bowers (1966)	10.6	5.8	16.4
Nofal <i>et al.</i> (1966)	28.0	—	—
Plested and Pollock .. (1967)	11.5	3.8	15.3
Wilson (1967)	24.0	4.0	28.0
Roy <i>et al.</i> (1967)	5.0	11.0	16.0
McNeill and Thompson (1968)	6.5	11.4	17.9
Murley and Rigg .. (1968)	7.6	0	7.5

of the patients, and the adequacy of the clinical and laboratory methods used to define the patients' thyroid status.

A survey of patients treated by subtotal thyroidectomy in Aberdeen in 1946-65 has been carried out. The results are presented in two parts: the identification and recall of patients and the thyroid status of patients who were followed up.

Identification, Location, and Recall of Patients

Identification.—The survey was based on a sample of 254 patients living within the City of Aberdeen. The basic identification information was obtained from the surgical ward admission registers, and additional information was found in the hospital medical records. Patients were included in the survey on the basis of a well-documented record of hyperthyroidism. In most patients treated after 1958 the diagnosis had been confirmed by radioiodine studies or estimation of serum protein-bound iodine (P.B.¹²⁷I). The histopathological reports were retrieved and the original histological sections examined in a proportion of patients. Care was taken to exclude doubtful cases and all patients with single nodules and multinodular glands.

Location.—A form containing the identification details of each patient was sent to the patient's last recorded general practitioner with a request for the data to be verified and permission to review the patient. All forms were returned. With additional information about four patients from the executive council a classification of the 254 patients was produced from general practice records (Table II), which showed

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TABLE II.—Identification of Patients Through Records in Hospital, General Practice, and Executive Councils

Information about Patients	No.	Percentage of Total
No. sampled	254	100
Identified by general practitioners	194	76.4
Traced by executive council	4	1.6
Total identified	198	78.0
No information	33	12.9
Migrated	17	6.7
Dead	6	2.4
Total Lost	56	22.0

that 198 (78%) could be identified while 56 (22%) were lost. Six (2.4%) patients were known to be dead, 17 (6.7%) had left the area, and 33 (12.9%) were unknown. Relatives, neighbours, and former employers provided information about the 17 who had left the district—10 (58.8%) had moved to other parts of Scotland or England, 5 (29.4%) had emigrated to Commonwealth countries, and 2 had husbands in the armed Forces.

Recall.—Over an 18-month period 179 (90.4%) of the 198 patients apparently in the care of their general practitioners were successfully traced and examined. Forty-five did not respond to the first recall letter; 19 of these were never examined and there was difficulty in tracing and following up the other 26. Twenty-one out of the 45 had incorrect addresses, but 19 of these were eventually traced and another patient was found to be dead. Seven patients responded to a second or third request and 16 were unwilling or unable to attend.

Thyroid Status at Follow-up

The data presented are from 146 patients in the group of 179 followed up, who were operated on in the same surgical unit. The group consisted of 132 females and 14 males (ratio 9.4:1). The interval between operation and follow-up ranged from 2 to 21 years (mean 9.3 years).

The findings in patients who had developed recurrent hyperthyroidism after operation are reported together with additional information obtained from a separate group of 12 patients with a recurrence. They did not belong to the original survey sample but were seen at the clinic during the period of the survey and had been treated in the same surgical unit. The operative procedure in these patients was designed to leave a thyroid remnant of 3 to 6 g. and was not dependent on the initial gland size. The mean estimated remnant size at operation for 128 patients was 4.3 g.

Methods of Investigation

The clinical assessment of thyroid status was based on diagnostic indices for hypothyroidism (Billewicz *et al.*, 1969) and for hyperthyroidism (Crooks *et al.*, 1960). An electrocardiogram (E.C.G.) was obtained, and in some cases an objective assessment of the ankle-jerk response was made from a velocity/time curve tracing (Bowley *et al.*, 1969). Both the E.C.G. and ankle-jerk tracings were made on a standard Cambridge recorder with a paper speed of 25 mm./sec. At the beginning of the study the serum P.B.¹²⁷I was estimated by a manual digestion method (Farell and Richmond, 1961), but later measurements were made by Technicon AutoAnalyzer (AutoAnalyzer methodology N.56) with allowance for the change in the normal range of values. The serum cholesterol was also estimated by AutoAnalyzer (AutoAnalyzer methodology N.24a).

The resin uptake of ¹²⁵I-labelled triiodothyronine was mea-

sured and the free thyroxine index calculated (Clark and Horn, 1965).

Diagnosis of Hypothyroidism

If after a full assessment of all the clinical and laboratory data doubt remained about the presence of hypothyroidism, a therapeutic trial with thyroxine was begun. A daily dose of 0.025 mg. or 0.05 mg. was given initially and increased at monthly intervals to 0.2 to 0.3 mg. daily. Serial assessments of the patient's thyroid status during the trial were made using the diagnostic index for hypothyroidism, serum cholesterol, E.C.G., and ankle-jerk response. Changes in the objective measurements were regarded as significant if: (a) the serum cholesterol level fell with increasing doses of thyroxine and was reduced by 70 mg./100 ml. or more with 0.1 mg. of thyroxine, and the fall was sustained; (b) the ankle jerk response decreased by 40 msec. for each 0.05-mg. increase in thyroxine; or (c) there was a resolution in serial E.C.G.s of prolonged P-R intervals, low voltage P waves, and QRS complexes and resolution of T wave flattening or inversion. A diagnosis of hypothyroidism was made if these changes occurred in two of the three criteria. Patients satisfying only one of the criteria were classified as "equivocal."

In the case of patients already taking some form of thyroid replacement therapy their records in hospital or general practice were examined for confirmatory pretreatment evidence of hypothyroidism, or the response of the four-hour gland uptake of radioiodine (¹³¹I) to exogenous thyrotropin was observed (Greig *et al.*, 1967). If doubt remained replacement therapy was withdrawn for a trial period.

Diagnosis of Hyperthyroidism

When the diagnostic index and serum P.B.¹²⁷I indicated hyperthyroidism the four-hour gland uptake of ¹³¹I was measured and the response to triiodothyronine observed (Hobbs *et al.*, 1963). If doubt remained the final diagnosis was based on the outcome of a therapeutic trial with antithyroid drugs.

Results

On completion of the initial screening tests in the 146 patients it was found that 39 were receiving some form of thyroid replacement therapy and 107 were untreated. In the non-thyroxine-treated group 56 patients were shown to be euthyroid, nine were hypothyroid, and five had recurrent hyperthyroidism. Doubt existed about the thyroid status of the remaining 37. Hypothyroidism was suspected in 36 and hyperthyroidism in one. The 36 with suspected hypothyroidism were selected for a trial with thyroxine, but 12 declined further investigation and for statistical purposes have been regarded as euthyroid. At the completion of the trial in 24 patients, 5 were shown to be hypothyroid, 7 were graded "equivocal," and 12 were euthyroid. The diagnosis of recurrent hyperthyroidism in the remaining patient was confirmed by a negative triiodothyronine suppression test and a pronounced clinical and biochemical response to antithyroid drugs. In the seven "equivocal" patients treatment with thyroxine produced significant changes in the E.C.G. in two, the ankle-jerk measurement in three, and the serum cholesterol in two.

The final classification of the 146 patients (Fig. 1) shows that 80 (54.8%) were euthyroid and 7 (4.8%) were graded "equivocal." Thirty-nine patients (26.7%) with hypothyroidism were receiving some form of replacement therapy and an additional 14 (9.6%) had untreated hypothyroidism—half of these had previously received thyroxine but the tablets had been stopped. Six patients (4.1%) had untreated hyperthyroidism, while a total of 9 (6.2%) in the sample had a past or present history of recurrent hyperthyroidism.

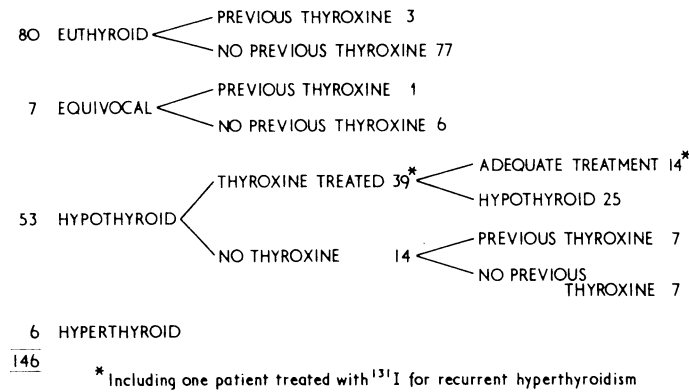


FIG. 1.—Thyroid status of 146 patients after investigation at follow-up.

Only three patients in whom previous thyroxine therapy had been stopped were euthyroid. Of the 39 thyroxine-treated patients, 14 (36.8%) were euthyroid and the remainder hypothyroid. Only 10 patients were receiving the dose originally prescribed. It had been increased in 11 patients by the general practitioner, by the hospital, or on the patient's own initiative, and reduced or stopped in 18 patients, sometimes during a hospital admission for an unrelated condition.

Seven (27%) of the 26 patients whose follow-up was difficult had an abnormal thyroid status; four had not been detected before the survey. Two of the 14 untreated hypothyroid and two of the six hyperthyroid patients were found in this group.

Hypothyroidism

It was not possible to determine with certainty from the hospital records available or the patient's verbal history the point in time at which the hypothyroidism had occurred in those who were not receiving thyroxine. The proportion of patients successfully followed up decreased with the time which had elapsed since operation ($\chi^2 = 19.9, P < 0.001$), and there was also a downward trend in the proportion of hypothyroid patients detected ($\chi^2 = 10.8, P < 0.01$). Thirty-seven (71%) of the hypothyroid patients had been operated on between 2 and 10 years before the survey, the other 16 had been treated from 11 to 21 years previously.

Recurrent Hyperthyroidism

This survey showed that though the incidence of hypothyroidism in the group was high an appreciable number of patients had developed recurrent hyperthyroidism. To obtain more information about patients who develop recurrent hyperthyroidism after surgery, the characteristics of a separate group of 12 patients treated by the same surgical team were examined together with the six patients detected by the present follow-up survey. Fifteen were hyperthyroid at review and three had been previously detected and treated. Ten were specifically recalled for review, another was detected while attending the diabetic clinic, and seven were referred by general practitioners. Six patients had undergone a second operation for a previous episode of recurrent hyperthyroidism.

After operation three patients developed recurrences within the first five years, two of these within 12 months of operation, and nine within 10 years. The remaining nine developed recurrences between 10 and 20 years after operation, but the time of onset for many is uncertain. After a second operation five patients had a further recurrence of hyperthyroidism and

the other patient developed hypothyroidism which was undetected until the survey. One patient had a recurrence within three months and three patients within five years. The other two were detected at between 13 and 18 years after operation.

Efficacy of Diagnostic Methods

The hypothyroid diagnostic index correctly labelled 68 (85%) of the 80 euthyroid patients, and placed 12 (15%) in the doubtful range (Fig. 2). In the group of 14 untreated hypothyroid patients only four were graded hypothyroid by the

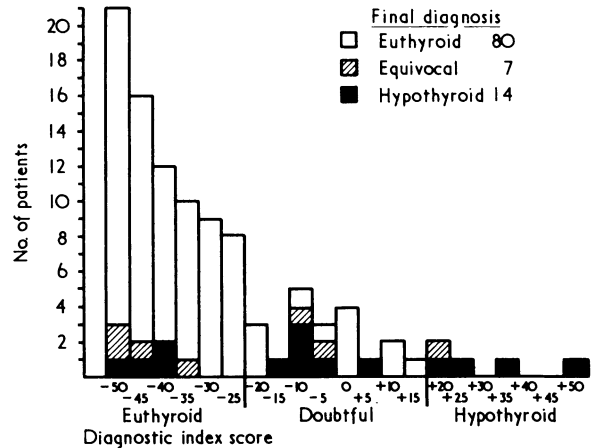


FIG. 2.—Classification by hypothyroid diagnostic index of 101 patients not receiving thyroxine.

index and 10 appeared in the doubtful or euthyroid range. Four of the seven "equivocal" patients were graded euthyroid two as doubtful, and one as hypothyroid.

Twelve (85.7%) of the 14 patients euthyroid on replacement therapy were placed in the euthyroid range and two in the doubtful range. Twelve (48%) of the 25 inadequately treated patients were graded euthyroid, and 13 appeared in the doubtful or hypothyroid range (Fig. 3).

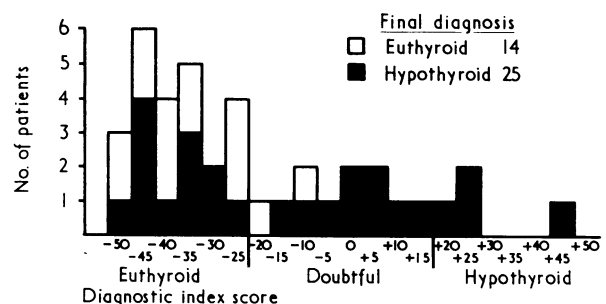


FIG. 3.—Classification by hypothyroid diagnostic index of 39 patients receiving thyroxine.

The P.B.¹²⁷I did not give good separation of euthyroid, "equivocal," and hypothyroid patients with either method used. For patients in these categories overlap occurred in 47 (78.3%) out of 60 values determined by the manual method and 25 (61%) out of 41 values determined by AutoAnalyzer. Hyperthyroid patients were clearly separated from the rest apart from pregnant euthyroid patients or those taking oral

contraceptive agents. The free thyroxine index clearly separated the hyperthyroid patients but did not improve on the performance of P.B.¹²⁷I as 25 (48%) out of 52 values for euthyroid, equivocal, or hypothyroid patients overlapped.

Discussion

The present study indicates that a retrospective review of this kind is an unsatisfactory method of assessing the long-term effects of surgical treatment for thyrotoxicosis. The large number lost to follow-up precludes an accurate assessment of the total morbidity which has accrued since operation. The identification data needed to carry out the follow-up were retrieved, for most patients, only after a difficult and laborious search. Records in hospital, general practice, or the executive councils were inaccurate for 75 patients, and as a result 20% of the original patient sample, who were not known to have emigrated or died, were lost to follow-up.

The fall in the numbers followed up with increasing time from operation closely parallels the fall in the proportion of hypothyroid patients found over the same period. The reason for this observation is not clear, but one possible and disturbing explanation is that the presence of thyroid dysfunction itself may be in part responsible for the reasons why follow-up has failed. The importance of lost patients is underlined by the fact that 28% of the group whose follow-up was difficult had an abnormal thyroid status; 14% of the untreated hypothyroid patients and one-third of all patients with active hyperthyroidism were in this group. One criticism sometimes made of screening procedures of this kind is that many of the abnormal patients detected have only mild disease. This was certainly not true in this study, and some patients were seriously ill. This finding indicates that patients' use of the health services is often random and not related to the presence of symptoms or their severity.

The finding of several patients without any subjective complaints or objective clinical findings of thyroid dysfunction who had clear evidence of thyroid insufficiency from thyroid function tests, and the fact that only four untreated hypothyroid patients showed pronounced clinical evidence of the disease, emphasized the difficulty in diagnosing hypothyroidism in patients treated with destructive therapy for thyrotoxicosis.

In the 46 patients who had been started on life-long thyroxine replacement therapy, treatment had been stopped in 15.2% and was inadequate in a further 54.3%. Default in drug taking has been described in other situations by Porter (1969) and Bonnar (1969), and Philp *et al.* (1968) found that 14% of patients receiving thyroxine defaulted on treatment during a two-year period of regular surveillance. Our studies on the behaviour of the thyroid remnant have shown that the gland uptake of radioiodine in some hypothyroid patients fails to suppress with triiodothyronine, and similar observations have been made by D. A. Koutras (personal communication, 1969). Hypothyroidism in these patients may be corrected with lower doses of replacement therapy than would be required for patients whose gland function is ablated. If the extrapituitary stimulus to the gland decreases at a later date and full suppression then occurs, it is possible that hypothyroidism may develop in some thyroxine-treated patients several years after stabilization on adequate replacement doses. It is clear, therefore, that there are several reasons why the initiation of life-long replacement therapy does not obviate the need for regular and effective long-term monitoring of the thyroid status of these patients.

In this survey the finding of several patients with recurrent hyperthyroidism together with a large number of hypothyroid patients suggests that there is a group of patients who respond to surgical treatment in a fundamentally different way from

the rest. This idea is supported by the fact that none of the six patients treated with a second subtotal thyroidectomy for recurrent hyperthyroidism were rendered euthyroid and all but one had a further recurrence. Similar findings have been reported recently by McLarty *et al.* (1969). It is evident that there can be no justification for a second operation for recurrent hyperthyroidism, as it is unlikely to render the patient euthyroid.

It has been suggested by Green and Wilson (1964), Nofal *et al.* (1966), and Bronsky *et al.* (1968) that there is a cumulative incidence of hypothyroidism after subtotal thyroidectomy. There is no evidence of this in the present series, as hypothyroidism had been present in most patients from the early post-operative period, but more complete observations on a prospective basis are needed to evaluate this problem.

It has been suggested by Crile and McCullagh (1951), Painter (1960), and Wilson (1967) that in some centres the incidence of hypothyroidism and recurrent hyperthyroidism is inversely related to the size of the remnant left at operation. The high incidence of hypothyroidism in this series might then be attributed to an over-radical resection of tissue. In 13 reports published between 1927 and 1967, the estimated remnant size at operation ranged from 0.4 to 30 g., but the values for 9 out of 13 reports lie between 2 and 8 g. Even accepting that the assessment of remnant size is wholly subjective and therefore open to considerable error, the present operation is comparable to the other series in which the incidence of hypothyroidism ranged between 2.4% and 24%. Recent experience has shown that larger remnants do not protect 30% of our patients from hypothyroidism, and one must therefore question the justification for leaving more tissue and incurring greater numbers with recurrent hyperthyroidism at a later date.

Environmental factors such as the prevailing dietary iodine level may be of greater importance than previously recognized in determining the outcome of treatment. B. Thjodleifsson (personal communication, 1968) carried out a parallel study to this one using the same diagnostic methods in a group of 146 patients treated for thyrotoxicosis by surgery in Iceland, where dietary iodine is relatively high. A radical subtotal thyroidectomy had been employed, and the mean estimated remnant size at operation was about 4 g. The incidence of recurrent hyperthyroidism is 25% after a follow-up period of 29 years. The corresponding incidence of hypothyroidism is 7.5%.

An association between the presence of thyroiditis and post-operative hypothyroidism has been described by Whitesell and Black (1949), Greene (1951), and Levitt (1953), but the relative incidence of thyroiditis in different geographical regions is unknown. More information on this point is being sought from a detailed investigation of the immunological status of patients with thyrotoxicosis in the north-east of Scotland and Iceland.

In our experience the response to the surgical treatment of thyrotoxicosis is unpredictable in the individual patient. It is disturbing, therefore, that so few morbidity data are obtainable from comparable studies. All the information in this and other series has had to be specially collected, and on this occasion it led to the treatment of one-third of the patients. Incomplete retrospective studies provide incomplete data and may be misleading about the efficacy of treatment.

It seems unrealistic to embark on large-scale screening programmes for the detection of natural pathology and ignore other "at risk" groups simply because the original disease has been treated. The feasibility of following up patients "at risk" from iatrogenic disease has been shown in the north-east of Scotland, where the aftercare of all patients who have been treated by destructive therapy for thyrotoxicosis in the Aberdeen clinic is now controlled by their general practitioners using an automated follow-up register with central data-processing facilities (Hedley *et al.*, 1970). The system provides a

means of combining the follow-up of patients and the early detection of complications with a prospective study of the long-term results of treatment.

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Amniotic Fluid Cells; Prenatal Sex Prediction and Culture

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Summary: Sex chromatin studies were carried out on small amounts of amniotic fluid obtained by amniocentesis or from intact amniotic sacs removed at hysterotomy. Provided that satisfactory preparations were obtained the accuracy of fetal sexing was 87%. Nevertheless, in the management of a pregnancy in which there is a risk of a serious X-linked recessive disorder, repeat amniocentesis may be necessary to ensure satisfactory specimens.

Of 90 samples of fluid cultured, satisfactory growth was obtained in 49; the success rate was not increased by the addition of stimulants to the culture medium. It is suggested that between the 13th and the 16th week of pregnancy is the optimum time for amniocentesis to obtain cells for culture, since sufficient cells are then present in a small volume of fluid and therapeutic abortion would still be possible once the results were available.

Introduction

It is now accepted that the cells present in amniotic fluid are of fetal origin (Votta *et al.*, 1968; Wachtel *et al.*, 1969). The exact source of these cells, however, has not yet been established (Wachtel *et al.*, 1969), though it seems likely that skin and amnion are the major source (Votta *et al.*, 1968).

The cells in the amniotic fluid have become the subject of

much interest recently because of the possibilities of antenatal diagnosis (Emery, 1970). Uncultured cells have been used for sex chromatin studies (Amarose *et al.*, 1966) and for enzyme studies (Nadler and Gerbie, 1969). Cultured cells have been studied for chromosome abnormalities (Steele and Breg, 1966; Thiede *et al.*, 1966; Jacobson and Barter, 1967; Valenti and Kehaty, 1969) and for enzymes (Nadler, 1968). Unfortunately the limitations and complications of these techniques have usually received little attention and have not been emphasized.

The present study had two main objects: (1) to determine the accuracy of sex prediction under conditions which obtain in practice—that is, using *small* amounts of fluid, and (2) to determine the conditions necessary for satisfactory culture of amniotic fluid cells.

Materials and Methods

This report is based on our findings in the first 200 specimens received in this laboratory. Of these, 143 were obtained by transabdominal amniocentesis during the management of Rh-negative pregnancies, 17 by amniocentesis for other reasons, and 40 from intact sacs removed at hysterotomy.

At amniocentesis the usual volume obtained was 3 to 10 ml. The fluid was collected in sterile plastic universal containers. Specimens were either transferred within one to two hours to the laboratory or, where this was not practicable, they were stored at 4°C. for up to 18 hours. Sacs obtained at hysterotomy were collected as soon as possible after the operation and as much fluid as could be obtained without contamination with blood was aspirated by syringe from the sac. Specimens from

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