Summary

Eggs of *T. canis* and ascarid worm of dogs hatch in man's intestine and give rise to larvae which several studies have shown may damage the sight of man ; a further case of this is here reported.

A survey carried out among dogs and cats in Southern England indicated that approximately 20% are infected with either *T. canis* or the related species *T. cati.*

There is therefore a considerable possibility that infection with these parasites may occur more commonly than is generally realized among households in which a dog or cat is kept.

The seeming predilection that toxocara larvae have for invading the eye is thought to be more apparent than real. When, however, the larvae invade tissues other than the eye, diagnosis of the infection is difficult and clinically may be manifest only by a transient allergic state.

In view of this, experiments have been carried out using an intradermal test with antigen prepared from adult *T. canis.*

When antigen in a dilution of 1 in 1000 is used, cross-reactions do not seem to occur in patients infected with worms other than *T. canis* or *T. cati* and false-positive reactions rarely if ever occur in controls free from demonstrable infections.

The use of this test in a series of 35 patients with a history of past or present asthma, urticarial skin eruptions, choroido-retinitis, or otherwise unexplained eosinophilia indicated that 11 of them had been infected with *T. canis* or *T. cati* in the past.

It is suggested that more attention should be given to the danger these infections constitute to the public health.

Many members of the medical unit at the Hospital for Tropical Diseases have assisted in this work at various times and we are particularly grateful to Dr. S. Bell, Dr. Z. Farid, Dr. B. Bisseru, and Dr. M. Lowenthal. To Dr. D. S. Ridley, pathologist to the Hospital for Tropical Diseases, to Dr. H. A. Dutton, to Dr. A. P. M. Page, and to Professor J. J. C. Buckley we are grateful for much help and data.

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Thyrotoxicosis Treated By Surgery or Iodine-131. With Special Reference to Development of Hypothyroidism

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Treatment of thyrotoxicosis with ^{131}I has been available in Britain since 1949. The attractiveness of the method lies in its simplicity from the patient's point of view and in the almost complete absence of any immediate complications. Admission to hospital is often not required. These are considerable advantages in comparison with partial thyroidectomy. However, with more experience certain disadvantages have emerged ; these include delay in controlling hyperthyroidism and a high incidence of subsequent hypothyroidism (Blomfield, *et al.*, 1959). For several reasons it has not been possible to arrange an ideal comparison of these two methods of treating thyrotoxicosis.

In this country, on account of the uncertainty regarding possible late ill effects of irradiation, the use of ^{131}I is usually restricted to those over 40 years of age unless there are complicating factors which might increase the risk of surgery. These include the recurrence of thyrotoxicosis after operation, severe heart disease, and the presence of other disorders such as diabetes mellitus. In these circumstances several patients under 40 years of age have been treated with ^{131}I. On the other hand, partial thyroidectomy has been most commonly performed on otherwise fit patients under 40 years of age. There is a range of patients over this age with uncomplicated thyrotoxicosis amongst whom a scientifically designed comparison might be carried out, but it is difficult to arrange this on a large scale as the method of treatment is so commonly selected before arrival at hospital, depending on whether the patient has been referred to a physician or surgeon. An exact comparison of the therapeutic value of the two methods has not been possible, but the progress of a large number of patients has been investigated after both forms of treatment, with particular reference to the development of subsequent hypothyroidism.

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Patients Treated by Partial Thyroidectomy

A search was made of the operation registers covering the period 1 January 1949 to 31 December 1960 at the Sheffield Royal Infirmary and at an associated unit at Wharncliffe Hospital, where some of the patients were transferred for surgery. From them a list was prepared of all patients who had a partial thyroidectomy on account of established or possible thyrotoxicosis. The case records of these patients were studied to confirm the diagnosis. In the earlier years the assessment had been made largely on the clinical features, but in the later years fuller investigation, including radioactive iodine tracer tests (Wayne, 1954), protein-bound-iodine measurements (Acland, 1958), and serological tests for autoimmune reactions had been carried out. Histological study of the excised tissue had been made in all the cases, but establishment of the diagnosis on this basis alone was not possible as pre-operative treatment with iodide had invariably been given in all suspected cases of thyrotoxicosis. In many the operation had been carried out on account of nodular goitres or solitary nodules associated with anxiety symptoms and there was no well-substantiated evidence

of hyperthyroidism. However, it was nearly always possible to decide from the available details whether the patient was in fact thyrotoxic. Where any doubt remained the patient was excluded from the series.

A total of 251 patients with thyrotoxicosis treated by partial thyroidectomy was achieved in this way; 236 of them were finally traced and 213 attended for examination during the period 1 November 1960 to 31 December 1962. Thirteen had died, information about them being obtained from their relatives and medical practitioners and from the Registrar of Births and Deaths. The 10 remaining patients were unable to attend for examination but they and their doctors supplied information by post. Fifteen could not be traced.

The patients had been treated by three different surgical units and thus the results are assembled from the work of many surgeons. The same general methods were used by all. Thyrotoxicosis was treated first by an antithyroid drug, usually carbimazole, to render the patient euthyroid; the drug was then stopped and iodide was given for about two weeks before operation.

When these patients attended for review they were examined clinically and further investigations, including ^{131}I-tracer tests and protein-bound iodine determinations, were carried out as required to confirm the clinical assessment.

Results of Treatment by Partial Thyroidectomy

Operative Complications

Mortality.—One patient died after a cerebral haemorrhage on the fifth post-operative day. She was a 68-year-old woman who was making normal progress until her sudden death, which was clearly not directly attributable to the operation. No other deaths occurred during the post-operative period in hospital.

Tetany.—Three developed mild tetany which was transient and required no treatment. Clinical signs of latent tetany could not be induced at subsequent reviews and the patients appeared in good health.

Vocal Cord Paresis.—Some hoarseness of the voice due to damage to the laryngeal nerve occurred in 12 patients (5%) but persisted in only three. Two of these have little difficulty; one, however, is a school teacher who has some residual disability owing to hoarseness of the voice towards the end of the day. There was no evidence that the amount of thyroid gland removed in these patients was excessive. Of the 12 patients involved, nine became euthyroid and three remained thyrotoxic. None developed tetany or hypothyroidism.

Wound Infection.—Small collections of serous fluid requiring aspiration or small haematomata occurred in 39 patients. They did not delay healing of the wound or discharge from hospital. Nine patients developed stitch abscesses which caused irritating delays in healing though all were treated as out-patients.

Imperfect Wounds.—Slight keloids or nodules causing cosmetically imperfect scars occurred in 10 patients but none was gravely disfiguring.

Other Complications.—One patient had a small segmental pulmonary collapse and a corneal abrasion, both of which resolved satisfactorily but caused some delay in discharge from hospital. There were no thyrotoxic crises.

Subsequent Thyroid Function

Euthyroid Patients.—The results in the 236 patients were analysed at the time either of the follow-up examination or of death (Table I). Within six months of operation 161 patients (68%) became euthyroid, and 183 (78%) within a year: the remaining 22 in this group showed slow improvement and eventually became euthyroid without requiring any further treatment.

Persistent or Recurrent Thyrotoxicosis.—Nineteen patients either remained thyrotoxic after operation or had a recurrence necessitating further treatment. Thirteen subsequently received

TABLE I.—*Results of Treatment*

Total	Euthyroid		Hypothyroid		Hyperthyroid	
	No.	%	No.	%	No.	%
Partial Thyroidectomy						
236	205	87	12	5	19	8
^{131}I Therapy						
918	648	71	180	20	90	9

^{131}I therapy and the others who survived became permanently euthyroid after a course of treatment with antithyroid drugs.

Development of Hypothyroidism.—Twelve patients ultimately became hypothyroid. The diagnosis was confirmed by investigations at hospital clinics in all cases. The incidence is related to the length of the follow-up period (Table II). After one year it is less than 2%, but with the passage of time it rises to about 6% in the survivors. Among the 153 patients under 40 years of age there were seven (4.6%) who developed hypothyroidism, while among the 83 over 40 years of age there were five (6.1%).

Histological Features and Hypothyroidism

Histological sections of the excised thyroid tissue were available from 227 patients and were examined for the presence of focal thyroiditis (Williams and Doniach, 1962). Focal thyroiditis was considered negligible if there were fewer than two foci of lymphocytic infiltration in the whole section, slight if fewer than 10 foci per sq. cm., and marked if more than 10 foci per sq. cm. The presence of germinal follicles was usually associated with conspicuous lymphocytic infiltration. All the

TABLE II.—*Incidence of Hypothyroidism after Partial Thyroidectomy or ^{131}I Therapy*

Years after Treatment	Partial Thyroidectomy									^{131}I Therapy								
	Age <40			Age 40 or Above			Total			Age <40			Age 40 or Above			Total		
	No. of Cases	Hypothyroid		No. of Cases	Hypothyroid		No. of Cases	Hypothyroid		No. of Cases	Hypothyroid		No. of Cases	Hypothyroid		No. of Cases	Hypothyroid	
		No.	%		No.	%		No.	%		No.	%		No.	%		No.	%
1	153	1	0·7	80	2	2·5	233	3	1·3	82	4	4·9	822	76	9·3	904	80	8·9
2	132	2	1·5	74	2	2·7	206	4	1·9	79	6	7·6	694	83	12·0	773	89	11·5
3	114	2	1·8	71	2	2·8	185	4	2·2	72	5	6·9	567	79	14·0	639	84	13·2
4	102	3	2·9	65	2	3·1	167	5	3·0	68	7	10·3	461	75	16·3	529	82	15·5
5	81	5	6·2	60	2	3·3	141	7	5·0	62	7	11·3	390	78	20·0	452	85	18·8
6	70	4	5·7	53	3	5·7	123	7	5·7	59	9	15·3	307	67	21·8	365	76	20·8
7	53	3	5·7	47	2	4·3	100	5	5·0	53	8	15·1	239	54	22·6	292	62	21·2
8	43	1	2·3	40	2	5·0	83	3	3·6	41	7	17·1	163	45	27·6	204	52	25·5
9	34	1	2·9	30	2	6·7	64	3	4·7	31	5	16·6	100	31	31·0	131	36	27·5
10	24	1	4·2	23	2	8·7	47	3	6·4	21	3	14·9	45	16	35·6	66	19	28·8
11	19	1	5·3	15	0	0·0	34	1	2·9	6	2	33·3	13	6	46·2	19	8	42·1
12	6	0	0·0	8	0	0·0	14	0	0·0	1	1	100·0	4	1	25·0	5	2	40·0

sections were classified by one of us (M.G.) without knowledge of the clinical results. In addition 20 sections were examined independently by Dr. J. Tighe, of the department of pathology at the Royal Infirmary, and close agreement was found between the two observers. Finally, 30 sections were re-examined two years later by M. G. under code lettering so that their identity was hidden ; five were placed in different categories, and these involved a change of only one stage.

The incidence of hypothyroidism increased with the greater degrees of focal thyroiditis (Table III).

TABLE III.—*Relation Between Clinical Result of Partial Thyroidectomy and Histology*

Focal Thyroiditis	No. of Patients	Euthyroid		Hypothyroid	
		No.	%	No.	%
Negligible	160	155	97	5	3
Slight	21	19	90	2	10
Marked	27	22	82	5	18

Focal Thyroiditis and Serological Reactions

Thyroglobulin tanned-red-cell agglutination and complement-fixation tests were performed using the methods described by Roitt and Doniach (1958). Most of the blood samples for these tests were obtained only at follow-up examinations at varying intervals after partial thyroidectomy. It is thus important to ascertain whether the operation itself has any effect on these reactions.

Tanned-red-cell agglutination tests were carried out in 16 patients shortly before operation, and further blood samples were obtained several months later. There was no change in 11 patients, and a rise or fall by only one dilution in five ; these changes were regarded as insignificant. Complement-fixation tests were similarly carried out before and after the operation in 17 patients. There was no definite change in 12 ; in the remaining five the titre rose in two and fell in three by more than two dilutions. The operation thus had no consistent effect on the serological reactions.

The results of the tests in all the patients studied are shown in Tables IV and V. There is some correlation between the presence of focal thyroiditis and the occurrence of high titres, but this is by no means absolute.

TABLE IV.—*Relation Between T.R.C. Titre and Histological Evidence of Focal Thyroiditis*

Focal Thyroiditis	No. of Cases	T.R.C. Titre					
		0–25		250–2,500		25,000–2,500,000	
		No.	%	No.	%	No.	%
Negligible ..	107	85	80	17	16	5	4
Slight ..	20	12	60	4	20	4	20
Marked ..	17	7	40	5	30	5	30

TABLE V.—*Relation Between C.F.T. Titre and Histological Evidence of Focal Thyroiditis*

Focal Thyroiditis	No. of Cases	C.F.T. Titre					
		0–8		16–64		128–512	
		No.	%	No.	%	No.	%
Negligible ..	99	89	90	8	8	2	2
Slight ..	17	14	82	2	12	1	6
Marked ..	13	8	62	3	23	2	15

Serological Reactions and the Development of Hypothyroidism

A similar correlation is evident between the incidence of high titres and the occurrence of hypothyroidism after partial thyroidectomy (Table VI). This complication is more likely to develop in those with strongly positive reactions. However, several patients with high titres were euthyroid at the time of examination, which varied from two to ten years after operation.

TABLE VI.—*Relation Between Clinical Result of Partial Thyroidectomy and Serological Studies*

	No.	Euthyroid		Hypothyroid	
		No.	%	No.	%
C.F.T. :					
0–8	110	106	96	4	4
16–64	19	17	90	2	10
128–512	5	4	80	1	20
T.R.C. :					
0–25	96	93	97	3	3
250–25,000 ..	26	24	92	2	8
25,500–2,500,000	11	9	82	2	18

Patients Treated by ^{131}I Therapy

Between 1 January 1949 and 31 December 1960 925 thyrotoxic patients were treated by ^{131}I. To confirm the diagnosis detailed investigations had been carried out in all of them before treatment. Preliminary tracer tests were done as a routine, and these were frequently supplemented by other laboratory investigations. Most of these patients have attended regularly at a follow-up clinic, but inevitably some have lapsed. In order to review the results of treatment an attempt was made to ascertain the condition of all these patients in the period between 1 November 1960 and 31 December 1962. The condition of 738 was known, as they were either attending the clinic or information regarding death had been received. The remaining 187 were not attending regularly, but in response to a postal request 139 reported for review in person. Postal information was received concerning a further 41. It was impossible to trace seven patients. Seventy-nine were dead, and the cause of death was ascertained in all. There was one case of leukaemia, which has already been reported (Green *et al.*, 1961).

The general policy in the selection of patients for treatment has not been changed over the whole period since 1949. Patients under 40 years of age have not been treated unless some complicating factors have been present. The method of determining the dose of ^{131}I has been kept constant since 1951, the aim being to deliver 7,000 rads to the gland (Blomfield *et al.*, 1959). The uncertainties in this determination are fully realized, but it has not been altered, so that the long-term follow-up of these patients is not confused by changing methods.

The clinical diagnosis of hypothyroidism was confirmed in every case by ^{131}I tracer tests, serum cholesterol measurements, electrocardiograms, and to an increasing extent since 1955 by serum protein-bound iodine determinations. All but three of the patients who became hypothyroid were seen at our clinic before treatment with thyroxine was started, and in these three the details supplied fully justified the diagnosis. Transient hypothyroidism may occasionally be observed a few months after ^{131}I therapy, and a certain degree of recovery may apparently ensue on further observation. During the first year after treatment with ^{131}I it has been our practice to watch these patients carefully for about two or three months after clinical suspicion of hypothyroidism has been aroused. Treatment with thyroxine was not started unless it was clear that the hypothyroidism was progressive. Although the occurrence of merely transient hypothyroidism has been stressed by many, it has been our experience that all patients who show some definite signs of hypothyroidism in the first year after therapy eventually go on to fully established hypothyroidism. Progress of the condition may be slow and the full features may not be evident until a year or two later: hypothyroidism appearing more than a year after the ^{131}I therapy is never transient.

Results of ^{131}I Therapy

The results in 918 patients treated with ^{131}I are shown in Table I. However, a crude analysis of this type is misleading as the patients still hyperthyroid received further treatment which eventually brought the condition under control. Indeed, in studying the results in detail it becomes apparent that time is the most important factor to be considered in any analysis of the effects of ^{131}I therapy.

Immediate Complications of ^{131}I Therapy.—These have been rare. In two patients a severe exacerbation of the thyrotoxicosis occurred and a state resembling a thyroid crisis developed. In both patients this was apparently precipitated by a severe infection—bronchopneumonia in one and acute pyelonephritis in the other. Both survived the crisis. In two other patients there was a transient and much less severe exacerbation of symptoms, again associated with infection. In a few cases a slight aching in the neck has been noted lasting a few days and causing only minimal discomfort. There have been no other complications directly attributable to the ^{131}I therapy.

Euthyroid Patients.—At the time of review 71% of the patients were euthyroid. However, this was often achieved only after considerable delay. Only 466 (51%) patients became euthyroid after a single dose, 257 required two doses, 73 three doses, 18 four doses, and 2 have received five doses, one eventually needing even further treatment. Within six months of the initial dose of ^{131}I 442 patients (48%) became euthyroid; a further 202 became euthyroid within a year. Thus 644 (70%) were euthyroid within one year. After the first dose there is almost always some improvement even though the patient does not rapidly become euthyroid. The general trend is a slow decrease in thyroid activity. Several patients, euthyroid at the end of a year, eventually became hypothyroid. There was no case of recurrence of thyrotoxicosis after successful ^{131}I therapy.

Hypothyroidism.—The incidence of hypothyroidism in surviving patients is shown in Table II. This rises steadily with the passage of time after the first treatment with ^{131}I, to reach 29% after 10 years. The higher figures of about 40% after 11 and 12 years refer to the first patients treated with ^{131}I in Sheffield in 1949 and 1950, before the present method of determining the dose was introduced. They received slightly larger amounts of ^{131}I. Subsequent patients were all treated by one standard method, and in them a linear rise in incidence of hypothyroidism is evident. This is a striking contrast with the patients treated by partial thyroidectomy (Fig. 1).

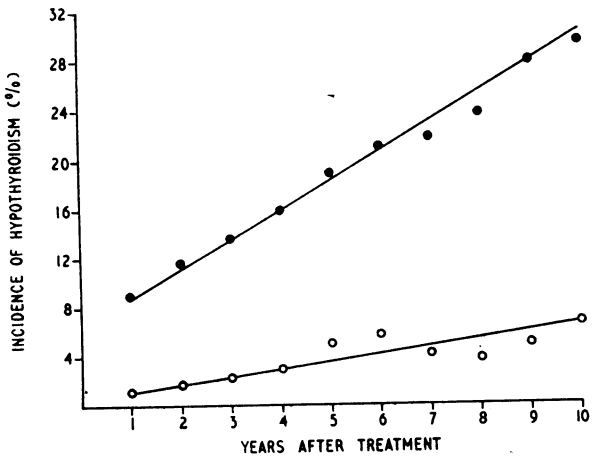

FIG. 1.—Rise in incidence of hypothyroidism after treatment by partial thyroidectomy (open circles) or ^{131}I therapy (closed circles).

Several factors apparently increase the liability to develop hypothyroidism apart from time after treatment, but in general they are closely associated with the size of the gland. The incidence is greater in the patients with less thyroid enlargement and rises more steeply with the passage of time (Table VII).

TABLE VII.—*Incidence of Hypothyroidism After ^{131}I Therapy in Patients with Thyroid Glands Estimated as Under and Over 40 g. in Weight*

Time after Therapy (Years)	Thyroid under 40 g.			Thyroid 40 g. or More		
	No. of Cases	Hypothyroid		No. of Cases	Hypothyroid	
		No.	%		No.	%
1–4	354	64	18	564	116	21
4–8	89	27	31	398	59	15
8–12	14	6	43	136	38	28

The incidence is also high in patients who have been treated with ^{131}I following a recurrence after a partial thyroidectomy—21% in the period one to four years after therapy, 37% in four to eight years, and 42% in eight to 12 years. Again this is probably associated with the relatively small mass of thyroid tissue in these patients. The incidence of hypothyroidism is consistently less in those under 40 years of age (Fig. 2). However, this difference is probably not primarily a factor of age as the younger patients had on average larger glands. The mean estimated thyroid weight was 48 g. in those over 40 years of age but in those under 40 it was 84 g. Furthermore, in those under 40 who remained euthyroid the mean gland weight was 88 g. while in those becoming hypothyroid it was only 59 g. The greater resistance of the thyroids of the younger patients to the action of ^{131}I may thus be merely due to the larger size.

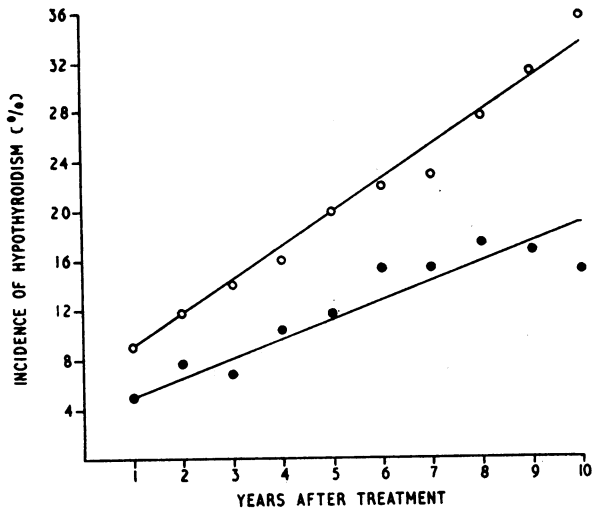

FIG. 2.—Rise in incidence of hypothyroidism after ^{131}I therapy in those over 40 years of age (open circles) and those under 40 years (closed circles).

Serological Tests in Relation to Hypothyroidism after ^{131}I Therapy

As in the partial thyroidectomy series, most of the tests were carried out at different times only after the treatment had been given. However, the effect of ^{131}I therapy has been ascertained in 51 patients by performing the tests both before and several months after administering the ^{131}I. Tanned-red-cell agglutination reactions show no significant change in 41 patients (25 euthyroid, 7 thyrotoxic, and 9 hypothyroid at the time of the second test), a rise of more than two dilutions in five (all euthyroid) and a fall of more than two dilutions in five (three euthyroid, one thyrotoxic, and one hypothyroid). Complement-fixation tests showed no significant change in 37 patients (21 euthyroid, 10 thyrotoxic, and 6 hypothyroid at the time of the second test), a rise of the titre by more than two dilutions in nine (five euthyroid, two thyrotoxic, and two hypothyroid), and a fall by more than two dilutions in five (two euthyroid, one thyrotoxic, and two hypothyroid). Thus administration of a therapeutic dose of ^{131}I commonly did not have any effect on

the serological reactions, and when changes did occur they did not shown any definite trend.

When the results of these tests are examined in relation to the clinical state of the patient two to three years after administration of the last therapeutic dose of ^{131}I no correlation is evident (Table VIII).

TABLE VIII.—*Relation Between Clinical Result Two to Three Years After ^{131}I Therapy and Serological Studies*

	No.	Euthyroid		Hypothyroid	
		No.	%	No.	%
C.F.T.:					
0–8	243	170	70	73	30
16–64	82	52	63	30	37
128–512	23	14	61	9	39
T.R.C.:					
0–25	222	156	70	66	30
250–2,500 ..	84	50	60	34	40
25,000–2,500,000	44	30	68	14	32

Discussion

The most notable differences between the two methods of treatment lie in the rapidity of controlling the hyperthyroidism and in the frequency of subsequent hypothyroidism. After partial thyroidectomy most of the patients are relieved of their symptoms within a few months and few become hypothyroid, the incidence rising only to about 6% ten years after operation. This is in keeping with much experience elsewhere (Bartels, 1952; Thorén and Wijnbladh, 1956; Riddell, 1962; Macgregor, 1963). The association between the development of hypothyroidism after surgical treatment and autoimmunity as shown by lymphocytic infiltration of the gland and positive serological tests has been demonstrated in several previous reports (Whitesell and Black, 1949; Greene, 1950; Goudie *et al.*, 1959; Schade *et al.*, 1960; Irvine *et al.*, 1962; Buchanan *et al.*, 1962). The incidence of other complications following surgery in our series is in general similar to that reported elsewhere. Post-operative hypoparathyroidism may be commoner than previously suspected (Jones and Fourman, 1963), but there is some divergence of evidence (Rose, 1963).

The delay in controlling the hyperthyroidism with ^{131}I therapy is inconvenient but usually acceptable as slow improvement follows each dose. A higher incidence of hypothyroidism than is commonly seen after partial thyroidectomy has been reported in many large series (Werner *et al.*, 1957; Cassidy and Astwood, 1959; Volpe *et al.*, 1960; Segal *et al.*, 1961). It has also been noted that hypothyroidism may develop many years after treatment (Chapman and Maloof, 1955; Blomfield *et al.*, 1959; Sheline and Miller, 1959) and a steady increase with the passage of time was reported by Beling and Einhorn (1961). Blagg (1960) reported a higher incidence of positive tanned red-cell agglutination tests in patients hypothyroid after ^{131}I therapy. However, the development of hypothyroidism after this form of treatment is not generally associated with positive serological tests for autoimmunity, in contrast with the findings after partial thyroidectomy (Irvine *et al.*, 1962; Buchanan *et al.*, 1962). After successful ^{131}I therapy there is gross histological derangement of the gland (Curran *et al.*, 1958) and its capacity to respond to a stimulus is much reduced (Eckert *et al.*, 1960). Experimentally in rats irradiation reduces the capacity of the thyroid cells to divide (Doniach, 1958). ^{131}I therapy probably interferes with the normal turnover and replacement of cells in the human thyroid, and thus leads to the steadily increasing incidence of hypothyroidism in the surviving patients.

Treatment of thyrotoxicosis with radioiodine is convenient in many elderly patients who are liable to cardiac complications and who particularly appreciate the avoidance of a surgical operation and the necessity of admission to hospital. In them the use of this form of treatment is fully justified. In other patients with uncomplicated thyrotoxicosis the subsequent high liability to develop hypothyroidism is a considerable disadvantage. The onset is insidious and the condition may remain undetected for a long time, with the patient in a reduced state of health unless there is a careful follow-up. Though hypothyroidism can be rectified by thyroxine, many patients resent the condition and the necessity of having to take tablets for the rest of their lives, and some are undoubtedly erratic in taking them. Accordingly, the main problem now in ^{131}I therapy is to reduce the liability to develop hypothyroidism. Some evidence from the present study suggests that with a lower dose the rise in incidence with the passage of time is not so steep. The dose used in Sheffield since 1952 has been slightly less than that employed in Scotland (Macgregor, 1963) and in Stockholm (Beling and Einhorn, 1961), and the rise in Sheffield of 2% per year is correspondingly slightly lower. Accordingly, a reduced rate may result if a smaller initial dose is given. The difficulty is that a smaller amount of ^{131}I leads to less rapid control of the thyrotoxicosis, but this can be overcome by starting treatment with an antithyroid drug soon after the therapeutic dose.

A clinical trial on this basis was started in Sheffield three years ago, one group of patients receiving a single dose of ^{131}I calculated to yield 7,000 rads and the other group half this amount. Preliminary results show that in the group receiving the lower dose the rise in incidence of hypothyroidism is much flatter, resembling that seen after partial thyroidectomy, and that 30 months after treatment 86% are euthyroid without drug therapy and under 5% hypothyroid. Severely ill patients with cardiac complications were excluded from this trial; they always receive a large dose of ^{131}I, as subsequent hypothyroidism is acceptable in these cases. On the other hand the high incidence of hypothyroidism after conventional ^{131}I treatment of uncomplicated thyrotoxicosis is most unsatisfactory, and further controlled clinical trials of different methods of therapy are clearly desirable.

Summary

After partial thyroidectomy for thyrotoxicosis the incidence of hypothyroidism rises slowly to about 6% after 10 years. The condition is more likely to appear in patients showing positive autoimmune reactions.

After ^{131}I therapy there is a much steeper linear rise in the incidence of hypothyroidism with the passage of time. This reaches 29% after 10 years and shows no indication of reaching a plateau. Liability to develop hypothyroidism after ^{131}I therapy cannot be predicted by autoimmune reactions. The rise is less steep in those with large glands, and this is probably due to a reduced radiation dosage. The present results in relation to hypothyroidism are unsatisfactory and may possibly be improved by using a lower initial ^{131}I dose followed by antithyroid drug therapy.

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Chromosome Studies During Early and Terminal Chronic Myeloid Leukaemia

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The presence of the Philadelphia chromosome (Ph^1) is invariably associated with chronic myeloid leukaemia (Baikie *et al.*, 1960; Nowell and Hungerford, 1960a, 1960b, 1961; Tough *et al.*, 1961, 1962, 1963; Sandberg *et al.*, 1962b; Fitzgerald *et al.*, 1963), although its absence is probably not sufficient evidence to deny this diagnosis (Tough *et al.*, 1963). As all the patients so far reported had haematologically and, usually, clinically apparent leukaemia when the chromosome studies were first performed, the timing of the appearance of Ph^1+ cells, in relation to the initiation of the disease process, remains undefined.

The purpose of this communication is to demonstrate that Ph^1+ cells are present before the disease is even haematologically obvious and to stress the value of early definitive diagnosis whereby treatment might be started before conventional haematological criteria are available. We report the findings from one patient in whom Ph^1+ cells were observed before there was any haematological or clinical evidence of the leukaemia but who subsequently developed chronic myeloid leukaemia which rapidly progressed into an acute phase: a terminal myeloblastic proliferation was associated with further chromosome abnormalities. Also reported are the findings from four patients who presented as problems of diagnosis and in whom Ph^1+ cells were observed before the disease had become fully manifest. None of these cases had received antileukaemic treatment when they were first studied. Case 1 was studied during an investigation of the chromosome complement of bone-marrow cells from patients with polycythaemia vera, and the initial findings have been reported elsewhere (Kemp *et al.*, 1961).

Methods

Although examination of bone-marrow specimens by a "direct" method is preferable for the cytogenetic study of primary bone-marrow disease, it is not always practicable, especially with serial studies, for, as in Case 1, repeated marrow aspiration is not well tolerated by certain patients. So long as the leukaemic cells are circulating, and if every attempt is made to harvest them when they are dividing, peripheral blood specimens have, in our laboratory, proved more informative than has been the experience of certain other workers (Sandberg *et al.*, 1962a). The peripheral blood leucocytes were cultured by a modification of the technique of Moorhead *et al.* (1960), aliquots being harvested at regular intervals from the time when each specimen was first set up in order to make available for study any cells that divided during the early periods of culture but not subsequently; these would be missed if the cultures were not terminated until the conventional 48 hours or more had elapsed. When possible, leucocyte cultures with and without phytohaemagglutinin were studied in parallel. Exclusion of phytohaemagglutinin from the cultures prevents contamination with metaphases from transformed lymphocytes and permits any divisions that are seen to be attributed more confidently to an abnormal cell population present in the inoculum. The leucocytes from several specimens were set up in fresh homologous plasma as well as in autologous plasma, the former on occasion providing a more active culture.

Both short-term cultures (Ford *et al.*, 1958) and a "direct" method (Tjio and Whang, 1962) have been used for the study of bone-marrow specimens, the final preparations of either blood or marrow being made by air-drying. As is the practice with other workers, we have assessed the presence or absence of the Ph^1 chromosome only in cells in which all the small acrocentric chromosomes have been clearly defined.

Histochemical assessment of the polymorphonuclear neutrophil leucocyte alkaline phosphatase (L.A.P.) content was performed on peripheral blood specimens, using the modified azo-dye coupling technique and scoring method described by Hayhoe and Quaglino (1958).

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Case 1

The patient was a man aged 39 in 1959. Polycythaemia rubra vera was first diagnosed in March 1959, when albuminuria, noted when he was undergoing treatment for chronic eczema, was being investigated. The findings at this time were: haemoglobin (Hb) 19.4 g./100 ml.; packed-cell volume (P.C.V.) 59%; white-cell count (W.B.C.) 25,200/c.mm. (neutrophils 68%, lymphocytes 25%, monocytes 7%); platelets 486,000/c.mm.

The patient was effectively treated, initially by venesection; later, in addition, he received three injections each of 5 mc. of ^{32}P. The haematological findings in this patient from the time of diagnosis until death are shown in Fig. 1.