

RESULTS OF NONSURGICAL TREATMENT OF HYPERTHYROIDISM*

E. PERRY McCULLAGH, M.D.

Department of Endocrinology

IN considering therapy for hyperthyroidism, it is important to keep clearly in mind the type of disease with which the hyperthyroidism is associated. This is because the choice of management of the hyperthyroidism may be influenced by the characteristics of the goiter itself.

Hyperthyroidism may arise in one of three types of goiter:

1. The diffuse goiter of Graves' disease (fig. 1).
2. Multinodular or so-called adenomatous goiter (fig. 2).
3. Discrete adenoma (fig. 3).

Some of the outstanding features of these three conditions which have important influences on diagnosis and choice of treatment are outlined in table 1.

Graves' disease may be considered a systemic disease of which hyperthyroidism is just one part. At present, it appears plausible that it arises in the nervous system emanating through the anterior lobe of the pituitary gland. According to current theory, it is the excess of the pituitary thyrotropic hormone which causes the diffuse thyroid hyperplasia. This change supplies the visible evidence of the abnormal increase in activity of thyroid cells producing the excess of thyroid hormone. Eye signs may not be noticeable in some cases throughout the course of the disease, in some they advance with the hyperthyroidism, and in some they demonstrate that they are not the result of thyroid hyperfunction by appearing months or years before or after hyperthyroidism has become present. This disease may occur at any age, but is common under 40 years. The goiter may be small and barely palpable or it may reach a size of 120 Gm. or more. The hyperthyroidism varies from mild to severe thyroid crisis. Clinical malignancy in such glands is almost unknown.

The multinodular or so-called adenomatous goiter is the result of degenerative changes occurring in a goiter which may have existed for years. It is most common in areas where iodine deficiency exists. The hyperthyroidism arises from multiple areas of focal thyroid hyperplasia. Eye signs are absent. The disease is one of middle age to old age. The goiter itself may go unnoticed or may be a huge mass in the neck or in the upper thorax. The hyperthyroidism may be mild or moderately severe, tends to be unremitting, chronic, and often declares itself chiefly by producing auricular fibrillation or cardiac decompensation. The disease is common and, in comparison to its frequency, malignant change is unusual.

Discrete adenoma is a true neoplasm. It produces a type of hyperthyroidism closely comparable to that of multinodular goiter and without eye signs. The

*Read at the postgraduate course conducted by the Cuban Medical Society, El Colegio Medico de Camaguey y la Sociedad de Estudios Medicos y Quirurgicos de Camaguey, December 1950.

age distribution of its hyperthyroidism is similar and, for this reason, cardiovascular evidences are the same.

There are three major types of therapy and each has such outstanding merits that it may, at times, be a difficult matter to choose the most suitable. The three types are: (1) surgery; (2) antithyroid drugs, and (3) radioactive iodine.

In considering each patient's problem it is usually necessary to decide whether or not surgery is the treatment of choice. Therefore let us consider briefly some of the outstanding advantages and disadvantages of subtotal thyroidectomy.

Surgery, although not as safe as the other methods of treatment has, however, a mortality rate (when handled competently) which has dropped to something in the neighborhood of 0.1 per cent. The safety of surgery at the



FIG. 1. Diffuse goiter of Graves' disease.

present time is not only the result of well-developed technic and antibiotics but because preoperative treatment is so effective that hyperthyroidism can be abolished before operation. In the event that the patient remains a poor surgical risk, other forms of therapy may be used.

Unless the surgical risk is prohibitive, surgery is undoubtedly the treatment of choice in all patients in whom there is a reasonable suspicion of carcinoma, in all who have discrete adenoma of the thyroid because of increased propensity to carcinoma, and in those in whom it is desirable to remove a large mass of nodular thyroid tissue for cosmetic reasons, or because of intrathoracic extension with pressure symptoms severe enough in themselves to require relief.

The advantages of surgery in general are the speedy control of the hyperthyroidism and removal of the existing goiter mass. It has the disadvantages

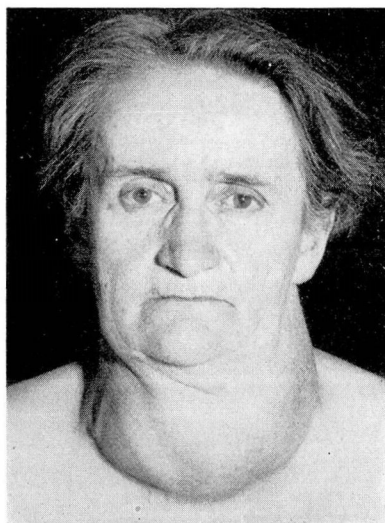


FIG. 2. Multinodular goiter with hyperthyroidism.

of a mortality rate, even though small; a definite recurrence rate, especially in Graves' disease; the production of certain lasting complications such as hypothyroidism, parathyroid tetany, and vocal cord paralysis. In addition, it presents the discomfort of operation, the necessity for hospital care, work loss, and a greater over-all expense than other forms of treatment.

Propyl and methyl thiouracil present the advantages of no discomfort, no hospitalization, and no lasting complications. Moreover, in cases with lasting remissions, the thyroid gland itself is intact. The over-all cost is less than that of surgery. These drugs have the disadvantages of slower control. Usually the goiters remain and may enlarge during treatment although in Graves' disease some goiters eventually disappear. There is an extremely low mortality rate which amounts to 1 patient in approximately 5,000 treated. Toxic symptoms, however, may prevent the use of the drug. Its greatest disadvantage is that of a recurrence rate of 23 per cent in our series in selected patients with Graves' disease, 50 per cent in completely unselected cases, and more than 65 per cent in adenomatous goiter.

Radioactive iodine in Graves' disease has the advantages, where it is available, of great safety, and ease of treatment. There is no hospitalization or work loss for the treatment itself, and in Graves' disease the goiter disappears in most cases. There is a high rate of lasting remission and the few recurrences are readily treated. It is followed by no complications except hypothyroidism. Its over-all cost is less than that of other forms of treatment. In nodular goiter, radioactive iodine has the disadvantage of not removing the goiter. To date the rate of control is slow, requiring many months in most patients and, at present, complete control has not exceeded about 75 per cent in 4 months to

as long as 1 year of treatment. In general, radioactive iodine is indicated in nodular goiter only when surgery is not acceptable.

The opinions offered regarding propyl and methyl thiouracil are based chiefly on the study of a group of 179 patients whose treatment was begun between January 1946, and April 1947. Among these were 141 patients in whom the drug was used in an attempt to produce a cure. The group contains previously untreated Graves' disease, recurrent Graves' disease, and nodular goiter.

The Dose and Method of Handling

Effective doses of the drug are outlined in table 2. One hundred and fifty mg. per day controlled about 58 per cent of the patients within 2 months; 200 mg. per day controlled about 87 per cent; 300 mg. controlled 96 per cent and the remainder, approximately 4 per cent of the patients, required more than 300 mg. per day. It is important that the drug be given in at least 4 daily doses because each dose is effective for only a few hours. Toxicity may be demonstrated by the appearance of fever, arthralgia, leukopenia, urticaria or other skin eruptions including exfoliative dermatitis. With regard to leukopenia, it is well to remember that a relative granulopenia is a common accompaniment to untreated Graves' disease. It may be found necessary to stop the drug in 2.5 per cent of patients due to toxic symptoms and occasionally because of thyroid enlargement. Agranulocytosis has appeared once in several thousand cases in this country. It is to be suspected if sore throat or fever appear. We have found no advantage in frequently repeated white cell counts but all patients are warned to discontinue the drug and report immediately in

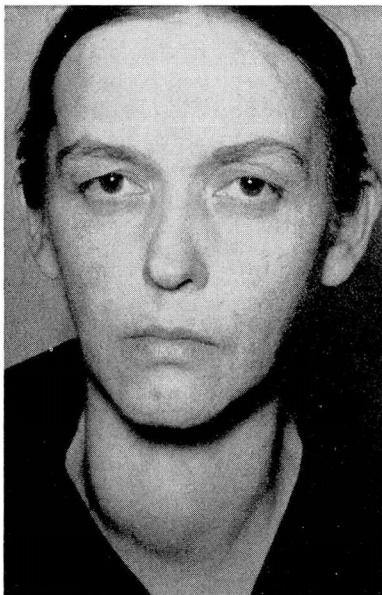


FIG. 3. Discrete adenoma with hyperthyroidism.

Table 1
HYPERTHYROIDISM ORIGINATES IN THREE TYPES OF GOITER

	I. Diffuse Goiter of Graves' Disease	II. Multinodular or Adenomatous	III. Discrete Adenoma
Nature of Disease	Systemic	Degenerative	Neoplastic
Origin of excess hormone	Diffuse hyperplasia	Focal hyperplasia	Local hyperplasia
Eye signs	Absent Present Before or after	Absent	Absent
Age at onset	Any Common under 40	Middle age Uncommon under	or beyond 40
Size	Small to moderate 20 - 120 Gm.	Small to enormous 40 - 250 Gm.	Minute to large 1 - 150 Gm.
Severity	May be pronounced with crisis	Chronic with auricular fibrillation and decompensation	
Malignancy	Rare	Uncommon	Common

the event such symptoms occur. If agranulocytosis results, the treatment is generous doses of penicillin and repeated blood transfusions. The approximate rate of response is shown in table 3. A fall of about 1 per cent a day in the basal metabolic rate is maximal, approximating the rate of a thyroxin decay curve.

Patients are asked to return at intervals of 1 to 2 months for observation, a basal metabolic rate determination, blood cholesterol, eye measurements, or other tests considered desirable.

The Use of Iodine with Propyl Thiouracil

It has been our practice to give 10 to 20 mg. of iodine daily from the beginning of treatment in order to avoid the excessive vascularity of the gland which may accompany the use of the thioureas. We believe also that it may be an advantage to add desiccated thyroid to the treatment if the basal metabolic rate tends to be below minus 10 per cent. The same dose of propyl thiouracil may be continued unless thyroid enlargement becomes a problem. In this event, it is important to reduce the dose to the minimum required for regulation.

After complete control of symptoms and a strictly normal basal metabolic rate are obtained, the treatment is continued for 9 to 12 additional months. At the time of discontinuance, desiccated thyroid in a dose of 65 mg. to 130 mg. per day may be continued advantageously, if the symptoms and basal meta-

EFFECTIVE DOSE OF PROPYL THOURACIL IN GRAVES DISEASE

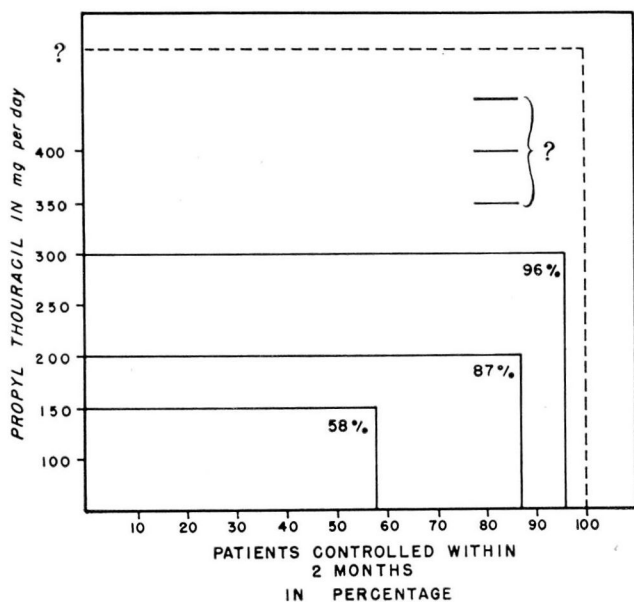


Table 2

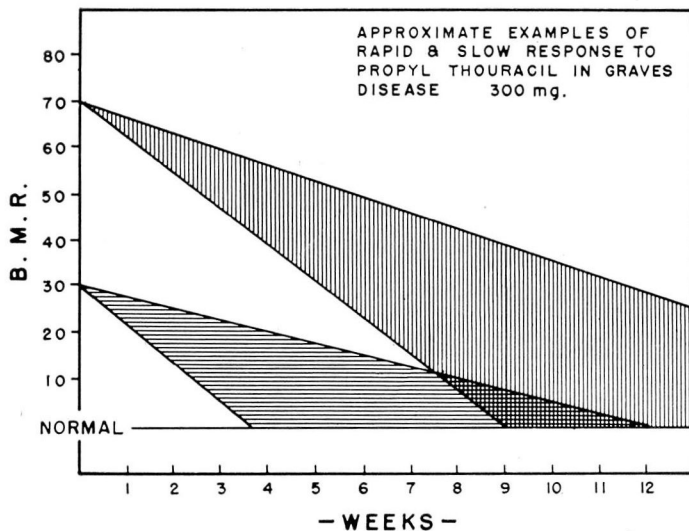


Table 3

Table 4

PATIENTS IN WHOM PROPYL THIOURACIL HAS
NEVER BEEN DISCONTINUED AMONG 141 STARTING
THERAPY PRIOR TO APRIL 1947

Clinical Condition	No. of Cases
Auricular fibrillation with cardiac decompensation	2
Cardiac decompensation (rheumatic)	1
Angina pectoris	1
Postop. tetany and recurrent hyperthyroidism . . .	1
Senility	1
Dwarfism and diabetes mellitus	1
Prescribed elsewhere	3
Not stated in record	1
Total	11

Table 5

PATIENTS IN WHOM HYPERTHYROIDISM WAS NOT
COMPLETELY CONTROLLED

Cause	No. of Cases	Dose in mg. per Day	Comment
Failure of drug?	2	400	Would larger doses have been effective?
Inadequate dose	2 5 4	50 - 75 100 - 150 150 - 200	Recurrence appeared in one of these after subsequent thyroidectomy
Toxicity	1		Leukopenia
Drug stopped	1		Exfoliative dermatitis
Poor cooperation	3	Irregular use of drug	One controlled later on 400 mg. per day
Total	18		

Enlargement of the gland was a factor in discontinuance in 2.

bolic rate permit, with the hope that it may produce enough pituitary suppression to reduce the rate of recurrence.

Among the 141 patients mentioned, there are 11 in whom the drug has not been discontinued. They have remained in good control. We have not wanted to risk a recurrence and this small group demonstrates that the drug may be continued for months or years if desired (table 4).

In 18 patients control of hyperthyroidism never has been obtained. This does not mean necessarily that the drug has failed pharmacologically. Larger doses in some of these patients might have been effective (table 5). It is probable that this is the case with doses of 400 mg. It is extremely likely with doses of 200 mg. or less. There are, however, some patients represented here in whom the drug could not be continued because of toxic symptoms; in 3 the unsatisfactory results obtained were due to poor patient cooperation. The last two categories represent weakness of the method which probably never will be eliminated entirely. Although these patients are classed as failures in the figures given, the majority would not be so classed if treated today.

The duration of remissions at the conclusion of this study refers to the length of time we are certain that remission has continued. In most of these we hope such remissions may be permanent (table 6). Of the entire unselected group, 70 were in remission when last heard from. Of these, 89 per cent maintained a remission for 6 months or more after cessation of therapy. In those patients showing a relapse, conversely, 78 per cent demonstrated recurrence before the sixth month.

Various factors have an obvious bearing on the results of this type of treatment. First and most important is the type of goiter (table 7). Among our patients all with previously untreated Graves' disease have maintained remissions in approximately the duration mentioned in 66 per cent of the cases. This is in striking contrast to the postoperative recurrences and the patients with nodular goiter who maintained remissions in only one-third of the patients treated.

The frequency of more lasting remissions bears some relationship to the severity of the disease as judged by the basal metabolic rate. Those patients who had basal metabolic rates under plus 30 per cent at the beginning of treatment showed a 55 per cent chance of remission as compared to a 48 per cent chance if the metabolic rate was more than plus 50 per cent. Men obtained remissions more frequently than women, and younger patients more frequently than older ones. In both of the latter groups, we are inclined to ascribe the difference chiefly to the fact that adenomatous goiter is more common in women and in older persons of both sexes and, as has been stated, responds less well to propyl thiouracil than does diffuse goiter.

The results which have been produced in the most suitable prospects for such treatment are interesting. There were 60 such patients; all had Graves' disease, none had been operated upon previously, and all had small to medium-sized goiters. The severity of the disease and the duration of the control were disregarded (table 8). A remission rate of 77 per cent in such patients as these, we believe, can be improved further because of knowledge gained during the

Table 6
KNOWN DURATION OF REMISSION IN 70 OF 141
PATIENTS IN WHICH IT WAS OBTAINED

2 - 6 months	11%
6 - 12 months	44%
Over 12 months	45%
In patients showing relapse, this occurred in less than 6 months in 78%.	

Table 7
FACTORS INFLUENCING DURATION OF REMISSION
AFTER PROPYL THIOURACIL

Per cent in Remission			
Type of Goiter	Graves' 66	Nodular 34	
Postop. recurrences	33		
Basal metabolic rate	Under +30% 55	Over +50% 48	
Sex	Men 63	Women 45	
Age	Under 50 yrs. 54	Over 50 yrs. 41	

Note: Adenomatous goiter is more common in women and in all patients over 50 yrs. of age.

Table 8
REMISSION RATE IN SELECTED CASES OF GRAVES'
DISEASE TREATED WITH PROPYL THIOURACIL

Remission	46 or 77%
Relapses or recurrences	14 or 23.3%
Total	60

Table 9
INDICATIONS FOR I^{131} AS TREATMENT OF
CHOICE IN GRAVES' DISEASE

1. Postoperative recurrence at any age.
2. Other patients chiefly over 40 years of age.
3. Because of preference of patient or physician.
4. Old age.
5. Poor cardiac status.
6. Severe concurrent disease.
7. Recurrence of hyperthyroidism after antithyroid drugs.

past few years. Improved results would be contingent upon more adequate dosage and longer control. The eventual answer will be dependent largely upon the number of late relapses which occur.

Exophthalmos seems to react no differently under this treatment than it does postoperatively. Some patients become worse; in the majority, measurements show an increase in the exophthalmos for a few months, followed by eventual improvement. Some enlargement of the thyroid frequently occurs during the early months of treatment. When such a change is pronounced, it suggests a more than average tendency toward exacerbation. Excessively large doses of the drug will aggravate such a tendency. In most patients, the gland tends to become softer and smaller during continued treatment in those who still have considerable thyroid enlargement at the end of therapy; further gradual reduction in the size of the gland is to be expected when remission continues longer.

Table 10
INITIAL DOSE OF I^{131} (IN MILLICURIES) IN
GRAVES' DISEASE

Size of Gland in Grams	B.M.R. Below +50%	B.M.R. Above +50%
30	4	6
60	7	9
90	10	12
120	14	16

JUDGEMENT AS TO REPETITION OF TREATMENT BASED ON 2 MONTHS IMPROVEMENT

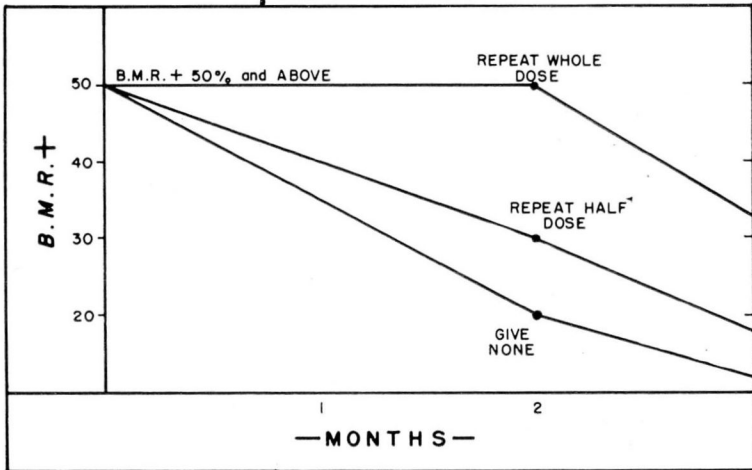


Table 11

In the past few years propyl and methyl thiouracil have been used less frequently than would have been the case in those parts of the United States where radioactive iodine is available. These drugs still have a useful place in the treatment of hyperthyroidism, not only in preoperative preparation of patients with severe hyperthyroidism, but for continued control in those patients who are not suitable for surgery and as a definitive cure in patients with Graves' disease.

Radioactive Iodine

Radioactive iodine has been used in the treatment of the hyperthyroidism of Graves' disease for about 10 years. The first report of its use in patients was that of Hertz and Roberts in 1942.

There are 12 radioactive isotopes of iodine. The only one in use today for the treatment of hyperthyroidism is I^{131} .

I^{131} has a half-life of 8 days and is suited peculiarly to the treatment of hyperthyroidism for a number of reasons among which are the following: a large proportion of the dose given is absorbed and held by overactive thyroid tissue. A common percentage uptake in Graves' disease is 75 per cent. Its concentration in the thyroid is as much as 10,000 times the concentration found elsewhere in the body. It is held in the thyroid until most of its radioactive energy is dispersed. It emits chiefly Beta rays which penetrate the tissues to a depth of only about 2 mm.; thus damage does not occur to other tissues. Its half-life is long enough to permit its ready transportation while it is still active. It can be given in a drink of water, is tasteless, and is quickly absorbed from the gastrointestinal tract. The supply of I^{131} which is used in our clinic comes

to us in a lead container by air express every 2 weeks in a prearranged dose from Oak Ridge, Tennessee, where it has been produced in a chain reacting pile. One mc. is contained in 2 cc. of water. After arrival, its activity is measured. It is properly diluted in colored water, handled with special equipment at a distance of three-fourths of a meter from the operator, and handed to the patient in a paper cup. In necessary dosage it almost never produces a perceptible reaction. We have used I^{131} in the treatment of 360 patients. Patients with Graves' disease are selected for treatment with I^{131} largely on the consideration stated in table 9.

The judgment of the dose necessary is a matter which has not been settled finally. In some clinics it is prescribed after measuring the thyroid uptake of a tracer dose of 50 to 300 microcuries with a Geiger-Muller counter, calculating the size of the gland by palpation, and estimating the number of microcuries per gram of gland. In our practice the total dose is judged chiefly on the basis

Table 12
PATIENTS WITH GRAVES' DISEASE REQUIRING SPECIAL
CONSIDERATION IN I^{131} THERAPY

1. Those previously treated with I^{127} (I_2) in whom I^{131} uptake is low.
 - a. Give propyl thiouracil.
 - b. If disease is severe, gradually withdraw I^{127} .
 - c. When controlled withdraw propyl thiouracil 4 days, test I^{131} uptake and, if high, give I^{131} treatment dose.
2. Those in whom control of Graves' disease is urgent.
 - a. Treat with I^{127} and proceed as above or as in 3.
3. Impending crisis.
 - a. Give I^{131} and follow immediately with I^{127} .
4. In pregnancy do not give I^{131} except prior to the tenth week of gestation.

Table 13
RESULTS OF I^{131} THERAPY FOR THE HYPERTHYROIDISM
OF GRAVES' DISEASE

1. The patient is not incapacitated.
2. The goiter shrinks markedly or disappears.
3. In our first 200 patients, only 4 remained with hyperthyroidism 6 months after the initial treatment.
4. The only complication is hypothyroidism in 10% of the patients.
5. A tendency to mild recurrence has been seen in 2% of the patients.

of the physiologic response to an original dose which is estimated to be approximately the minimum curative dose. This is based on the size of the gland and the severity of the hyperthyroidism. In doubtful cases uptake of a tracer dose is measured first, but it has not been demonstrated to our satisfaction that an increase in cure rate with a single dose can be obtained by using such data. The initial dose commonly used is shown in table 10.

If the basal metabolic rate is less than plus 50 per cent and the gland estimated to be 60 Gm. in weight, 7 mc. are given. For glands estimated at various weights, the approximate doses are as shown. If the basal metabolism is more than plus 50 per cent, 2.0 mc. or more is added to this dose.

Adjunct treatment is prescribed which includes a high caloric diet, sedation, and cardiac therapy as necessary. The treatment may be followed with iodine or propyl thiouracil for temporary control if essential. In 2 months the severity of the disease is re-evaluated and, if necessary, another dose of I^{131} is prescribed. The second dose is judged on the basis outlined in table 11.

If the basal metabolic rate has not fallen, the whole dose is repeated. If the rate has fallen to approximately plus 30 per cent, half of the original dose is given again. If the metabolic rate has fallen to approximately plus 20 per cent and the symptoms continue to improve, no further treatment is given. This is because experience has taught us that a continued fall in the basal metabolic rate may occur causing hypothyroidism in some patients as late as the fourth month following the original dose of radioactive iodine. Under special circumstances the treatment may need to be modified (table 12).

With the doses mentioned in the preceding table, 65 per cent of the patients enter complete remission with 1 dose, 25 per cent with 2, and only 10 per cent

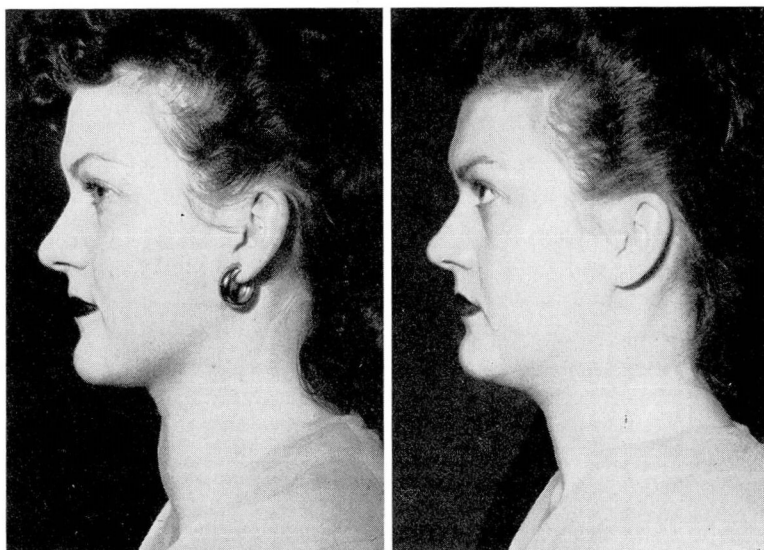


FIG. 4. Disappearance of goiter after radioactive iodine therapy.

Table 14

CERTAIN FEATURES OF THREE TYPES OF TREATMENT
OF HYPERTHYROIDISM

	Thyroid- ectomy	Antithyroid Drugs	Radioactive Iodine
Speed of control Graves' Adenomatous	1-2 mos. 1-2 mos.	1-4 mos. 2-6 mos.	2-4 mos. 2-12 mos.
Length of observation	2-4 mos.	10-12 mos.	2-12 mos.
The Goiter Graves' Adenomatous	gone gone	may enlarge remains	reduced or gone reduced
Mortality	0.1-1%	0.05% (toxic 2.5%)	?
Hypothyroidism Graves' Adenomatous	5-20% 0.5%	0 0	10-20% 0
Tetany	0.5-2%	0	0
Vocal cord paralysis	0.5-5%	0	0
Recurrence rate Graves' Adenomatous	3-15% 1%	25% 60%	2% 1%
Discomfort	+++	0	0
Hospital care	+	0	0
Loss of work	+	0	0
Cost of treatment	++++	++	+

require 3 or more doses. Although the average curative dose approximates 10 mc., doses as high as 80 are sometimes needed. The results are excellent. No complications have arisen except hypothyroidism which has occurred in 10 per cent of the patients treated, and this may be transient. Some of the outstanding features of the results obtained in the treatment of Graves' disease with I^{131} are shown in table 13.

Figure 4 shows disappearance of the goiter in a young person treated with I^{131} . In this case treatment was carried out before the age of 40 because the patient was a vocalist and refused operative treatment.

I^{131} is the least suitable major treatment for hyperthyroidism of nodular goiter. Although effective it is much slower in its action in the doses we have used. We consider it a satisfactory treatment in nodular goiter where, for some reason, surgery is not acceptable. The dose required is much larger than that needed in Graves' disease, averaging 34 mc. in our cases. Doses totaling as high as 100 mc. are required at times.

In 80 such patients treated to date, we can only claim 75 per cent in whom the hyperthyroidism is completely controlled. Some still show hyperthyroidism for as long as a year after the initial dose. In our cases of nodular goiter treated with I^{131} we have seen no recurrent hyperthyroidism to date and no hypothyroidism or other complications.

Table 14 shows a comparison in general terms of some of the outstanding features of the three main types of treatment of hyperthyroidism.