PRESENT STATUS OF THE SURGICAL TREATMENT OF HYPERTHYROIDISM

GEORGE CRILE, JR., M.D., AND ROBERT S. DINSMORE, M.D.

The surgical conquest of hyperthyroidism, initiated at the turn of the century and established in safety by the preoperative use of iodine, had become so well accepted that until the introduction of thiouracil, few chose to consider hyperthyroidism anything other than a surgical problem. Today, as a result of the discovery of powerful and effective drugs, the controversial issue of whether hyperthyroidism is better treated by conservative (medical) management has again arisen.

Even before the introduction of thiouracil the mortality rate of hyperthyroidism treated by experienced surgeons was less than 1 per cent. Improvement in anesthesia, in surgical technic, in preoperative and postoperative care, and a keener appreciation of the factors that increase the risk of operation contributed materially to this advance. Since at the present time the safety of thyroidectomy performed by a competent surgeon is about the same as that of thiouracil therapy, the decision as to which is the treatment of choice must be decided on the basis of end results and morbidity.

When hyperthyroidism arises as the result of functional activity in a long-standing adenoma, it is not surprising that removal of the benign tumor which is responsible for the hyperthyroidism is followed by cure of the disease and an almost negligible incidence of recurrent hyperthyroidism. The factors responsible for the development of the original adenoma may no longer be in operation, and if excision has been complete, there is no reason for the hyperthyroidism to recur.

In diffuse goiter with hyperthyroidism, however, the entire gland is stimulated to hypertrophy, hyperplasia, and hyperfunction by causes which are not fully understood. It seems unlikely that the primary seat of the disease is in the thyroid gland itself. Subtotal thyroidectomy, moreover, does nothing to eliminate the factors that originally stimulated the hyperplasia and hyperfunction. Hence, the surprising clinical feature is not that hyperthyroidism occasionally recurs, but rather that the disease does not *always* recur.

The incidence of persistent hyperthyroidism following operation is easy to determine. Persistence of the hyperthyroidism represents a technical error resulting from insufficient removal of thyroid tissue. This accident is rare and occurs only in a fraction of 1 per cent of all cases of hyperthyroidism if thyroidectomy has been well done. The true incidence of recurrent hyperthyroidism, on the other hand, is most difficult

to determine and will depend almost entirely on the length of the follow up. Although the greatest incidence of recurrent hyperthyroidism is in the first two years following thyroidectomy, it may occur at any time. A patient may remain well for twenty years only to develop, late in life, recurrent hyperthyroidism. It is estimated that the over-all incidence of persistent and recurrent hyperthyroidism does not exceed 5 per cent.

If these figures are further broken down to separate the diffuse goiters with hyperthyroidism (true Graves' disease) from the nodular goiters with hyperthyroidism, it is apparent that the vast majority of patients with recurrent hyperthyroidism are those who had diffuse hyperplastic goiters. It is the true exophthalmic goiter that has the highest tendency to cause recurrent hyperthyroidism after thyroidectomy.

Total thyroidectomies are seldom performed in the treatment of hyperthyroidism because of the prohibitive incidence of parathyroid tetany. Studies conducted in relation to total thyroidectomy for heart disease and experiments on animals have shown that unless every vestige of thyroid tissue is removed, regeneration of the thyroid promptly restores its function to normal. This regeneration occurs as a compensatory hypertrophy and hyperplasia stimulated by the pituitary gland in response to a deficiency in circulating thyroid hormone. Since (1) the normal thyroid is capable of regeneration, (2) a considerable portion of the thyroid is left following subtotal thyroidectomy, and (3) the true causes of hypertrophy, hyperplasia, and hyperfunction of the thyroid in hyperthyroidism are not removed by thyroidectomy, why is it that the remnants of the thyroid do not always enlarge and cause a recurrence of the disease?

On the basis of present knowledge there is no answer to this question unless it is assumed that surgery merely breaks a link in a "vicious circle" of nervous and/or endocrine disorders. It is possible that subtotal thyroidectomy, by accomplishing a reduction to or below normal in the output of thyroid hormone, secondarily causes a subsidence of the factors that incited the thyroid gland to hyperfunction. The fact that recurrent hyperthyroidism and postoperative hypothyroidism are most commonly seen after operations for diffuse goiter with hyperthyroidism, and are seldom seen following operations for nodular goiter, is further evidence that some factor other than the amount of thyroid tissue left is responsible for the unpredictable occurrence of postoperative hypothyroidism and recurrent hyperthyroidism. If enough tissue is removed to induce a remission of the symptoms of Graves' disease, it is impossible to predict whether this interruption of the "vicious circle" will produce myxedema, will stabilize the function of the thyroid at a normal level, or will act but temporarily until the gland is again stimulated, and the

disease recurs. It is clear, therefore, that surgical treatment of diffuse goiter with hyperthyroidism is empiric in approach, unpredictable in outcome, and unphysiologic in principle, but from a clinical standpoint is safe, simple, and satisfactory.

Following subtotal thyroidectomy the mechanism of compensatory hypertrophy and hyperplasia and the factors which caused the original hyperfunction of the thyroid would be expected to continue to operate and to produce a recurrence of the goiter and of the hyperthyroidism. Yet this occurs in only a small percentage of cases. An unphysiologic procedure is proved empirically to be a sound clinical treatment. Is the treatment of hyperthyroidism with thiouracil safer, more predictable in its end results or more physiologic than removal of the gland?

So far as has been determined, the effect of thiouracil is primarily on the thyroid gland. By blocking formation of active thyroid hormone *thiouracil accomplishes a physiologic instead of an anatomic subtotal thyroidectomy.* If given in large enough doses over a long enough period of time it might often produce the physiologic equivalent of a *total* thyroidectomy.

The same questions can be asked about the results obtained with thiouracil as were asked about those following thyroidectomy. Why does not the thyroid in humans invariably enlarge rapidly as it does in animals? The pituitary gland is stimulated by the deficiency of thyroid hormone to pour out its thyroid-stimulating hormone. Hyperplasia of the thyroid results, but the enlargement of the gland usually is negligible. Occasionally there is a case in which the thyroid grows with incredible rapidity to enormous size,[1] but these cases are the exception and not the rule.

Why does not the hyperthyroidism invariably recur after withdrawal of the drug? Thiouracil, so far as is known, has no effect on the master system that first stimulated the thyroid gland. Prolonged remissions from hyperthyroidism, nevertheless, are obtained following thiouracil therapy in perhaps 50 per cent of the patients who receive adequate treatment. How long these remissions will last is uncertain. It would appear that physiologic thyroidectomy by thiouracil therapy breaks the "vicious circle" just as anatomic thyroidectomy does. When a remission is obtained with thiouracil the end results are unpredictable, just as they are following thyroidectomy. Recurrence of hyperthyroidism, however, is more common after a course of thiouracil than following an adequate thyroidectomy.

When severe postoperative hypothyroidism or myxedema occurs, the subsequent development of recurrent hyperthyroidism is extremely rare. Is this because the "vicious circle" is more completely broken by the

induction of severe hypothyroidism? I am convinced that it is not always because an excessive amount of thyroid tissue has been removed and that it is not because there is insufficient thyroid tissue left to regenerate and cause a recurrence if the stimulating mechanism were in operation. If thiouracil were less toxic and large doses could be given safely over a long period of time to produce a true myxedema and to maintain it for several months, the "vicious circle" might be so completely interrupted that recurrences would be rare.

Subtotal thyroidectomy and thiouracil therapy accomplish essentially the same end by different means. Both methods of treatment depend upon inducing a temporary remission of the hyperthyroidism. During this remission the "vicious circle" of the pathologic physiology is broken, and in those patients who are to remain well the abnormal stimulation of the thyroid is abolished.

Any drug which is as safe as a surgical operation and which can accomplish the same ends without incurring discomfort and occasional morbidity is a better therapeutic measure than surgery. Thiouracil has nearly but not quite fulfilled these qualifications. The risk of fatal agranulocytosis following its use is approximately the same as the risk of thyroidectomy for hyperthyroidism before thiouracil was known. But the risk of thyroidectomy for hyperthyroidism has been enormously reduced by the availability of thiouracil for preparation of the bad risk cases. Today, the risk of thyroidectomy for hyperthyroidism should be the risk of operating on a simple goiter. In the past the majority of deaths following thyroidectomy were in 3 groups, (1) hyperthyroidism in the aged, (2) hyperthyroidism complicated by organic heart disease, and (3) severe hyperthyroidism with basal metabolic rates above +75 per cent. Today hyperthyroidism in the aged and in those with serious heart disease can be controlled by thiouracil, without the risk of surgery. The surgeon is no longer faced with the decision as to whether he must risk a high mortality to effect a cure or see his patient slowly expire under palliative therapy. Medical management in these problems is clearly preferable to surgery.

Nor is there often cause to lose a patient from thyroid crisis no matter how severe the hyperthyroidism. Although routine preparation of all patients with thiouracil would entail a risk nearly equivalent to the sum of the two risks, it would be equally unwise to disregard the advantages of thiouracil preparation for a patient with severe hyperthyroidism. Such cases constitute perhaps only 3 per cent of all cases of hyperthyroidism, but it is in this group as well as in the aged and in hyperthyroidism associated with other diseases that the mortality of thyroidectomy occurs.

It is necessary, therefore, to revise established opinions of the safety of thyroidectomy for hyperthyroidism. We are accustomed to estimate the risks of thyroidectomy for hyperthyroidism as approximately 0.5 per cent. But with modern methods of preparation 734 consecutive thyroidectomies have been performed at the Cleveland Clinic without a death. Nearly half of these patients had hyperthyroidism. The surgical mortality of thyroidectomy for hyperthyroidism has thus become extremely low and should be comparable to that of operations for simple goiter—a small fraction of 1 per cent. With penicillin to control pneumonia and infection it is hard to see why mortality following thyroidectomy should occur as a result of anything other than embolic phenomena and unpredictable accidents.

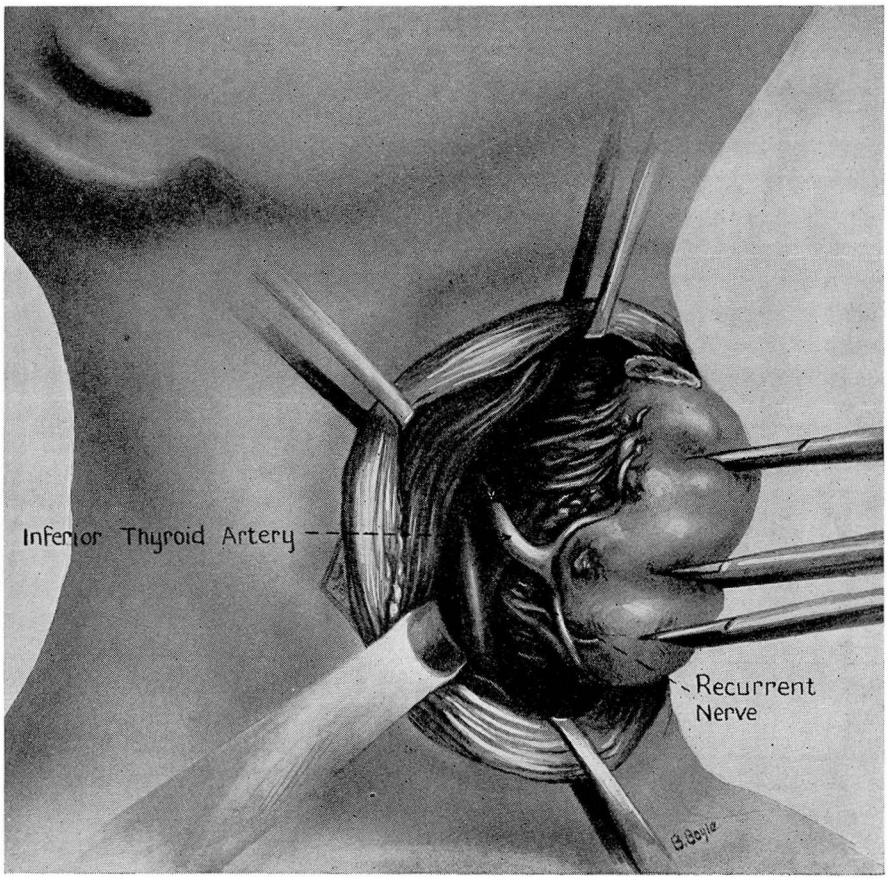

FIG.—Site of ligation of inferior thyroid artery.

The morbidity of thyroidectomy is still a consideration worthy of discussion. Again, the majority of technical accidents that occur are in a specific group of cases—thyroiditis, recurrent hyperthyroidism, and carcinoma. If these cases were eliminated, the treatment of primary hyperthyroidism by thyroidectomy would have an even smaller morbidity. For example, in a consecutive series of 400 cases, including recurrent goiters, thyroiditis, and carcinomas, there have been only 3 permanent recurrent nerve palsies. Two of these resulted from carcinomas in which the recurrent nerve was visualized and purposefully sacrificed in order to facilitate complete removal of the tumor. The third was a unilateral persistent paralysis occurring unaccountably in the course of an easy thyroidectomy. Laryngeal examination was made on all cases. The incidence of accidental injury to the recurrent nerve in this group is thus 0.25 per cent.

The adoption of a technic in which the inferior thyroid artery is ligated extracapsularly at the point where it passes behind the carotid (fig.) has been helpful in reducing the incidence of injuries to the recurrent nerve.* This procedure coupled with a more complete division of the superior pole and complete rotation of the thyroid gland from its bed has resulted in a better exposure of the vulnerable posterolateral surface of the gland, improved hemostasis, and in much greater facility in the handling of the friable vascular glands of patients who have been prepared for operation with thiouracil. Extracapsular ligation of the inferior thyroid vessel has not increased the small fraction of 1 per cent which constitutes the incidence of parathyroid tetany.

Since the mortality and morbidity of thyroid surgery are now so low, it is not surprising that the dangers of thiouracil have prevented its wide acceptance for use in the average case of hyperthyroidism. With the advent of newer, more powerful, and probably less toxic drugs, such as propyl thiouracil, now under trial, this attitude may change. There is always the danger that continued use of the drug may over a period of years result in gradual development of adenomas, as is seen in animals,[2] but as yet this tendency has not been apparent. In any case it is to be hoped that a drug will be found which will safely and completely break the "vicious circle" of thyroid stimulation and produce a lasting remission after its withdrawal. When this drug is discovered a means will have been found to replace anatomic thyroidectomy by physiologic thyroidectomy, and it can be hoped the remissions so induced will be as permanent and as satisfactory as are obtained by our present methods of treatment. The low toxicity of propyl thiouracil suggests that this

* No claim to originality in the development of this technic is made. Extracapsular ligation of the inferior thyroid artery is as old as surgery of the thyroid.

drug or a similar thiouracil derivative may be the ultimate answer to the problem of the small diffuse goiter with hyperthyroidism.

SUMMARY

1. The development of the anti-thyroid drugs has obviated the necessity of performing thyroidectomy on bad-risk patients at least until the hyperthyroidism is completely controlled.

2. If the bad-risk patients are treated or prepared for operation by thiouracil, the mortality following thyroidectomy performed on the remaining (good-risk) patients is less than that of treatment with thiouracil.

3. The morbidity (injury of recurrent laryngeal nerves, tetany, etc.) associated with thyroidectomy is less than 1 per cent.

4. In view of the low mortality and morbidity of thyroidectomy thiouracil is not recommended for routine treatment or preparation for operation and its use is reserved for those cases presenting unusual risks.

5. Thiouracil accomplishes a physiologic rather than an anatomic thyroidectomy and the mechanism by which it produces a remission is comparable in many respects to that of thyroidectomy.

6. It is hoped that some of the newer anti-thyroid drugs (propyl thiouracil, etc.) now under trial will prove to be non-toxic and will afford a means of effectively controlling hyperthyroidism without recourse to thyroidectomy.

REFERENCES

1. McCullagh, E. P., Dinsmore, R. S., and Keller, F.: Thiouracil in the treatment of complicated hyperthyroidism. Cleveland Clin. Quart. **12**:3-15 (Jan.) 1945.
2. Griesbach, W. E., and Purvis, H. D.: Studies on experimental goitre; thyroid adenomata in rats on Brassica seed diet. Brit. J. Exper. Path. **26**:18-24 (Feb.) 1945.

PRESENT STATUS OF THIOURACIL*

E. PERRY McCULLAGH, M.D.

It is now four years since Kennedy and Purves reported the effects of feeding Brassica seed diets to rats,[1] the goitrogenic effects of which were later shown to be due to their content of allyl thiourea. Their early studies showed that this goiter-producing effect was absent in hypophysectomized animals.[2] Since that time the work of the Mackenzies[3] and Astwood[4] has been followed by a flood of experimental and clinical literature on the subject.

* Presented in part as a lecture at the Post-graduate Course under the Auspices of the American College of Physicians, Chicago, November, 1945.