THYROTOXICOSIS IN AN ENDEMIC AREA*

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The problems of thyrotoxicosis concern physicians and surgeons alike. As Breitner has taught, as a result of 30 years of work on surgery of the thyroid, there is no true distinction between the surgical and medical management of this disease. It is therefore a great privilege to present to you some experiences with thyrotoxicosis which we have had as surgeons in an endemic area.

The main European goitre belt runs along with the Alps from the Rhône river to the Danube. The Tyrol, where I come from, is situated in the eastern part of the Alps. It has an area of 4,889 square miles, its highest peaks and glaciers range up to 12,000 feet. The towns in the Inn valley are 2,100 feet above sea level and some villages, well known skiing resorts, are at 6,000 feet. The water, with a hardness up to 18 degrees, is of good drinking quality but poor if not totally devoid of iodine. Especially among the hard working farmers, goitre is a serious endemic disease in spite of many years of iodinized salt supply. In Innsbruck, with 100,000 inhabitants, approximately 1,500 goitre resections are made every year out of the total population of the Tyrol of 400,000. The relative incidence of thyrotoxicosis is on an average 4%. The absolute incidence is difficult to assess. We do not agree with the traditional belief that Morbus Basedow (Graves' disease) is the disease of the non-endemic goitre area while mild hyperthyroidism is the equivalent and more frequent event in an endemic district.

When we compare our figures with those of Sallström (1935, Sweden), Thompson (1932, Chicago), Means (1948, Boston) and Fonio (1953, Switzerland) we find that thyrotoxicosis is far less modified by geographic conditions than simple goitre and there seems to be no significant difference in the variety and the severity of thyrotoxic symptoms and signs in endemic and non-endemic regions. For example there is no significant difference in the distribution of the BMR or of the pulse rate in Boston, Bern and Innsbruck and of the distribution of the classic triad and the age. The only fact distinguishing thyrotoxicosis in endemic and non-endemic areas and which is of importance for the diagnosis and the treatment is the type and the degree of thyroid hyperplasia already present at the onset of thyrotoxicosis. Whereas in non-endemic regions hyperthyroidism starts with only a slight enlargement of the thyroid gland or with no visible enlargement at all (Hunziker, 1924; Eggenberger, 1925), in the Tyrol more than 90% of thyrotaxic patients already have large nodular goitres before the onset of the disease. In other words, the specific problem of thyrotoxicosis in an endemic area is the management of toxic nodular goitres as compared to the diffuse toxic goitres which one has to treat mainly in non-endemic areas.

With rare exceptions, Tyrolean toxic goitre shows the picture of the struma diffusa et nodosa parenchymatosa with either papillary epithelial hyperplasia and lymphocytes in the stroma or no typical morphological signs of abnormal activity at all. A 'toxic adenoma' was found in only two patients (0·4%). The histological findings rarely correspond with the clinical picture. There is no doubt that thyrotoxicosis is more likely to develop in a goitrous person than in a person who has a normal thyroid gland (Riddel, 1956). In the same way a healthy thyroid gland is less sensitive towards thyrostatic treatment. The occurrence of hyperthyroidism seems to be dependent on the ability of the thyroid to compensate for a pathological stimulation. Thyrotoxicosis is reported to be unknown in places such as Bordeaux and Florence where the normal thyroid weight of 17 grams has been found (Klose, 1929).

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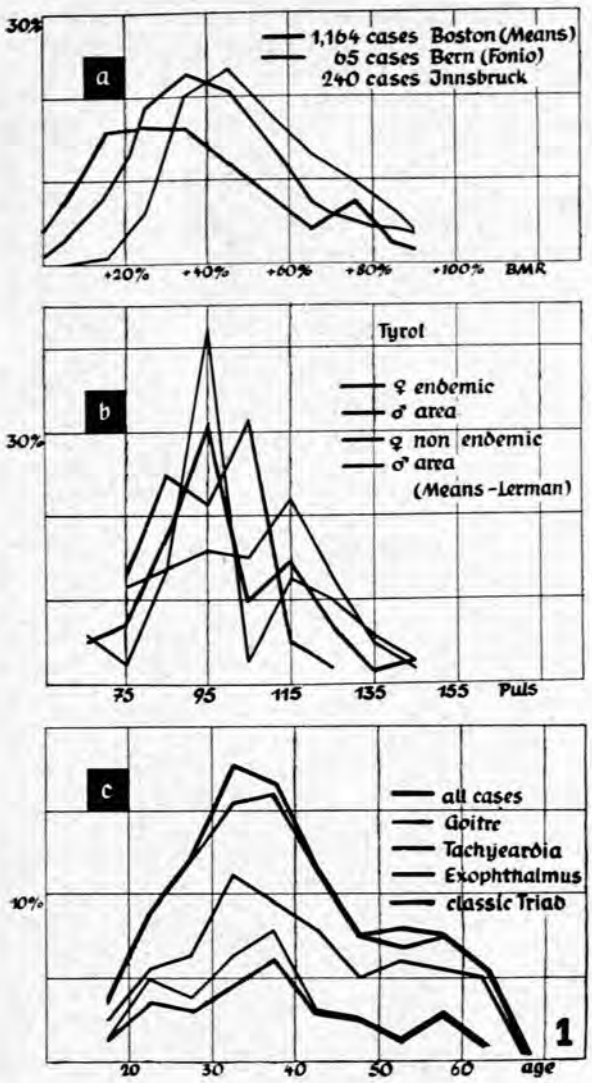

Fig. 1. Frequency distribution in 200 thyrotoxic patients of (*a*) BMR in endemic and non-endemic areas, (*b*) pulse rate in endemic and non-endemic areas, (*c*) classic Basedow signs and age in an endemic area.

DIAGNOSIS

Because of limited time at my disposal I shall restrict my discussion to the part which the predominant nodular type and the size of the goitre plays in the diagnosis and treatment of the thyrotoxicosis. In the presence of endemic goitres the correct diagnosis of thyroid function is often by no means easy. Frequently a kind of focal infection (focal toxicosis) caused by the common regressive changes, the formation of cysts or haematomas in larger nodules, a state of anxiety caused by tracheal obstruction or psycho-neurosis, neuro-circulatory asthenia, may produce a clinical picture which is perplexingly similar to many kinds of true thyrotoxicosis.

Since fatal thyroid crises have occurred after resection of even mild toxic nodular goitres, doctors become very anxious not to overlook any degree of hyperthyroidism. This leads to the practice of treating as thyrotoxic far too many nervous patients with an elevated BMR (Huber, 1950). Because of this diagnostic error euthyroid patients are deprived of their euthyroid state and thyroid enlargement is induced or—as we have observed several times—thyroid resection and thyrostatic treatment have been suggested in cases which were truly *hypo*thyroid. Furthermore, thyrotoxic patients with underlying nervous state were treated too long with thyrostatics or regarded as thiouracil- or iodine-resistant cases (Wilflingseder, 1955).

In spite of the fact that the final diagnosis has to be made on the basis of the clinical findings, a reliable thyroid function test is highly desirable in many of our patients. Especially in an endemic area it is important to bear in mind that the various tests measure different aspects of thyroid function. Thyroid function is composed of two main components, the activity of the gland and the utilization of the hormone by the cells (Breitner, 1928). The level of the serum protein-bound iodine and the many ^{131}I tests measure the activity of the gland. The cholesterol level and the BMR indicate the action of the hormone on the peripheral cells. On account of the iodine absorption, tests measuring the activity of the gland are misleading in endemic goitres in 50% of cases (Meckstroth, 1952; Rapport, 1951; Pabst and Pilz, 1956; Marcel Roche, 1957; Curtis and Fertman, 1945; Gutzeit and Parade, 1938; Holst, 1928) and are furthermore inadequate for the control of therapy when iodine or thiouracil are given (Levitt, 1954). McConahey, Owen and Keating (1956) from the Mayo Clinic tried 7 different types of ^{131}I diagnostic tests, and none of them was decisive in determining whether a patient was or was not hyperthyroid.

The cholesterol and lymphocyte test, according to personal studies on 187 persons, is in our region also of no diagnostic significance (Wilflingseder, 1952, 1954).

The BMR is easily obtained and is the largest established thyroid function test, but it is of limited usefulness in just those borderline cases of anxiety neurosis or neurocirculatory asthenia where it is most needed. The BMR technique of Robertson (1946), Fitting and Eiff (1956) is too time-consuming for clinical routine work, and has still a wide range of uncertainty. The SMR of Bartels (1948) has been found helpful by several authors (Rapport, 1951; Meckstroth, 1952; Pegni, 1949; Frases and Nordin, 1955; Leonhardt, 1953; Wilflingseder, 1948, 1955). It measures a truer basal metabolic state, because it is 'void of all nervous and muscular factors' (Bartles, 1949). Having returned from the Lahey Clinic in 1948 we studied the SMR in more than 400 cases at the Innsbruck General Hospital and have made it a routine test in border-line cases. (Wilflingseder and Villinger, 1955).

After 2 determinations of the BMR, up to 500 mg. of Narkothion* is given intravenously and 2 or 3 consecutive metabolic tests are taken while the patient is breathing quietly in a short somnolent stage. We found it not necessary to induce a deeper sleep. In the first 100 cases pentothal was used and laryngospasm occurred in 3 patients; in the last 300, with the use of Narkothion, laryngospasm was entirely avoided. Most patients wake up at the end of the second determination and are well within one hour after completion of the test. Our work at Innsbruck indicates that the range of diagnostic error using the BMR is 18-54% whereas using the SMR it is only 11-23%.

* Manufactured by Sanabo, Wien XII, Anton Scharff-Gasse.

The SMR has proved to be most helpful under the following circumstances:

1. In children, whose basal metabolic rates are notoriously unreliable.
2. In psychoneurotic patients when a basal metabolic rate determination cannot be obtained at all.
3. In all cases in which the BMR does not conform with the clinical picture and seems to be altered by extrathyroidal nervousness.
4. When hypothyroidism is suspected but masked by an elevated BMR.

The SMR is also superior to the BMR in the control of therapy (Fig. 6).

TREATMENT

The treatment of choice in toxic nodular goitre is bilateral subtotal resection. Opinions differ only as to the best pre-operative treatment. In an endemic area iodine is advised only for mild cases. We do not believe that iodine is such a dangerous weapon in the battle against goitre and thyrotoxicosis in an endemic goitre region (Breitner, 1928; Fonio, 1953) but we restrict iodine because it is effective for a quiet post-operative course in only one-third of our patients (Thompson, 1930; Means, 1948; Jackson, 1948; Wilflingseder, 1957). Our mortality remained high until the thiouracil derivatives were introduced into our country.

If the iodine-lacking case of endemic goitre receives exactly the amount of iodine lacking, say 50 or 100 micrograms, the parenchyma may become able to produce suddenly more (or a more effective) hormone, which sometimes produces a kind of hyperthyroidism known as 'Iodine-Basedow' or an exacerbation of an already existing thyrotoxicosis (Baumgartner, 1939). But if an excessive dose of iodine is given—depending on the size of the goitre, say 6-200 mg., a thyrostatic effect of some degree will result even in toxic nodular goitres. Out of 8,000 goitres only 64 cases with probable 'Iodine-Basedow' have been admitted to our department and none of these cases had received more than a small goitre-prophylaxis iodine dose.

Propyl- and methylthiouracil have had a full thyrostatic effect in all our cases treated so far. Depending on the size of the goitre, 300-600 mg. is given until a euthyroid state is reached. We have observed toxic reactions in only 3%. The mercaptan derivatives have not had a great thyrostatic effect in our nodular toxic goitres but tend to affect the haematopoietic system. In one such patient we continued treatment with the administration of 50 mg. of hexamethonium chloride 6 times a day. Within 11 days a complete remission of thyrotoxicosis was obtained. It is important to stop the thiouracil drugs for one week before operation, because leukopenia or agranulocytosis may begin several days later (Wilflingseder, 1957). We have seen a young woman die from septicopyaemia on the third post-operative day probably from this cause. We found it useful to give iodine for a week before operation not only to the diffuse toxic goitre but also to the nodular goitre. They all have a mixed parenchyma and become smaller and harder as a result of giving 50 or 100 mg. of iodine per day.

For 25 years the bilateral subtotal resection has been performed as the operation of choice in our department. Controlled hypotension was used in over 100 goitre resections (Villinger and Wilflingseder, 1955). This was helpful in certain cases but is not recommended for routine use. The thyroid remnants should not be less than 5 g. of good parenchyma on each side (30 by 20 by 15 mm.) in our endemic area. Our follow-up studies show only 2% of persistent symptoms or relapse of hyperthyroidism. They do not indicate that reduction of this figure would depend on a more radical resection. Although the ligation of all 4 arteries is preferred from the technical point of view, there was no difference in the immediate and late post-operative functional state of the thyroid when only 2 or all 4 arteries had been ligated.

In our region a relapse of thyrotoxicosis which can easily be controlled by thyrostatic drugs is regarded as a lesser evil than a permanent post-operative hyperthyroidism because we find that patients do not cooperate well on substitution therapy.

There is another technical point I should mention. Tracheomalacia because of long trachael obstruction is not infrequent in our area and tracheotomies were often necessary at the end of the operation. In a few years we have used steel ring-protheses (Wiethe, 1948) (Fig. 2) to prevent the tracheal collapse during inspiration. One or two rings are stitched to the perichondrium where the trachea has become too soft (Fig. 3). 36 patients treated in this way as reported by Haas

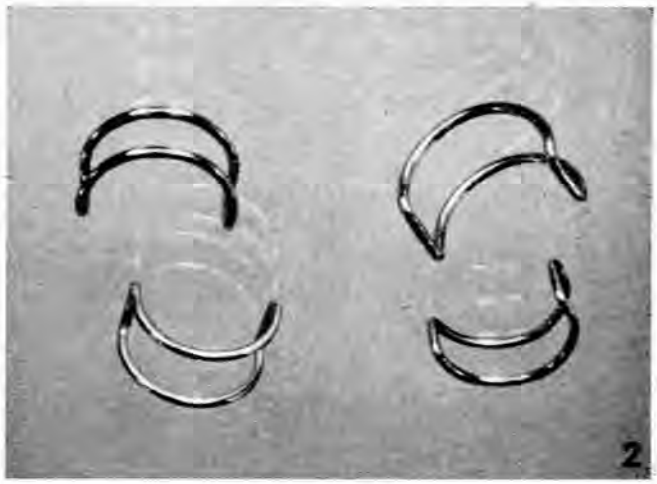

Fig. 2. Stainless steel rings used in tracheo-malacia to stabilize the tracheo post-operatively.

(1955) from our department were free from all breathing troubles and have had an uneventful post-operative course. In only 2 patients did the ring have to be removed later because of fistulas. We do not feel that tracheotomy—if done at the end of operation—is a serious complication but the steel tracheal rings safeguard respiration in cases with tracheomalacia just as well and spare the patients the burden of an additional tracheostomy after an already extensive operation.

A malignant exophthalmos developed in one patient (0·4%) 14 months after subtotal resection. Large doses of desiccated thyroid, ACTH and X-ray treatment did not stop the progress of the prostrusio bulbi. The eyes were saved by bilateral orbital decompression (Poppen, 1951).

The post-operative treatment in all thyrotoxic patients consists of simple goitre prophylaxis. Depending on the BMR and SMR, iodine or desiccated thyroid tablets are given. In purely diffuse and not too large toxic goitre, the medical regimen has been successful. Mild cases were

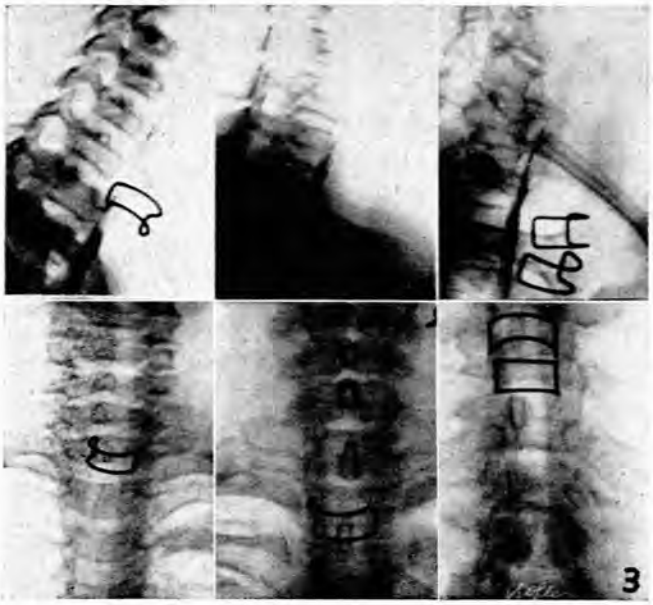

Fig. 3. Three cases showing stainless steel rings in side tube. Post-operative.

treated with desiccated thyroid only. In severe thyrotoxicosis propylthiouracil combined with desiccated thyroid is given, followed by thyroid only until the goitre has disappeared.

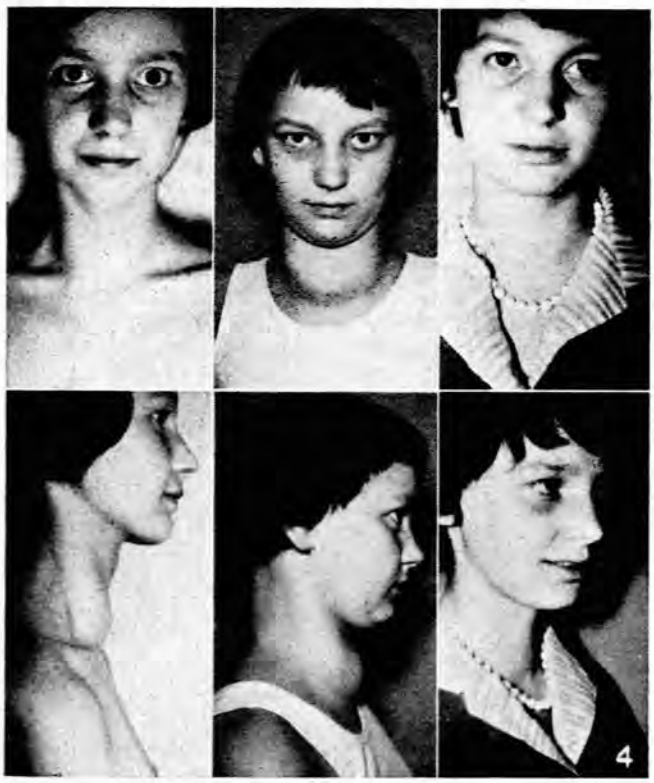

Fig. 4. A series of photographs illustrating Graves' disease in a child treated with propylthiouracil and thyreosan. The two figures on the right illustrated the end result.

CASE REPORT

This girl (Fig. 4), our only case of Graves' disease in a child in 20 years, received 200 mg. of propylthiouracil and 0·5g. of Thyreosan until euthyroidism was obtained. Thyreosan administration followed for two years. Goitre prevention is also a prophylactic against thyrotoxicosis (Eggenberger, 1926) and desiccated thyroid has been recommended by Steyrer (1917) for that reason.

SUMMARY

What is essentially the aim of surgical subtotal resection must also be attempted with our medical treatment, viz. reduction of the hyperplastic gland to a normal one. In a case of purely functional hyperplasia we may succeed with thyroid substitution therapy and cure thyrotoxicosis permanently in that way. In addition to the modern thyrostatic therapy, which has benefited our thyrotoxic patients so much, I feel we should emphasize the importance of this functional treatment especially in an endemic area.

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