THE MEDICAL TREATMENT OF HYPERTHYROIDISM

WALTER REDISCH AND WILLIAM H. PERLOFF
From the New York University Medical School and the University of Pennsylvania School of Medicine
NEW YORK CITY AND PHILADELPHIA, PA.

THE CONCEPTION that treatment of Graves' disease (1) is primarily surgical, is widespread despite the fact that American as well as European literature contains numerous reports of satisfactory results with non-surgical treatment in selected cases. It is undoubtedly true that since Plummer and Boothby (2, 3, 4) inaugurated routine preoperative iodine preparation, the prognosis of surgical procedures in Graves' disease has been markedly improved. It is also true that a high percentage of cures is obtained by subtotal thyroidectomy, but the results are by no means universal. Because of these operative failures, and because of those cases not amenable to surgery, it is the immediate concern of the internist, from a practical point of view, to continue his search for a satisfactory medical treatment.

The mode of action of different types of therapy is still far too speculative to be discussed in this purely clinical paper, but one must admit that it is extremely difficult for patho-physiologists to comprehend how a large number of hyperthyroids are cured or helped by simply cutting out a piece of an overactive gland. It appears likely that the enlargement of the thyroid is by no means the cause of the hyperthyroidism, but rather a sequel. The relationship between the size of this gland and the degree of hyperthyroidism has never been determined. Even the exact histological study of Sunder-Plassmann (5), in which he was able to show much damage to the local sympathetic fibers as a result of subtotal thyroidectomy, by no means covers the entire subject, as was first pointed out by Bauer (6, 7), and his conclusions were too far reaching. This lack of information as to the theoretical considerations relating to the mechanism of action confronts the research worker in the field with an important problem directly related to treatment.

In the face of present day literature, it is impossible for us to agree with Richter (8), when he claims that the treatment of Graves' disease is entirely surgical. On the other hand, we cannot concur with Jenkinsons' view (9) that every case should be treated primarily medically and only failures then subjected to surgery. We hold with the majority of workers that a certain group of cases are surgical, the remainder medical, to be treated surgically only after non-operative failure. Most workers agree, that as soon as it becomes apparent that the results of medical therapy are not good, surgery should be immediately resorted to with the least possible delay so that the optimal time for operation is not missed. On the other hand, too early surgical intevention, especially in early acute Graves' disease, is also not advisable because postoperative crises are most common in these cases, even with preoperative iodinization, and incomplete results as well as recurrences are relatively frequent. To this group belong the cases with diffuse hyperplasia, as pointed out by Barr (10). In contrast, patients whose hyperthyroidism is partly burned out by medical treatment, respond later to surgery with much better results.

Redisch (11, 12) considers the surgical indications as follows (Prague 1934).

(a) Those cases in which a local mechanical disturbance exists in conjunction with the hyperthyroidism even when this mechanical disturbance is mild.

(b) Cases of hyperthyroidism in which one or more nodules can be felt, firmer than the remaining gland, most commonly found in older goiters with secondary toxicity.

(c) Failures of conservative therapy, again stressing the point that one must not wait too long.

(d) Wherever an immediate danger of circulatory involvement is imminent (especially the development of auricular fibrillation in the absence of cardiac failure).

Harris and Rose (13, 14) express a similar point of view (1936) but favor x-ray over medical treatment because of the economic aspects, an argument which could of course likewise be presented by the surgeon.

Means and his associates (15) have worked out an excellent scheme to prognosticate the operative risks, so that their cases come to surgery not only satisfactorily prepared, but also very well selected. They have had a postoperative mortality of only 2.6% since the advent of routine preliminary iodinization. It is of great interest to note that in Means' clinic at the Massachusetts General Hospital in the period from 1923 to 1935, 97.6% of all cases were operated on, 1.5% treated with iodine alone, and 0.3% with x-ray and surgery, whereas since 1935 (personal communication) the percentage of medically treated cases (iodine alone) has risen to from 12 to 15%. In Biedl's clinic (Prague, 16) almost the same postoperative mortality figures are found, but there only 30% of the hyperthyroids were operated on. Of the remaining 70%, 10% were treated with iodine alone, 60% by x-ray alone, and 30% by x-ray and iodine with a mortality figure much under 1%. In this group are not included those cases of very mild hyperthyroidism with B.M.R. of less than +15, all of whom were treated conservatively and not considered for surgery (W.R.).

The Various Types of Conservative Therapy

Means and his associates (15) point out in their reports that of all the conservative methods available in the treatment of hyperthyroidism, only two are worthy of consideration at the present time as being complete in themselves, namely iodine and x-ray. Redisch (10) published a survey on the therapy of hyperthyroidism in 1934 and came to essentially the same conclusions.

There is, however, a third possibility which may show promise in the future: the treatment with normal blood serum, utilizing the antithyroid principle of Blum (17) which he called 'katechin.' It cannot be denied that in mild cases some favorable effects are often seen (18–21). One can certainly not recommend the employment of this means as a general rule at the present time because the nature of the material and its mode of action are entirely unknown.

It is postulated (17) that this inhibitory substance is produced physiologically in the body, circulates in the blood stream, and aids in the regulation of available thyroxin to the tissues. Certainly the theory of antibody production is in complete disagreement with every hormonal concept up to the present time and it may have been just such substances as this antithyroid principle with which L. Loev and others have been dealing (22–26). Very similar to 'katechin,' as noted by Means, is the 'antithyroidin' of Moebius (27), who was able to use effectively the serum of thyroidectomized sheep in hyperthyroidism. Here apparently, the antithyroid principle is unopposed by the thyroid hormone, accumulates in the blood stream and so is free to lower the recipient's own thyroxin activity. Moebius also employed a substance called 'rhodagen,' obtained from the milk of thyroidectomized goats (Burghart and Blumenthal). Successful reports continue to appear in the literature from time to time.

It seems, furthermore, from a clinical point of view, that patients who have

been previously iodinized are more susceptible to the inhibitory action of normal blood serum. Whether this depends on the degree of iodine saturation of the thyroid hormone, or simply on the level of iodine in the patient's blood serum, is not known. The whole problem is wide open for investigation at the present time and the writers are engaged in an attempt to elucidate this antithyroid principle.

There are a few remaining methods which may occasionally be employed as supplements, especially in mild cases. Some of these are purely symptomatic as the sedatives, of which the bromides require particular attention. Bromine replaces iodine even in thyroid and so disturbs the iodine balance (28–31) still further, adding to the therapeutic difficulties. Other types of treatment act on the vegetative nervous system, the relationship of which was pointed out particularly by Bramm (32), and and others (33). Hospitalization itself, is an important factor, particularly when high carbohydrate, high vitamin, low protein diet is used (16, 34). Marine and his coworkers (35) have done most of the pertinent experimental investigation on the vitamins but clinically, different ones have been stressed by various workers (15, 36, 37). Gynergen, which was employed with injurious effect in the past, has been universally abandoned.

It has been noted in Central Europe that even severe cases of hyperthyroidism sent to certain mountain climates (about 1000 to 1200 meters above sea level) showed an entirely unexplained but definite improvement (38, 39, 40). The large number of experiments designed to improve hyperthyroidism by acting on the correlation mechanism of the endocrine organs (41, 42, 43) need not be considered here because we are concerning ourselves only with nonsurgical methods which act directly on the thyroid. By the same token the complications of organic symptoms are not discussed.

Treatment with Iodine Alone

The relationship between iodine and the thyroid gland, particularly as regards function, was recognized as early as the beginning of the last century by Straub (1819) (44), and Coindet (1820) (45). After the syndrome of Flajani (46) was classically described by Graves (1) and von Basedow (47), iodine became the basis for treatment, with variable degrees of success (48), until that time when Kocher first described his hyperthyroidism presumably caused by iodine (49). This conception of the great Swiss surgeon caused such a sensation that the use of iodine was almost completely abandoned. Today, however, we are sceptical of the validity of Kocher's conclusions (15, 50).

In 1917 iodine was reintroduced into the therapy of hyperthyroidism by Chvostek (51). He reported improvement in some of his cases but aggravation of the condition in others. Similar results were obtained by Neisser (52) in 1920 and by Loewy and Zondek (53) in 1921. In the same year Plummer and Boothby began their extensive investigation which led to the universal acceptance of Lugol's solution in preparation for surgery. Starr and Means (54), Mason (55), and Read (56) gave added impetus to the renewed use of iodine, and with this came the desire on the part of many workers to find some classification which would serve as a general basis for indicating iodine treatment (51–65).

Plummer and the other workers at the Mayo clinic reaffirmed the experience that iodine causes a great improvement in some patients, has no effect in others, and makes still others clinically worse, and on this basis differentiated between 'exophthalmic goiter' and 'toxic goiter.' Today there is no doubt that this differentiation cannot be made, particularly because exophthalmos is an extremely variable and inconstant sign in hyperthyroidism with no definite relation to the action of iodine. Biedl and Redisch will not admit to inherent symptomatic nor marked histologic differences between the real Graves' disease on the one hand, and hyperthyroidism on the basis

of an old goiter on the other, but feel rather that the hyperfunction of the thyroid gland has very different manifestations according to the constitutional state of the person affected. Real Graves' disease involves individuals with the particular habitus of the type variously called 'status thymico-lymphaticus,' 'asthenic,' 'hypoplastic,' and these workers point to the changes found in the blood picture of Graves' disease after iodinization for confirmation.

Hertz and Lerman (66) found the same changes in the blood picture independently. Despite all classifications, the therapeutic test with iodine remains as yet the best method of ascertaining a patient's response, but even this should not be attempted with old goiters become toxic.

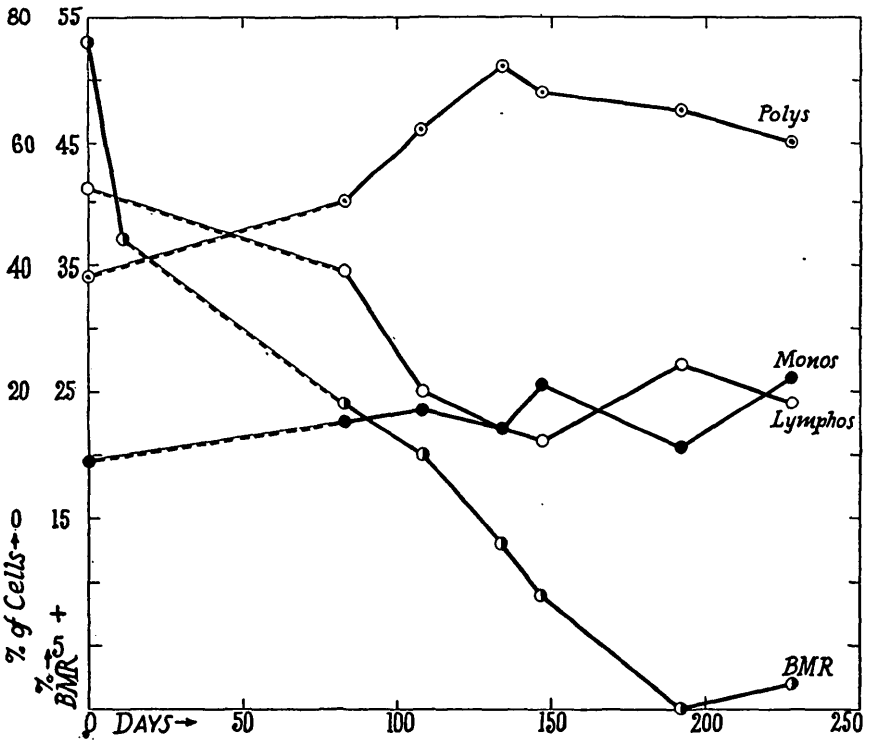

Fig. 1. THE PATIENT IS A 17-YEAR-OLD WHITE GIRL ON WHOM A THYROIDECTOMY HAD BEEN PERFORMED 2 YEARS BEFORE ADMISSION. Her complaints started 1 year after the surgery was completed.

The official Lugol solution in America contains 5 gm. of iodine and 10 gm. of potassium iodide in 100 gm. of water, giving 126 mg. of iodine in each 1 cc. of solution. According to Boothby one begins treatment with 78 mg. iodine daily (0.6 cc.) and works up to 100 to 300 mg. Because of the fact that sodium is known to cause no damage to the heart and circulation as does potassium, Biedl and Redisch employed a solution containing pure iodine 0.1 gm., sodium iodide 1.0 gm., and water 10 cc., making 70 mg. of iodine in 15 drops of solution, which was the average daily dose. Meanwhile, it was shown by Keller (67), in his work on the electric charge of molecules, that whereas in vitro potassium and sodium behave similarly, in the organism this is by no means true, which may explain the better results with sodium. The above mentioned solution (sodium iodide) was given for periods of 8 to 12 days followed by rest periods of 3 to 5 days. This procedure seems to avoid to a great extent the negative phase of continued iodine administration.

In Biedl's clinic (68) about 10% of the cases with favorable results were completely and permanently cured, 40% entirely symptom free so long as iodine was administered, and 50% almost symptom free but still showing some manifestations of the condition. The 'toxic symptoms' of acute Graves' disease (diarrhea, restlessness, insomnia) reacted especially favorably to iodine. The fact that the percentage of cases treated by iodine alone in Means' clinic has increased remarkably during the last 3 years, shows that the pendulum may be once again swinging towards the medical treatment of hyperthyroidism in this country.

The prophylaxis of goiter and its distribution are problems in themselves and we will not discuss them here except to point out the following.

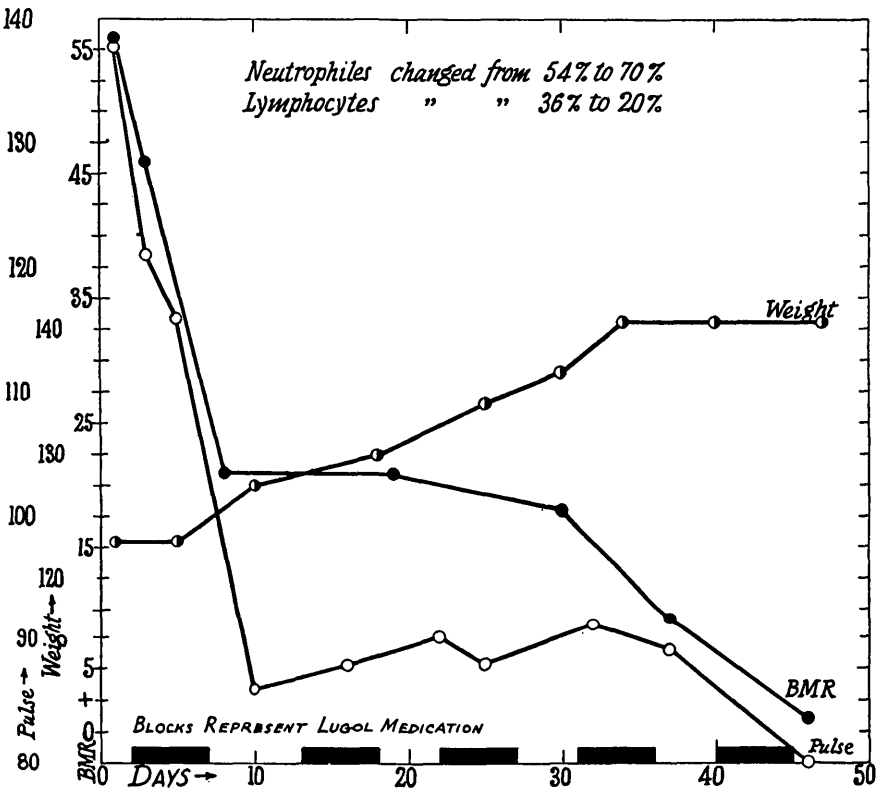

Fig. 2. The patient is a 24-year-old white woman who had a thyroidectomy 8 months before this study.

(*a*) Patients with real Grave's disease do not belong to that group particularly susceptible to iodine poisoning, De Quervain (69, 70, 71) to the contrary.

(*b*) There need be no particular fear of iodine poisoning in pubertal goiter.

(*c*) Toxicity symptoms after iodine occur relatively frequently in *a*), goiter with pregnancy, *b*), goiter with lactation, and *c*), individuals over 30 years of age with old nodular goiter.

X-Ray Treatment

Judging by the amount and quality of American contributions to the literature on the treatment of hyperthyroidism with x-ray, one would expect this means to be more in use than is actually the case. Pfahler (72), who can be considered the pio-

neer in this field, and others (13, 73–76) have demonstrated clearly the real value of x-ray therapy. As early as 1917 Means and Aub (77) were able to report favorable results, and in 1924 Holmes, Means and associates obtained cures in one-third of their cases and improvement in another third. Despite this fact, x-ray has been used hardly at all at Means' clinic since.

Pfahler and Vastine (78) obtained 86% satisfactory results in their series, and in a statistical study of over 10,000 cases, Menville (79) reports 66% cure, 21% improvement and 13% failure. Harris and Rose have defined in a classical manner the place of x-ray therapy in the treatment of hyperthyroidism and claim as special advantages: *a*) negligible mortality, *b*) lack of major complications, *c*) low cost, *d*) absence of physical as well as psychic shock and *e*) maintenance of patient's earning capacity during treatment in most cases. They found satisfactory results in 67% of cases that followed the prescribed plan. European literature is almost entirely favorable and British, German and French authors report figures similar to the American studies. For example, Poulton and Watt (80) obtained marked improvement or cure in 55%, definite but incomplete improvement in 35%, whereas Hess (81) found 47% and 31% respectively in the same classification.

Herrnheiser and Redisch (82, 83) published a report of part of their material in 1927 and again in 1929, and in about 200 cases their percentage cure was the same as in Means' series. They were particularly interested in ascertaining whether or not x-ray gave the same favorable results after iodinization as before and found that previous iodine administration had apparently no influence on the results except in a small group of patients in which the effects were even better. They concluded therefore, that x-ray was indicated when insufficient improvement was obtained with iodine alone. Their technic of treatment was to employ a series of 8 to 10 consecutive weekly irradiations of 80 to 120 r, with rest periods of 1½ to 6 months depending on symptoms. Two or 3, even to 5 and 6 series, may have to be applied, and x-ray shock, which is essentially the same as a postoperative storm (84) is avoided in this way. Modern American technic is similar to the above. Adhesion of the capsule to the gland is no longer considered a result of irradiation (85–87).

Borak (88) employed x-ray to the temporal fields in addition to the thyroid with special improvement of the nervous symptoms. Whether this is due to action on the pituitary or on the vegetative centers of the diencephalon, we cannot say.

Radium has no advantage over x-ray (89) but may often be used more conveniently in emaciated patients confined to bed (90, 91).

The new method of administering radioactive iodine as developed in Means' clinic and presented by Hertz, might represent an effective and practical combination of the action of iodine and rays.

SUMMARY

Conservative therapy has its place in the treatment of hyperthyroidism because: *a*) of a certain number of surgical failures, *b*) certain cases are not amenable to surgery, *c*) mild cases generally do not need surgery at all.

The two conservative measures, generally complete in themselves, are: *a*) treatment with iodine, *b*) treatment with x-ray.

Administration of serum containing the hypothetic 'thyroid inhibitory' factor is discussed and regarded as a possibility for the future. Investigations in this direction are in progress.

Treatment with iodine alone is discussed with: *a*) cures in 10% of the favorable cases, *b*) no symptoms on iodine in 40%, *c*) incomplete but definite improvement in 50%.

The differentiation of cases on a constitutional basis is discussed. Iodine should never be given to patients with old nodular goiters become toxic.

Brief discussion of indication for surgery and of susceptibility to iodine poisoning in goiter prophylaxis is given. The technic of iodine administration is described.

X-ray treatment is described. Results in American literature surpass those in European reports. Previous iodinization is no contraindication to x-ray. Combination of both may even improve the results.

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