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Exophthalmic Goitre.*

BY

SOLOMON SOLIS COHEN, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JEFFERSON MEDICAL COLLEGE; PHYSICIAN TO THE
PHILADELPHIA GENERAL HOSPITAL, ETC., PHILADELPHIA.



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THE NON-SURGICAL TREATMENT OF EXOPHTHALMIC GOITRE.¹

BY SOLOMON SOLIS COHEN, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JEFFERSON MEDICAL COLLEGE; PHYSICIAN TO THE
PHILADELPHIA GENERAL HOSPITAL, ETC., PHILADELPHIA.

GRAVES' SYNDROME NOT HYPERTHYROIDISM ONLY. The pathogenesis and pathology of Graves' syndrome are as yet obscure. "Hyperthyroidism," despite its present currency, is a faulty, as well as an insufficient, explanation. Excessive activity of the thyroid gland, sometimes accompanied with goitre and sometimes without appreciable enlargement, is often present and adds its symptomatology to that of the underlying disorder; but it is neither the origin nor the whole expression of the fundamental departure from the normal. The term "exophthalmic goitre" is unfortunate; and probably leads to belated diagnosis; early stages being overlooked, or mistaken for "nervousness," gastro-enteric disorder, etc. Luckily, "neurasthenia" and "hysteria" are often treated by rest.

OPERATIVE TREATMENT UNNECESSARY IN THE MAJORITY OF CASES. Holding the view set forth, I am unable to look upon Graves' disorder as essentially a condition for operative treatment; or to admit that the only alternative is cytotoxicity. That partial thyroidectomy, ligation of the thyroid arteries, and other approved surgical procedures are helpful in many cases and necessary in some, may be freely granted; and one may likewise acknowledge without reserve the great value of Beebe's serum in certain cases. Yet I have a strong conviction, based on more than twenty-five years' observation and study, that such measures are indicated only in a small minority of the cases that come under the eye of the alert physician.

INDICATIONS FOR OPERATION. Whether or not operation is indicated in an individual case, is to be decided upon the special circumstances of that case; and these cannot always be set forth categorically. Nevertheless there are certain general consider-

¹ An address delivered before the Medical Society of the State of New York, at Albany, April 17, 1912.

ations that may assist the decision. Thus there can be little question that operation should be done:

1. When the disorder has persisted for a long time, and is advancing despite skilful medicinal and hygienic management, including prolonged rest.

2. When the disorder is progressive or far advanced, and is either disabling or dangerous, or threatens to become so—even though no sufficient attempt has been made at medicinal and hygienic management, including rest.

3. When the patient's means or social status is such that rest is impracticable, and the disorder, although slight, is partially disabling and has persisted for a year or more under treatment, with no sign of yielding.

There are other circumstances, however, which need not be enumerated, in which the decision is not so easy. Usually no harm will be done in such doubtful cases by waiting and watching for a reasonable time, giving the patient meanwhile the benefit of rest and other appropriate measures. In a proportion, even of advanced or apparently progressive cases, arrest or partial recovery will take place to a degree sufficient to obviate the necessity for surgery.

While, therefore, avoiding an extreme position against the operative treatment of Graves' disorder, and on the contrary recognizing its necessity and its benefits in properly selected cases, I am, nevertheless, distinctly and unalterably opposed to the dictum that operative treatment is the sole means of remedy in any case, and should be the rule in all.

FALLACY UNDERLYING ARGUMENT FOR ROUTINE SURGERY. Underlying most of the arguments for making operative treatment the rule, is the false assumption that without such interference recovery cannot take place. On the contrary, the great difficulty acknowledged by most of those who have had large experience in the medicinal management of Graves' syndrome is the liability to overestimate the influence of some particular therapeutic measure, during the use of which the patient may have recovered spontaneously. For it must be remembered—and in connection with the claims of surgeons as well as with the assertions of physicians—that in a very large number of cases recovery will take place without any special method of mechanical or medicinal treatment, if only the patient be kept at rest, with regulation of diet, and under proper hygienic surroundings, *for a sufficient length of time*. Indeed, spontaneous recovery may occur, even without prolonged rest. This, however, is less common.

DANGERS FROM THE GOITRE. Let me repeat that I do not wish to be misunderstood as opposing operation under all circumstances. When the diagnosis has been unduly delayed, or when the hygienic and medicinal management has been faulty—and faulty chiefly by the failure to institute persistent rest—the thyroid complication

may in consequence become the predominant factor in the case. Pressure by the enlarged gland may cause mechanical difficulties in respiration or in deglutition; may obstruct circulation in the cervical vessels; or by compromising the pneumogastric or other nerves, may give rise to disorders of various kinds. Also, by excessive activity, the hypertrophied gland may disturb cardiac and other functions in great degree. In such instances surgery may indeed be the only remedy; or, as already intimated, it may be the remedy of preference; and it is quite probable that many surgeons, and especially those noted for their skill in thyroid operations, have formed their opinions concerning the nature and management of exophthalmic goitre in general, largely upon cases of this class. These are, nevertheless, but a small minority of the whole.

APPROXIMATE ESTIMATE OF SURGICAL AND NON-SURGICAL CASES, AND CASES OF SPONTANEOUS RECOVERY. I have no exact statistical data, but as a guess, not without reasonable grounds, 20 per cent. of all the cases of Graves' disorder may be looked upon as a rather large estimate of those belonging to this category of neglected cases. Again, there are cases in which the diagnosis is made reasonably early and the medical management, including rest, has been reasonably thorough, yet which nevertheless progress to a point at which surgical interference becomes necessary. If one may judge from his own experience, 5 per cent. would be a very large estimate for this category. Thus we have left, as a conservative estimate, about 75 per cent. of all the cases to form the great class in which recovery may be expected spontaneously or under non-surgical treatment. Of these, probably 50 per cent. will recover without special medication. In the remaining 50 per cent., that is to say, somewhere between 30 and 40 per cent. of all the cases of Graves' syndrome, careful medical management is necessary; and if skilful and persistent, will be successful.

GENERAL CONSIDERATIONS UNDERLYING THERAPY. Before taking up the details of such management it is necessary to consider briefly certain general questions. Therapeutics would be more direct and less empirical if we had more definite information concerning the actual etiology of the condition.

Unquestionably there are three factors in its causation, perhaps more. These three certain factors are: (1) A fundamental liability; (2) a provocative agent; (3) a local determinant.

1. The underlying fundamental liability is congenital, and usually hereditary. It predisposes not merely to exophthalmic goitre, but to disturbances of the autonomic nervous system in general. I have discussed this at length in many papers,² referring

² Vasomotor Ataxia: AMER. JOUR. MED. SCI., February, 1894; Trans. Assoc. Amer. Phys., 1902; and Medical Review of Reviews, January, 1912. Visceral Angioneuroses: Trans. Assoc. Amer. Phys., 1909; New York Med. Jour., February 19, 26, March 5, 1910. Graves' Syndrome, Raynaud's Syndrome, and Allied Disorders: International Clinics, 1909, vol. iii, S. 19.

to various forms of vasomotor and visceral disorders, and need not here elaborate.

2. There must be, however, a provoking agent; and this is not always the same. Psychic disturbances—and usually emotion of a depressing character, such as grief, anxiety, fear or fright, but sometimes of an exciting order, as anger—undoubtedly acts as a provocative in many instances, though it cannot always be traced when the patient comes under observation. It is possible that emotion acts indirectly through the generation of toxic substances. Be this as it may, toxic influences of various kinds apparently play a large part in the complex etiology. Their nature, however, is as yet highly obscure, and little is to be gained by enumerating the many guesses that have been put forward concerning intestinal toxins, bacterial toxins, the products of perverted metabolism, anaphylactic products, deranged internal secretions, etc., since the evidence is inconclusive, and, moreover, the correctness of one supposition does not exclude the possibility of the others being right also. Beyond doubt the etiology is multiple.

3. The local determinants are probably many, but they are also as yet unidentified. Suggestive are the variations in the size of the thyroid gland brought about by pregnancy, by parturition, by lactation, by ovulation, by menstruation, or by the failure or excess of some of the special functions of the female, and under sexual excitement in both male and female. I have observed in the immune members of tuberculous families, and in persons exhibiting very sluggish or very rapid tuberculosis, various autonomic disturbances, including thyroid enlargement and ocular symptoms; and the tendency of some cases of Graves' disorder to terminate in pulmonary or general tuberculosis is recognized. So, too, the occurrence of exophthalmic goitre in members of neurotic families, and the development of maniacal excitement and other forms of psychosis in a certain proportion of the patients, is well known. Glycosuria may be an accompaniment of Graves' syndrome, and in some instances diabetes mellitus may be the terminal manifestation. Here the reciprocal relations of pancreas and thyroid, or of both to the pituitary and nervous centres, may be involved.

Whether eye-strain is to be classed as a provocative or determinant, or both—or whether the changes in the refractive apparatus and the disorders of muscle and innervation are not, rather, collateral results of the more fundamental cause—cannot be dogmatically stated. Probably there is a "vicious circle."

Without enlarging further on this difficult problem, it is evident that the exciting factors are both multiple and obscure, and that any treatment that attempts to base itself upon an unvarying etiology must fail in a large number of cases.

THERAPEUTIC CLASSIFICATION. From a therapeutic standpoint it would be highly desirable, if possible, to classify our cases etio-

logically or pathologically, and analyze the results of treatment accordingly; but as yet we lack the basic data. So, too, clinical classification fails for a similar reason; that based upon the varying characteristics of the goitre being useful, but inadequate. A rough clinical division may be made by noting the order of development, or the relative severity, of the cardinal symptoms. There are cases in which the cardiac disturbance appears long before enlargement of the thyroid can be demonstrated; cases in which the thyroid enlargement is first noticed; and cases in which the ocular manifestations precede all others, though these last are rare. Again, there are cases in which cardiac disturbance, or thyroid enlargement, or exophthalmos are relatively slight or completely wanting; and cases in which one or the other of these symptoms overshadows all else. There are cases of apparently abrupt onset, and cases of slow and even insidious onset. There are cases in which the early symptoms are predominantly nervous; others in which visceral functions, especially of the digestive or respiratory apparatus, are most prominent. Each physician doubtless makes some such classification of his own patients, and governs his treatment, in a measure, accordingly. But there is no accepted classification satisfactory to all; and there cannot be until etiology and pathology are cleared up.

One feature of a possible clinical classification is, however, of much significance. That thyroid enlargement may be wanting throughout the whole progress of the case is attested by many observers. It has been my own fortune to observe and record a number of such instances. Those in which thyroid enlargement is slight, and sometimes intermittent or variable, are still more numerous; and those in which goitre is quite a late symptom form a considerable proportion, perhaps one-fifth, of the whole number of cases. Certainly in that group of cases in which thyroid enlargement is wanting, slight, or delayed, medicinal rather than surgical treatment is indicated.

RECOVERY—WHAT IS IT? This leads directly to another very fundamental question: What constitutes recovery? Until this is settled, it is impossible to give judgment not only as to the comparative merits of medical and surgical management, but also upon the relative merits or absolute effects of the various medicinal measures and surgical procedures suggested. If disappearance of thyroid enlargement is to be taken as the criterion of recovery, then those patients in whom there has never been such enlargement, can never be said to have recovered, despite the loss of all other symptoms—an evident *reductio ad absurdum*. But if in cases without thyroid enlargement recovery must be predicated upon the subsidence of cardiac and nervous disturbances, may not the same rule be fairly followed in cases in which similar disappearance of cardiac and nervous disturbances takes place, but thyroid

enlargement remains? And what shall we say concerning patients who no longer have goitre, but in whom all the other phenomena of Graves' disorder persist? And just what degree of reduction in exophthalmos is to permit the case to enter the list of recoveries, or what degree of persistence is to exclude it?

It so happened last fall that I was able to exhibit in one of my clinical lectures at Jefferson Hospital, two patients side by side. One was a girl who had had all the symptoms of pronounced Graves' disorder. Her heart and eyes were now practically normal; she had no tremor; she could sleep well; she had gained flesh, and indeed seemed in every respect restored to full functional health; but there still persisted a moderate enlargement of the thyroid gland. This girl walked into the clinic hall, and had been up and about her work for more than a year. The other patient was a man who had to be rolled into the arena in bed. He was emaciated; he still showed marked exophthalmos, almost continuous tremor of the hands, and tumultuous heart action; his face was continuously flushed; he was subject to fits of sweating, to insomnia, to gastro-enteric crises, to headache, and to violent nervous excitement; but he had no goitre. His thyroid gland had been removed thoroughly and skilfully about two years before he came into Jefferson Hospital by a western surgeon of high repute (let me add in parenthesis, not at Rochester). The parathyroids had probably been taken with it, for there was a history suggestive of mild tetany following the operation. Which of these two patients could be the more appropriately said to have recovered?

Mere survival after operation is not recovery!

The condition of the thyroidectomized patient described is not to be attributed to the completeness of the operation, for his symptoms were not those of *cachexia strumipriva*—of myxedema—but of Graves' disorder; of mis-called "hyperthyroidism." Someone may guess that he possessed overexcited supplementary thyroids, but that supposition need not be argued. His goitre was gone, but all that was essential in Graves' syndrome remained.

When a partial thyroidectomy is done, the condition of the patient with respect to the thyroid gland is not materially different from that of a patient whose thyroid gland has become reduced, although not to normal size, under non-surgical measures. Judging from the patients and photographs that I have seen, complete restoration of the eyes to normal, after any marked degree of exophthalmos, is exceptional. Material correction of ocular symptoms seems as frequent under non-surgical measures as after operation. It is therefore to the nutrition, and to the cardiac and nervous disturbances—including visceral disorders—that we must first look in order to determine the effect of treatment. Concerning the goitre and the exophthalmos we must require these to have so far subsided as to be neither dangerous nor disabling, but that is

all. We are not discussing the merits of either surgical or non-surgical management from a merely cosmetic viewpoint. As a matter of fact, however, there is rarely left any marked deformity of the eyes or of the neck, when the essential—that is to say the neurocardiovascular or autonomic—symptoms of Graves' disorder have been overcome.

ULTIMATE RESULTS. Recovery has to do, however, not only with the immediate result of treatment, whether surgical or medical, but with the patient's ultimate fate. This is not always easy to ascertain, especially with the large number of patients seen in hospitals. In Volume LXV (1911) of *Guy's Hospital Reports*, Dr. Hale White records the result of an attempt upon his part to trace the history of patients discharged after medical management during the last twenty years, and he finds that in above 80 per cent., the recovery has been permanent. Postoperative statistics of equal length are not at hand; but such reports as are available concerning the ultimate fate of patients submitted to operation and recovering therefrom are, at all events, no better than this. In my own personal and consultation practice I have had the opportunity to observe, directly or through the attending physician, a number of patients for periods of from a few months to twenty-five years after apparent recovery under non-surgical treatment. In but one instance has there been relapse, and in no case has death occurred from any condition with which Graves' disorder could be causatively associated. Among these cases, however, those of patients who have remained under prolonged, continuous observation are relatively few (somewhere between 25 and 30) and form but a small proportion of the whole number of cases treated in hospital and private practice. The attempt to trace out a sufficient number of the others upon which to base a statistical report of any special value has thus far failed. I have, however, numerous records of patients (approximately 100), in whom recovery had endured for periods varying from three to five years before touch with them was completely lost; and if in a matter of such importance one may speak of general impressions, I am inclined to believe that Dr. Hale White's result will represent pretty closely the general experience.

Since, then, under medical management one may reasonably hope for the recovery of not less than 75 per cent. of patients exhibiting Graves' syndrome; and since it is to be fairly expected that the recovery will be permanent in at least 80 per cent. of these, one is more than justified—he is bound—to give his patient the opportunity to recover without the risk and danger of operation and operative sequelæ; exception being made of those cases already alluded to, in which the size or characteristics of the tumor, the rapid advance in severity of symptoms despite proper medicinal management, or the circumstances and environment of the patient render immediate surgery necessary.

ELEMENTS OF MEDICINAL TREATMENT; REST. What then constitutes "proper" medicinal treatment? (1) Rest, (2) *rest*, (3) REST. This is the most important factor of all, especially in cases which have so far advanced as to exhibit a thyroid enlargement that may properly be denominated goitre; or in which, although goitre may be slight or absent, there is a decided tendency to loss of flesh and strength. There are, however, degrees and kinds of rest; and one must adapt this measure, as all others, to the symptoms of the individual case and to the personal peculiarities of the patient. Relief from worryment and other forms of mental disturbance, as well as from eye-strain and other sources of reflex irritation, forms an integral portion of the rest treatment. In arranging its details, the nutritional, cardiac, and nervous phenomena should be given the greatest weight—not only in determining whether the patient is to be kept at absolute rest for the twenty-four hours, or allowed a certain degree of movement for limited times, but also in fixing the period over which the treatment is to be prolonged, its modifications from time to time, its intermission and its resumption, as well as the necessity for adding to it other therapeutic measures.

AIR, FOOD, WATER. It is almost needless to say that the rest must be combined with regulation of diet, and that due care must be paid to the ventilation of the sick room, to cleanliness, to the sufficiency of the secretions and excretions, and to all other points of good nursing. A word or two, however, may be ventured concerning air, food, and water from another viewpoint.

Whether or not I am correct in the supposition that there is a curious (so to say, *inverse*) fundamental relation between Graves' syndrome and tuberculosis—namely, that one may appear instead of the other in different families of a common stock, in different generations of one family, or in different members of one household; and whether or not this has anything to do with the curative virtue of iodine in early tuberculosis and the specific function of the thyroid gland as an iodine accumulator—at all events, the diet and regime useful in tuberculosis will often be found correspondingly useful in Graves' disorder. Rest in the open air continuously, or for a large portion of the time, is superior to continuous indoor rest, albeit in the best ventilated room, in either instance. In my own experience, patients with pulmonary tuberculosis or intestinal tuberculosis do best on a diet consisting largely of raw or underdone broiled or roast beef and hot water; and I have found the same regime useful in many cases of Graves' disorder.

The hot water is sufficiently important to be emphasized by repetition. Given regularly and in sufficient amount, *i. e.*, from 250 to 500 c.c. (one or two tumblerfuls) and preferably the larger quantity, about an hour before food four times daily, and between meals also, *ad libitum*, it keeps the gastro-enteric tract clean and active; and it promotes elimination by the skin, the bowel, and the

kidneys. Thus it permits a sufficient quantity of beef to be eaten, digested, and assimilated; and causes the waste products to be excreted thoroughly.

In both Graves' disorder and tuberculosis there is a distinct failure in the digestion and utilization of carbohydrates, and in both conditions patients do well on a minimum of sugars and starches. In both, there seems to be the necessity for the administration of a sufficiency—the amount varying with the individual—of green vegetables and fresh fruits. By green vegetables I mean lettuce, celery, spinach, water cress, and the like; leaves, stems, and fruit, rather than roots and tubers. In both conditions not only sweets, but salty things and certain vegetable acids seem to be injurious; hence the patient must eschew candy, cakes, pastry, etc., as well as pickles, chow-chow, salads made with vinegar, tomatoes, and the like. The necessity to prohibit an excess of vegetable acids does not, however, imply the exclusion of citrus fruits in moderation; these are, as a rule, beneficial. Concerning milk and eggs, while their value as a special regime has been much exaggerated, they may be utilized judiciously. In fact, in some cases, during the first prolonged period of rest, milk will have to form the staple of diet. It should be given heated or predigested, or both, and not in excessive quantity. Too many egg yolks are not desirable, and some patients cannot take eggs at all. It is true that milk and eggs given to a patient taken from the slums and exhausting work and placed at rest under sanatorium conditions will bring about at first a large gain in weight, but the gain rarely holds when the patient returns to ordinary life, even under improved conditions. The gain that is made upon a beef diet is not so rapid, but it is more lasting.

There are, however, certain patients with Graves' disorder who cannot tolerate either an exclusive diet of beef, or even a large proportion of meat in an otherwise varied dietary. In such cases the necessary modifications must be made. The word "idiosyncrasy," it must be admitted, is a too convenient cloak for ignorance; yet in the absence of a better term, or rather, of better knowledge of the condition indicated, we are compelled to use it. It can therefore be said in summing up the question of diet, that patients with Graves' syndrome exhibit many idiosyncrasies in this respect. "One man's meat is another man's poison" here, to greater degree than in any other condition with which I am familiar. The physician must take the time and the pains to learn the "meat" and the "poison" of each individual patient; for there can be no doubt that toxic products of various kinds, alimentary and metabolic, play a large part in inducing or aggravating many of the Graves' phenomena, altogether apart from the direct influence of diet upon gastro-enteric disturbances.

INDIVIDUALIZATION IN HYDROTHERAPY. Individualization, indeed, is the keynote throughout the treatment; not only as regards rest

and diet, but as to all other measures also; including those of hydrotherapy, to which we may now give brief attention. Whether or not the view is correct, that as regards the production of the symptoms consisting the syndrome group described by Graves, as in various allied disorders, the autonomic nervous system, and especially the taxic mechanism of the cardiovascular apparatus, is primarily at fault, experience proves that one of the most potent influences in controlling these symptoms is re-education of the vasomotor taxis, peripheral and central, by alternate hot and cold applications to the surface of the body. There are many ways of doing this. The simplest, and in the case of patients under absolute rest treatment, the best method, is, after a preliminary cooling of the head and neck, to sponge the entire body rapidly with water as hot as can well be borne (in the neighborhood of 108° to 112° F.), and to follow this immediately by what is called a "cold friction rub" with water cold as can well be borne; which may at first be only 80° or 70° F., as but later as low as 60° or 50° F., or, in rare instances, even ice water. The whole process, including the final drying with a rough towel, should not take longer than from five to eight minutes. Here again, however, there are numerous modifications to suit the individual condition and the individual reaction. Also, in the progress of the case, the time and the temperature, and the method of the applications must be adapted to their effect on the one hand, and to the new conditions on the other. Hot and cold packs, sprays, dcuches, momentary plunges, and the like, are also applicable; the details being modified, of course, by common sense. It is well to instruct the patient to continue the hot and cold sponging or spraying throughout life; to make it a part of the morning toilet, altogether independent of the ablutions of mere cleanliness.

MASSAGE AND MANIPULATIONS. In the absence of fever, certain mechanical measures, as light massage, intermittent pressure upon the muscular masses along the spine, and other expedients for exciting spinal-autonomic reflexes, as the concussion or sinusoidalization of Abrams, may be useful. One must be guided largely by their effect upon the circulation, especially pulse frequency, blood pressure, and subjective sensations of heat and cold. Details cannot here be discussed.

PREPARATIONS OF DUCTLESS GLANDS. The therapeutic utilization of various preparations of animal tissues, and especially of the ductless glands, finds a peculiarly appropriate field in Graves' disorder. Nevertheless frequent disappointments must be looked for. The difficulties are two: (1) To choose the particular agent most appropriate to the individual case; (2) to procure a trustworthy preparation. It is to be regretted that many of the commercial preparations are uncertain, and some of them inert. This was long ago borne in upon me, not only by the difference in result in cases apparently alike in essential particulars, under what was meant to

be the same treatment, but also by the variation of effect in individual cases, with different preparations of the same agent. A fresh liquid extract in glycerin or other proper menstruum, administered by intramuscular injection, or if the menstruum be suitable, by intravenous injection, is, in my own experience, the most potent. Feeding the fresh raw tissue is also efficacious; but apart from the difficulty of obtaining it, there are few patients who will persist in eating the raw substance in sufficient quantity and for a sufficient length of time. The desiccated powders and tablets upon the market vary in efficacy with their source, as well as their freshness, and this there is no means of determining. Moreover, they commonly contain, together with the active principle desired, more or less putrid, or putrescent, or potentially putrescent, animal matter, which is quite likely to cause gastro-enteric disturbance, if nothing more.

With all these drawbacks, however, it is sometimes possible to bring about considerable improvement, even by the administration of the commercial powders, if care be taken to specify the products of manufacturing pharmacists worthy of confidence. There are also obtainable some good liquid preparations suitable for injection. The treatment to be successful must be persistent. Miracles are not to be looked for.

On the whole, *thymus gland* is the most useful of the ductless gland preparations in the largest number of cases. It must be given in sufficient quantity—from 0.5 to 3 grams (8 to 45 grains) of a good commercial desiccate or the equivalent in other forms—daily, for months together. I still, however, find, as reported to the American Medical Association³ fifteen years ago, the conjoint or alternate use of *adrenal* and *thymus* preparations, even better.

More recently I have been making observations with *pituitary* preparations. While the whole gland is useful, there is reason to believe that a certain antagonism exists between the anterior and posterior portions, and that the latter is the effective agent. I have not been able to observe any material difference between the therapeutic effect of the *pars intermedia* alone, and that of the whole posterior lobe (including the *intermedia* and the *nervosa*); and the whole posterior lobe is easier to obtain and cheaper. One of the earlier patients to receive *pituitrin* injections was a woman at the Philadelphia General Hospital who had been in the house for more than two years before she was brought to my personal attention, and who had during that period been under the care, from time to time, of several of my colleagues, as well as of one of my assistants. She had been treated in various ways, but chiefly as the Frenchman advised that coryza should be treated—"with contempt." Surgery had been proposed and declined. There had been ample time for spontaneous recovery, if it were to occur. The case was one

³ Jour. Amer. Med. Assoc., July 10, 1897.

of moderate severity, with periods of extreme tachycardia, and the exophthalmos was of such degree that about one-fourth of the eyeball was left uncovered when the attempt was made to close the lids. Intramuscular injections of pituitrin, at first in small (*circa* 5 minims, 0.3 c.c.), and afterward in rather large doses (20 to 30 minims, 1 to 2 c.c.) were given, at first once, and afterward thrice, daily. Improvement, both subjective and objective, was marked and rapid. Soon it became impossible to keep the patient in bed; and I was unable to exhibit her to the Philadelphia County Medical Society as arranged for, because a change in the date of some of the Society's work having caused postponement for a month, she refused to remain longer in the hospital, and afterward could not be traced. The heart had become quiet, the goitre was scarcely more than visible, and the eyelids closed almost completely. Such rapid and remarkable improvement is not the rule. The effect is gradual, but progressive, and the pituitary needs to be supplemented by thymus or other appropriate adjuvant.

Concerning the *theory* of treatment with ductless-gland preparations, so much could be said, and yet with so little certainty, that it is hardly worth while going into the subject here. Even should one master all the facts contained in Sajous's great work, he would not arrive at assurance concerning the interrelations of the hormones and hormonogenic tissues, but merely at a more comprehensive view of his ignorance. The rationale of organotherapy, or if the term be preferred, hormonotherapy, in Graves' disorder, is doubtless different in different cases. In some, a toxic agent—which may be merely an excess, or perhaps a perversion, of a normal secretion; or may be an excretion product abnormally retained; or may be a wholly abnormal substance—is inhibited, neutralized, or otherwise counteracted. In other instances, the product employed medicinally acts as an exciting agent, stimulating deficient normal activity—perhaps of an antagonizing gland. In others, it complements or supplements or replaces the action of normal or deficient organs or secretions. Thus the ultimate effect may be (directly) that of the tissue or organ administered, or (indirectly) that of some other tissue or organ which it arouses; or the entire action may be merely inhibitory. The somewhat contradictory pathology of the thymus gland aptly illustrates this fact. It is found abnormally persistent or enlarged in some cases of Graves' disorder; but also sometimes in myxedema, and frequently in acromegaly. We cannot yet dogmatize concerning the natural complementations and antagonisms which doubtless we avail ourselves of, in the administration of the organ-preparations. And as, furthermore, we have at present no means of ascertaining clinically just what is needed in any special instance, we are compelled in most cases to resort to the therapeutic test itself, by tentative administration of the various agents, before we

can determine which is best for the particular individual under treatment.

The great drawback to this sort of empirical choice is the fact that a few days does not suffice to make the test; a month or more may be required. Notwithstanding this, it is worth while; and, as one accumulates experience, he begins to formulate for himself certain *indications* that guide in the tentative selection, and most frequently guide aright. One such indication, upon which the use of the pituitary preparations or of epinephrin (the adrenal principle) may be based, is the systolic blood pressure. When this is especially low, say less than 100 mm. Hg., one of these substances should always be administered, whether or not thymus is given coincidentally. If pulse frequency diminishes and systolic pressure increases more than rest alone can account for, then one may be sure that he is on the right track.

Among other organic preparations that are sometimes useful, is *extract of spleen*, as in a remarkable case reported by H. C. Wood; but I have no personal experience with it. It is a curious fact that *thyroid gland* is remedial in some cases, even in patients with marked goitre and without myxedematous or other symptoms indicative of thyroid atrophy. One such instance, in a man under my care at the Philadelphia General Hospital some twenty years ago, I have reported. In this case there were marked exophthalmos, continuous tremor, fits of cardiac palpitation, and many and various nervous symptoms. Goitre had been present, but the thyroid, at the time I saw the patient, was not markedly enlarged. This might indicate, of course, a beginning atrophy. But, on the other hand, there are cases with incipient Graves' phenomena—*formes frustres* and others—but with little or no thyroid enlargement (or with intermittent thyroid enlargement) also benefited by thyroid substance; a fact suggesting the existence of a class of cases in which over-activity of the thyroid is at first a defensive reaction, only later becoming, by its excess, offensive. The medicinal use of thyroid substance permits the gland to become quiescent, and obviates the later pathological phenomena. Such treatment, however, is to be undertaken tentatively and cautiously; for in the ordinary case thyroid is harmful. Its administration should, indeed, be avoided altogether by those who have not had large experience, not only with Graves' disorder, but also with the use of thyroid preparations in various other conditions.

Parathyroid extract is useful in many cases, especially in controlling tremor and allied nervous symptoms. I frequently conjoin its use with that of the thymus, adrenal or pituitary preparations. Large doses are not necessary. From $\frac{1}{10}$ to $\frac{1}{2}$ grain (5 to 25 mg.) of the desiccated commercial preparation, given thrice daily for limited and recurrent periods, usually suffices. Its effect seems to be enhanced by the concurrent administration of a calcium salt,

and this latter may be given with food, if necessary, replacing table salt. It is possible and plausible that the tremor is indeed due to compromising of the parathyroid glands in the course of the pathological process.

Not only in the administration of parathyroid substance, but also in the use of the other glands, it is well to intermit and alternate; replacing thymus, for example, with adrenal or pituitary; or using in place of adrenal one of the mineral or vegetable drugs of similar pressor effect. One reason for this is that the antigen action of the animal products is a factor to be reckoned with. This is not theoretical only; in some of my cases, antibodies (to pituitary substance) have been demonstrated in the blood (by Drs. S. D. W. Ludlum and Ellen T. Corson-White). The antigenic effect is a double-edged sword, cutting both ways, and it complicates the therapeutic problem still further. I have never attempted to inject thyroid extract in minute quantities as an antigen—a vaccine—but it is not impossible that some such procedure might be worked out, and be useful so far as concerns mere hyperthyroidism.

The well-known connection of menstrual disorders with Graves' syndrome has suggested the use of *ovarian substance* and *mammary gland substance* to control special symptoms. I have seen no benefit from either. Incomplete observations with lutein (from the *corpus luteum*) are, however, more promising; but as yet nothing definite can be said.

INTESTINAL ANTISEPSIS. *Intestinal antiseptics* appear to be useful auxiliaries to treatment. Whether or not the disorder is originated by the absorption of toxic products from the intestine, it is certainly aggravated thereby. Dieting does much to diminish this liability. In addition, however, it is well to wash out the colon thoroughly with hot saline solution once or twice weekly, and to administer such agents as the salicylic compounds, beta naphthol, benzonaphthol, hexamethylenamin, guaiacol carbonate, and the like, singly or in association, from time to time. Also an occasional course of calomel, followed by a saline aperient, or the occasional use of castor oil, and the cholagogue purgatives, helps.

Menthol has been urged as a specific. Whether it acts as an intestinal antiseptic or otherwise, some cases are greatly benefited by it. I was first led to its use by the history of an intelligent patient presenting other symptoms of vascular disorder, but in whom I could not find enlargement of the thyroid gland or exophthalmos. Observing me search for these signs, the man informed me that he had had exophthalmic goitre some ten years previously, but had recovered while taking menthol. That may have been a coincidence, of course; but at all events the drug is useful in some cases; and it may be tried when other means have proved inefficacious, or as a succedaneum to the organ-preparations during the periods of intermission.

SYMPTOMATIC MEASURES. In addition to the general treatment of rest, fresh air and dieting, hot and cold applications, intestinal antiseptics, and the administration of organic extracts, there are various measures, medicinal and physiological, that may be useful in controlling or mitigating symptoms. Since these are familiar to most, they may be mentioned briefly.

For the nervous erethism, especially if there is a tendency to insomnia, *strontium bromide* in doses of from 2 to 4 grams (30 to 60 grains) twice or thrice daily, according to circumstances, may be given. *Hyoscine hydrobromide*, or, better, *scopolamine hydrobromide*, $\frac{1}{4}$ milligram ($\frac{1}{250}$ grain) or less, once or twice daily, is helpful. The treatment suggested by Forchheimer, namely, *neutral quinine hydrobromide*, 5 grains or more thrice daily, is also of considerable service in controlling the cardiac and nervous symptoms. I have sometimes observed even better results when *ergot* and *picrotoxin* are associated with the quinine salt, than when it is given alone. When there is considerable tendency to erythema, purpura, urticaria, and similar angioneurotic phenomena, these same drugs (neutral quinine hydrobromide, ergot, and picrotoxin) are also useful, and may be given singly or in conjunction, according to the effect in the particular case. *Hydrated calcium chloride*, calcium lactophosphate, calcium glycerophosphate, or calcium lactate may serve to control pruritus, and sometimes to mitigate urticaria. *Digitalis* and *strophanthus*, the latter especially, are useful in regulating cardiac action, the indications being familiar. When other measures have not proved sufficient to quiet the heart—especially when the patient is first put to bed, and, later, when modified activity is first resumed—small doses of *strophanthus* may be used continuously. Better than any drug, however, during rest, and also in the rest periods that punctuate activity, is the application of a *precordial coil* through which ice-water is allowed to run. The *ice-bag* is a convenient, but less effective and somewhat clumsy, substitute. In some instances the ice-bag or coil may be more effectively applied to the cervical or cervicodorsal (thoracic) spine; or the precordial and spinal applications may be coincident or alternating.

Another drug useful in many cases, sometimes alone and sometimes in association with *digitalis* or *strophanthus*, is *cactus*. This is talking heresy; but I have records, including blood pressure measurements and tracings, showing the effect of a good cactus preparation in reducing abnormal pulse frequency, correcting arrhythmia and elevating blood pressure, especially in cases of Graves' syndrome and allied conditions. It is not often that *aconite* or *veratrum viride* becomes indicated in Graves' disorder, when rest and hydrotherapeutic measures have been instituted. In exceptional cases the familiar indications for these drugs may be presented. I have no experience with the use of *atropine* in this

disorder, but I have heard it commended. Theoretically, it should be "guarded" with a digitalis drug.

TOPICAL TREATMENT. Is it, or is it not, advisable to attempt to reduce the goitre by local measures? I believe that it is, in many cases; and despite the fact that the internal administration of iodides usually aggravates the Graves' phenomena, I have observed no bad results, but only good result or no result, from topical applications of *iodine* preparations. Of these, the solution of iodine in liquid saponified petrolatum seems to be the best. Interesting theoretic considerations are suggested by this fact; but I will only say that if the gland has hypertrophied in response to a demand from the system for the storing of iodine therein, so that this element may be delivered into the blood stream in an acceptable form, the artificial supply may enable it to reduce its activity.

Electricity has been utilized in various ways. Cataphoric, or as it is now termed, ionic, application of iodine has been made; the galvanic current has been passed through the gland, and applied over the neck in the neighborhood of the cervical sympathetic. In my own hands, the most satisfactory form of electric application—in that minority of cases in which any such treatment has seemed necessary—has been the high frequency discharge from an Oudin "resonator" in connection with a Tesla coil, Leyden jar battery, and static influence machine. Sometimes the electrification is directed to the goitre; sometimes to the back of the neck in the neighborhood of the *vertebra prominens*; sometimes to both. This application, however, has been used only in mild, early cases, in which absolute rest has not been indicated; or else, when the improvement has so far progressed that rest may be intermitted or given up; for it means that the patient should be able to visit the physician's office two or three times weekly. It is of auxiliary benefit, but would not alone bring about recovery. How lasting the result may be one is not yet in position to say, as I have used this particular modality only during the last three years.

There are many other medicinal and physiological measures of more or less benefit in certain cases of Graves' disorder, but those discussed or mentioned are sufficient to indicate the general character of the non-surgical treatment that has been found of service. It is not specific, although it is special; and it is highly individualized.

SERUMS, ETC. Before concluding, a word should be said as to the various serums and antibodies that have been proposed and used. My own experience with *Rogers' and Beebe's serum* has thus far been inconclusive; although it is only fair to say that I speak after a very limited trial. It produced remarkable, but not permanent, good results in two cases; and failed entirely in two other cases. That it has great possibilities cannot be gainsaid;

and one should resort to it unhesitatingly, in any case in which cytolysis seems to be necessary.

Rodagen, a preparation made from the milk of thyroidectomized goats, I have used in but a single instance; that of a woman who was steadily improving under rest and treatment with thymus gland and strophanthus, but who became impatient at the prolonged restraint. There was immediate recurrence of subjective feebleness, anorexia, insomnia, and rapid action of the heart. The thyroid gland, which had been reduced, enlarged again, and considerably, in the course of a few days. The rodagen was stopped and the patient again improved. A month later it was again administered in smaller quantity, but with the same untoward result. The original treatment was resumed and the patient made complete recovery, which has now lasted for some seven years. This would appear to give color to the theory that in this case at least, the enlargement of the thyroid gland was a compensatory, defensive hypertrophy, the necessity for which vanished with the administration of the thymus preparation.

Antithyroidin and *thyroidectin* have also failed in my hands, although neither has been given extended trial. The necessity to do so has not been evident when good results were obtained without them, and surgery has seemed preferable in the cases that did not seem suited for, or did not yield to, the medicinal and hygienic management that has been outlined.

SUMMARY. To sum up, Graves' syndrome is a complex disorder, having many varieties, a multiple etiology, and an obscure pathology. The goitre is an incident, and the disorder may exist without it. When goitre occurs, existing symptoms are usually aggravated and new symptoms added.

Surgical treatment rarely becomes necessary in cases recognized early. In approximately 15 to 20 per cent. of cases, surgery is made necessary by failure or inability to institute prompt, or proper and persistent, non-surgical treatment. In about 5 per cent. of cases surgery may become necessary, despite early and skilful hygienic and medicinal management.

The first element in treatment may, therefore, be stated as *early diagnosis*. Cases of which the true nature is not recognized are likely to be termed "neurasthenia," "hysteria," "nervousness," "anomalous neurosis," "nervous dyspepsia," and the like. Adequate treatment may thus be not instituted until late; and sometimes, too late. This is probably owing, in part at least, to the unfortunate title "exophthalmic goitre;" for both goitre and exophthalmos are usually late signs.

There is no specific; but certain useful measures may be organized into a form of special procedure.

Non-surgical treatment is usually prolonged. Its keynote is *individualization*. It must be patient and persistent. Its principal

element is *rest*; to be modified according to circumstances. Rest must be mental as well as physical, and must include correction of ocular errors (eye-strain) and removal of all sources of reflex irritation. Instituted under diagnostic error, it is equally beneficial. Fresh air and regulation of diet are necessary, much as in pulmonary tuberculosis. Active elimination must be maintained. Educational exercise of the vasomotor system by hot and cold applications is always of benefit. Under such management, with perhaps occasional symptomatic medication, somewhere from 25 to 30 per cent. of all patients may be expected to get well—the cases of so-called spontaneous recovery.

The application of ice-water coils over the heart and over the cervical spine, the administration of trustworthy preparations of well-chosen organ-extracts and various forms of auxiliary medication; with perhaps the use of certain mechanical manipulations, topical applications, and electric modalities, will increase the number of recoveries to 80 per cent. or more.