

pill being taken after each meal. If the patient stands it well, another pill may be added at bedtime. At times a patient is met who cannot take more than two pills a day. He should be told to expect little or no benefit short of a month, and that the treatment must be continued for a long time. Usually, after a week or two the pulse rate becomes slowed, the thyroid reduced in size, and the sweating or tremor lessened. The treatment should be continued until all the symptoms have disappeared, which may be in four months or not for three years. The only unpleasant action of the drug, as a rule, is occasional tinnitus, especially if large doses be given. To prevent unpleasant effects, if such occur, and reduce the erethism of the cerebral centers (those of the pituitary in particular) I also give 20 grains (1.32 Gm.) of sodium bromide on retiring, adding 10 grains (0.66 Gm.) of chloral hydrate if the bromides do not counteract the insomnia. Relapses are not rare, but if taken in hand promptly they soon yield to the same measures.

In some highly nervous women, especially those who suffer from pseudo-hysteria, any preparation of quinine seems to increase discomfort. In these, the bromides at night, with chloral if necessary to counteract insomnia, should be supplemented by the use of phenacetin in the daytime, 5 grains (0.33 Gm.), gradually increasing the dose until 10 grains (0.66 Gm.) are taken three times daily. As stated above, the bromide reduces the pathogenic hypersensitiveness of the cerebral centers; the phenacetin maintains this action by causing constriction of the arterioles which supply them with blood—a common action of the coal-tar products (of which phenacetin is the safest), as stated in the second volume.⁴⁹

The favorable effects obtained by Rénon and Delille⁵⁰ with pituitary gland are explainable in much the same manner. In doses of 4½ grains (0.3 Gm.) of the whole gland (ox), which they subsequently deemed advisable to increase to 7½ grains (0.5 Gm.) in divided doses daily, they obtained marked improvement. Hallion and Carrion⁵¹ then found experimentally that pituitary extracts “always produced their effects by raising the arterial tension,” producing at the same time “an intense vaso-

⁴⁹ See vol. ii, p. 1283 to 1293.

⁵⁰ Rénon and Delille: Bull. gén. de thérap., May 8, 1907.

⁵¹ Hallion and Carrion: Soc. de Thérap., March 13, 1907.

constrictor action upon the thyroid body.” Briefly, we have here precisely the physiological action necessary—the vaso-constrictor power of the adrenal component of the pituitary gland superseding the vasodilator action of the thyroid.

The morbid effects of the excessive oxidation of the phosphorus to which the cellular elements are subjected require attention. The resulting exhaustion of the phosphorus in the muscular layer of the arteries aids powerfully the action of the depressor nerve in keeping the general vasodilation, including that of the thyroidal vessels, thus keeping up the disease. This phosphorus must, therefore, be replaced. Hence the value of sodium phosphate recorded by Kocher, Trachewski, Vetlesen (40 cases), and others of the glycerophosphate of sodium in 20-grain doses three times daily, noted by M. Allen Starr, and of lecithin in alcoholic solution praised by Berkley of Johns Hopkins.

In not a small proportion of cases, the disease may be traced to streptococcal infection through the tonsils, even though this may not be sufficiently marked to cause acute rheumatism. These organs should be carefully examined in every case, and all crypts be carefully cauterized. If hypertrophy be present tonsillectomy should be performed. In some instances a clear history of acute rheumatism is obtainable, the salicylates, preferably the sodium salt, is very useful and soon counteracts the hyperthyroidia when given in 10-grain (0.66 Gm.) doses three times a day. Pyorrhœa alveolaris may also act as cause. Evans, Middleton and Allen J. Smith^{51a} having found, in typically diseased tonsils, the crypts to harbor *Endamæba gingivalis*, gave emetin hydrochloride subcutaneously or intramuscularly, in ⅛- to 1-grain doses, with improvement in some cases.

Enteroclysis given at 108° F. is useful when, after clearing out the intestines by means of an enema, the solution, using a quart at a time, is retained sufficiently long to insure considerable absorption. If this is not the case, hypodermoclysis every other day, regulating the quantity according to the case, is indicated. By increasing markedly the osmotic properties and the viscosity of the blood, its toxicity and its exciting action on the thyro-adrenal center are greatly reduced, and the elimination of the pathogenic poisons is greatly enhanced.

^{51a} Evans, Middleton and Smith: Am. Jour. Med. Sc., Feb., 1916.

Thymus gland, which, as I have pointed out, owes its action to the phosphorus-laden nucleins it supplies to the nuclei of the tissue-cells, was found accidentally by Owen to be valuable in exophthalmic goiter. Obviously it is only of value where the thymus is not enlarged. It may either be given in the form of sweetbread as food, $\frac{1}{2}$ to 3 ounces (15 to 90 Gm.) daily, or in tablet form, from one to three 5-grain (0.3 Gm.) tablets being given three times daily during meals. It is also obtainable in the form of powder, which, given in capsules in the same doses, obviates the unpleasant taste. By supplying the nerve-cells their normal nucleins, their degeneration and particularly that of their ganglia, to which Charcot called attention, is materially counteracted. S. Solis-Cohen⁵² highly recommends thymus gland, but supplemented by intramuscular injections of pituitrin, beginning with 5 minims (0.3 Gm.) three times daily, then gradually increasing the dose until 20 to 30 minims (1 to 2 c.c.) were administered at a dose.

The causative condition must be carefully sought and, if possible, removed. In cases due to pregnancy, menopause, and inadequate ovarian development, the disorder is mainly due to inability of the thyroparathyroid apparatus to neutralize the increasing tide of wastes the blood contains. The organ is abnormally stimulated, in the sense that its arterioles are widely opened to allow a vastly greater volume of arterial blood than usual to enter it, and it becomes enlarged. Here, thyroid preparations, starting with 1 grain (0.066 Gm.) *t. i. d.* of the dried gland, are of great value by compensating for the organ's deficiency. If the toxæmia is of intestinal origin, meats should be banished and free saline purgation—in addition to the measures advocated in the preceding two paragraphs—resorted to. Highly nervous or pseudo-hysterical cases are also helped by the bromide, phenacetin, and saline solution treatment, but rest in these cases and in those due to traumatic shock is of great importance. In fact, it must be borne in mind that exertion increases toxic waste formation, and, therefore, the asset of pathogenic poisons, and that rest is always indicated. In most cases, in fact, absolute rest in bed is a *sine qua non* of success. A high altitude—about 2000 feet—is helpful.

⁵² S. Solis-Cohen: Am. Jour. of the Med. Sc., July, 1912.

Various sera obtained from animals deprived of their thyroid: Ballet and Enriquez's dog serum, Möbius's sheep serum, or "antithyroidin," Rogers and Beebe's serum, obtained from rabbits or sheep inoculated with extracts of exophthalmic goiter, are all of value in that they are all antitoxic substances which aid the blood in neutralizing the pathogenic poisons.

Thyroductin, the desiccated blood of thyroidectomized animals, has also given satisfaction in some cases, in 5- to 10-grain (0.33 to 0.66 Gm.) doses in capsules three times daily.

During the *transitional* stage the treatment depends entirely upon the progress made by the atrophic process. As a rule, however, signs of myxœdema are already present; in that case thyroid preparations are indicated, as they are during the *myxœdematous* stage. The latter is virtually a case of myxœdema and requires the measures recommended for that disease (*q. v.*). In both these stages, however, there is a marked tendency to cardiac failure, and digitalis or strophanthus are precious adjuvants.

The injection of boiling water into the goiter, first suggested by M. F. Porter⁵³ has given good results. The local discomfort is slight, and a fleeting headache is sometimes complained of. None of the 20 cases reported by Porter suffered any other untoward phenomena, a fact which indicates that the procedure is a safe one provided due care is taken to avoid the large superficial veins and to inject the water inside the capsule. The skin, after being cleansed, is anesthetized with Schleich's solution "by producing a small wheal at the points where the needle is to be inserted." A large, all-glass, graduated syringe, armed with a long and rather fine needle, is employed. It is boiled in the water used for the injection, over an alcohol lamp or a Bunsen burner. When more than one injection is given at one sitting the syringe proper being handled with long forceps, is reboiled each time, the object being to have the water penetrate the gland when as near the boiling point as possible. "With a long needle different areas may be injected through the same skin puncture by partly withdrawing the needle. In this way both right and left lobes and the isthmus may be injected through one skin puncture made in the center of the neck." The quantity injected by Porter varied from 40

⁵³ Porter: Jour. of the Am. Med. Association, July 12, 1913.

to 230 minims (2.6 to 15.3 Gm.), the largest quantity injected in the course of one treatment being 660 minims (44 Gm.). The immediate effect is destruction of thyroid tissue and colloid, a temporary increase in the size and density of the growth being followed by contraction and subsidence of the general symptoms. O'Day⁵⁴ has also reported satisfactory results. Quinine and urea hydrochloride injections are also used (see page 259).

X-ray treatment may now be used without risk of burning since the introduction of the Sabouraud pastille method of measuring the ray. Pfahler reported marked improvement in 75 per cent. of his cases. The X-ray is of especial value when the thymus is enlarged, a point which should be carefully determined in every case. The ray should not, however, be employed in young children, the thymus being necessary to their development.

The combined use of X-ray and the static current have been found superior to the X-ray alone by W. Benham Snow.^{54a}

When the foregoing resources fail, which is seldom the case, surgical measures may be employed. At the present time the tendency is to resort too freely and unwarrantably to surgery.

SURGICAL TREATMENT.—Indications.*—In hyperthyroidia, whether or not the syndrome of exophthalmic goiter be actually present, much care is required in the selection of cases for operation, many being poor surgical risks owing to bad general condition, acute symptoms, or signs of degeneration of important organs, in particular the heart. Where acute symptoms are present thyroidectomy should be postponed until they have disappeared. Irregularity and varying tension of the pulse, diarrhea, edema of the hands and feet, sleeplessness, and paroxysms of gastric pain are conditions that render postponement of radical operation for a period advisable.

Where partial thyroidectomy is not feasible for the time being, *e.g.*, in acute exophthalmic goiter uninfluenced by medical treatment or injections of boiling water, ligation of both superior thyroid arteries may be performed with advantage, sometimes at one operation, but more usually in two sittings, at

⁵⁴ O'Day: New York Med. Journal, April 3, 1915.

^{54a} Snow: Jour. of Electrother. and Radiology, Jan., 1916.

* This subdivision of the subject was written by the author's son, Dr. Louis T. de M. Sajous.

a week's interval. Arterial ligation is considered of particular utility in cases with pronounced thyroid pulsation and a thrill in the superior thyroid arteries. Well-advanced cases can thus be made fair or good surgical risks. Some advise injections of boiling water as a measure secondary to arterial ligation, *i.e.*, where the latter fails.

If the reaction attending the first arterial ligation—usually at left upper pole—is not marked, partial thyroidectomy, consisting in removal of the opposite lobe, the isthmus, and possibly a portion of the same lobe, may be performed a week later; if evidences of shock be pronounced, on the other hand, an interval of several months (four months—Mayo), during which time will have been given for improvement in the patient's general condition, should be allowed to elapse before partial thyroidectomy is resorted to.

In a small proportion of cases a relapse occurs some years after partial thyroidectomy, the residual glandular tissue undergoing hypertrophy and symptoms returning. If medical treatment be not, under these circumstances, soon beneficial, the vessels at the upper pole of the remaining lobe should be ligated, unless this has previously been done, in which case ligation of the inferior thyroid artery is to be advocated. If arterial ligation fails to prove sufficiently effective, a portion of the lobe may be removed. The risk of provoking myxœdematous symptoms if too much tissue is removed should always be borne in mind.

In some already seriously affected patients, preparatory treatment by absolute rest, heart tonics, diuretics, and the X-rays is required even before arterial ligation is permissible. The X-rays have been serviceable in helping exophthalmic cases through acute attacks, previous to operation.

The superior thyroid arteries are generally ligated in preference to the inferior because they are more accessible and less closely related to important nerves and vessels. Ligation of the inferior thyroid, a more difficult and serious procedure, is only infrequently performed. Ligation of all four arteries in a single case is warned against by Kocher, in view of the danger of cachexia strumipriva where there is such a complete interruption in the blood-supply to the gland.

Early cases of exophthalmic goiter, according to Mayo's experience, sometimes show marked improvement under ligation of both superior thyroid arteries. A complete cure may even follow, rendering subsequent partial thyroidectomy unnecessary. In the more severe cases, general health is frequently so improved by ligation that later removal of the larger thyroid lobe can be effected with but little risk. The possibility that too much glandular tissue for purposes of subsequent sufficient thyroid functioning may thus be removed is not denied by Kocher, but resulting symptoms of hypothyroidism are seldom met with.

According to Mayo, the proportion of exophthalmic goiter cases coming under the surgeon's observation in which removal of the larger thyroid lobe and isthmus can be undertaken without undue risk is about two-thirds. The sphygmomanometer, electrocardiography, X-ray examination of the heart, and the blood-count are all factors of value in the selection of an operation suitable for a case in hand.

Simultaneous excision of one lobe and ligation of one or both arteries on the other side have been advised by some surgeons, notably Landströmme and Klemm. Though good results have been reported, the risk of inducing hypothyroidism would seem to be greater in this connection than with procedures ordinarily followed.

In unilateral goiter with hyperthyroidism, three-fifths of the enlargement may be readily removed, after due preparation of the patient by measures calculated to improve the general condition (Bainbridge).

Where goiter with hyperthyroidism recurs after an initial partial thyroidectomy, the production of atrophy of the remaining thyroid lobe through ligation of one or both of its arteries may be attempted. Thyroidectomy for recurrent goiter is generally more difficult than an initial similar operation owing to the presence of adhesions or scar-tissue.

At times in pregnancy hyperthyroidism develops, rapidly or gradually, with a severity sufficient to require prompt surgical intervention. Generally some degree of hyperthyroidia has existed before conception in these cases, and the increase in the severity of the symptoms is noted early in pregnancy. Matlack

operated three times in such cases, with good results, the patient's going on safely to term.

Removal of the thymus gland has been advised by some in exophthalmic goiter, in view of the recently ascertained causal relationship of the former organ to the disease. A persistent thymus has been found in about 90 per cent. of all operations for exophthalmic goiter in which the condition of the organ has been investigated (Bainbridge). Good results have already been recorded by many from thymectomy in exophthalmic goiter cases in which a persistent thymus is found.

Haberer's experience has been that a combined partial operation on both the thyroid and the thymus in these cases yields better results than partial removal of either organ alone. A promising procedure also is the use of the X-rays to reduce the thymus before an operation on the thyroid is undertaken.

Operative Risks and Results.—Even simple and apparently innocuous procedures have been followed, in hyperthyroid cases, by serious symptoms and even death. The chief danger is collapse preceded by extreme tachycardia and nervous excitement. The symptoms witnessed have been ascribed to intoxication with thyroid material or to violent excitation of the local vasomotor and trophic nerves. Death within a few hours or days may follow. Matlack, in a series of 202 operated cases of exophthalmic goiter, had 4 deaths from postoperative hyperthyroidism. Other attendant dangers are tetany, due to removal or crushing of parathyroid tissue, myxœdema, due to excessive removal of thyroid tissue, and injury to the recurrent laryngeal nerves. The author of the present work considers the belief that death is due to thyrotoxis in these cases a grave error and the cause of several deaths. He attributes these results to shock and the temporary arrest of function of the various glands which cooperate with the thyroid, and has saved life by the immediate use of hypodermoclysis and adrenalin, 20 drops of the latter (1:1000 solution) being injected drop by drop into the rubber tube conveying the saline solution to the tissues.

With careful selection of cases, however, as well as painstaking technique, the operative mortality in exophthalmic goiter should be low. Mayo in 1912 was able to report a consecutive series of 278 operated cases of exophthalmic goiter without a

death. On the whole, the mortality in this condition has in recent years undergone a marked reduction, not only through earlier operation and technical improvements, but because of more careful preparation of patients, safer anesthesia, and adaptation of the type of operation to conditions in the individual case. The general mortality from operation at present is from 1 to 4 per cent. In advanced cases with marked tachycardia, irregularity of the pulse, pronounced emaciation, and loss of strength, death occasionally takes place in a few days after partial thyroidectomy, even though the operation has been done under local anesthesia, and in the absence of infection of the wound. The author of this work advocates organotherapy, *i.e.*, adrenalin or pituitrin injections with hypodermoclysis as a protective measure. Such risks may also, as already suggested, be avoided by a preliminary arterial ligation. The thyroidectomy may be effected later if, in spite of general symptomatic improvement, evidences of compression of the trachea persist. Arterial ligation is, moreover, so much safer than thyroidectomy that through its performance the surgeon is enabled to accept as surgical risks cases so advanced that there is but little hope of cure.

As regards the results of operation, the recent experience of surgeons has been that either cure or improvement follows operation in a large majority of cases of exophthalmic goiter. Kocher, in a series of 320 cases, obtained a complete cure in 150 and improvement in 148. In the "improved" cases individual symptoms such as exophthalmos and functional disturbances due to the thyroid disorder, had not been removed, though pronounced betterment in the general condition was noted. In the remaining 22 cases the final results were not good, either because of inability to complete the operation, recurrence, or the persistence of renal or hepatic disturbances.

The immediate beneficial effects of operation in exophthalmic goiter may not be maintained, either by reason of recurrence or through transformation of the residual thyroid tissue into a goiter. Symptoms of hyperthyroidism relieved by the operation may thus return after a long or short interval of health.

After partial thyroidectomy the tendency of the remaining lobe and isthmus is to a lessened hyperplasia, but in 6 or 8 per

cent. of cases a compensatory hypertrophy takes place instead and causes persistence or exaggeration of the symptoms (Brenizer). On the other hand, myxœdematous symptoms may appear early in some cases. Although one-fourth of the normal amount of thyroid tissue is generally considered sufficient to fulfill, where the necessity arises, the functions of the entire gland. Conversely, signs of myxœdema may be observed even where but a comparatively small amount of the tissue has been resected. Such myxœdema may prove only temporary, the remaining thyroid tissue finally assuming sufficient activity to meet the needs of the organism. Such a serious mistake has, however, been made as to perform an additional thyroidectomy where signs of hypothyroidism—confused with those of persisting hyperthyroidism,—were already present.

In some instances a return of pressure symptoms due to cysts left in the thyroid at the first intervention and subsequently increasing in size demands a second operation.

In the favorable cases, such conditions as tachycardia, palpitation, chronic lung congestion, and edema of one of the arms rapidly disappear when the excessive thyroid action has been corrected. Difficulty in swallowing, where previously present, is likewise soon relieved, though it may be maintained or increase during the first week. Dyspnea rapidly disappears after operation in the great majority of cases. Hoarseness and even a total laryngeal paralysis may be relieved by the operation. In 2 cases reported by Bérard neuralgic disturbances of the upper extremity, with beginning atrophy of the shoulder-muscles, were caused to disappear by partial thyroidectomy.

On the whole, when all the possible complications and drawbacks attending the operative treatment of exophthalmic goiter are taken into account, and the results are compared with those obtained by medical treatment, the latter should invariably be given thorough trial before surgical measures are resorted to.

GOITER.

(Struma; Bronchocele.)

Goiter, an enlargement of the thyroid gland, may be of limited or prolonged duration. It differs from the disease just considered, exophthalmic goiter, in that it does not give rise,

in its characteristic form, to systemic symptoms. It is important to bear in mind, however, that goiter is sometimes the precursor of exophthalmic goiter, and that in such cases the routine use of iodine or thyroid gland may initiate the latter far more serious disease. Considerable evidence to this effect was adduced in the preceding article.

ETIOLOGY.—Although goiter in its various forms may be said to exist in all countries, irrespective of race, it shows a predilection for certain countries, Switzerland, France, Austria, Germany, Italy, and certain parts of England and of the United States. This applies also to special districts of these countries; thus, according to Lobenhoffer,⁵⁵ some towns of Bavaria show a proportion of 21 to 26 per cent. of cases of goiter; in France, the greatest number of cases are found in the departments bordering on the Alps and the Pyrenees, and in America, in Michigan, and in Ontario, Canada.

As to the topographical characteristics of the countries in which goiter occurs, much prominence has been given to the influence of altitude because Bircher's map indicates a predilection of goiter for the mountainous districts of Middle Europe. That this cause is of secondary importance is shown by its presence in flat countries such as those stretching from the north of Paris toward Belgium, along the valley of the Thames, the low-lying districts of Ontario and Michigan, and in the Chitral and Gilgit of India, where, according to McCarrison,⁵⁶ goiter is endemic. In the Philippines, the disease, according to Duncan,⁵⁷ is very prevalent in the municipality of Macabebe, which is but a few feet above sea-level on the northeast shore of Manila Bay.

The drinking-water of goiter districts has long been recognized as the intermediary of agents capable of producing it. In such districts families which received and used faithfully water from elsewhere avoided the disease. Certain fountains in the Canton of Berne, Switzerland, were found to produce goiter almost invariably in the children who drank it. The residuum of filtered water derived from such fountains or springs, when added to the usual and harmless water adminis-

⁵⁵ Lobenhoffer: *Mittel a. d. Grenzgeb. d. Med. u. Chir.*, Bd. xxiv, Nu. 3, 1912.
⁵⁶ McCarrison: *London Lancet*, Jan. 25, 1913.
⁵⁷ Duncan: *American Med.*, Nov. 18, 1905.

tered to dogs, guinea-pigs, and monkeys, was found by Wilms⁵⁸ to cause goiter in these animals. Much evidence is available in literature proving definitely the rôle of water in transmitting the causal agent of the disease.

As to the nature of this cause, ample modern evidence has eliminated the idea of a single agent being the common factor in all cases, and shown that goiter could be produced by many different agents, inorganic and organic, acting as poisons. Calcium is a widespread agent of this sort, districts in which the geological formation contains vast quantities of limestone showing a large proportion of goitrous inhabitants—50 per cent., for example, in some of the limestone districts of India. In such districts in England, where goiter is exceedingly common, those inhabitants who use rain-water as sole beverage are, according to Morris, free from the disease. The silicates, magnesia, alum, iron, manganese, copper, lead, and many other minerals have also been incriminated by various investigators.

An abundance of organic matter in drinking-water is increasingly asserting itself as an important cause. This is emphasized by the fact that during the rainy seasons of India, when organic matter is rapidly disseminated, the number of cases among the whites and natives is greatly increased. Kocher has urged the importance of this causal agent in Switzerland. The promiscuous use of human feces in their natural state so common in that country, which stands first in its proportion of goitrous individuals, recalls the experiments of Suzuki, who produced enlargement of the thyroid in rats by feeding them with cooked rice mixed with rat feces, and also by injecting the latter subcutaneously. McCarrison observed a similar result in animals allowed to drink only water polluted with feces.

While the ingestion of organic matter of this class may bring into activity a large number of pathogenic agents it recalls the stress laid on some pathogenic organism or its toxin as an exciting cause of goiter by Poncet, Jaboulay and Rivière, Klebs, Kocher, Lustig and Carle, Waters, and others. Kocher, in fact, found that "goiter water differs from goiter-free water in containing many more micro-organisms." McCarrison has also ably defended the same views, the soil deposits at the

⁵⁸ Wilms: *Deut. Zeit. f. Chir.*, Jan., 1910.