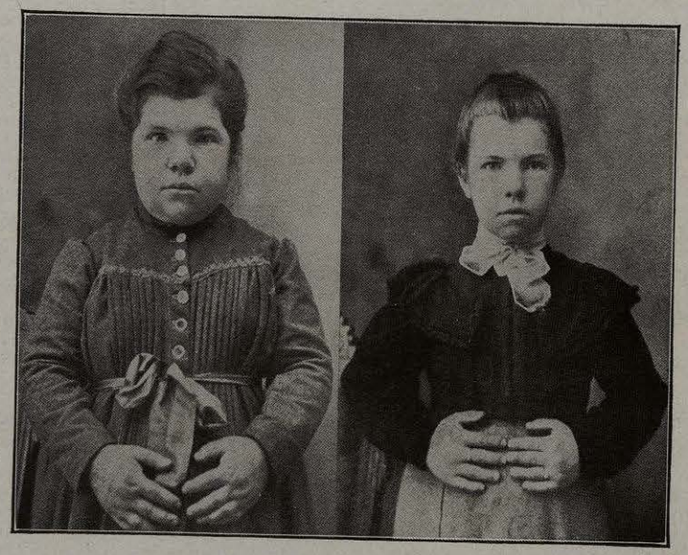
points stand out prominently in these cases: (1) the dose was too large, the initial dose being 5 grains (0.33 Gm.) *t. i. d.*, and (2) cases were selected "in which epilepsy had been a prominent feature in the patient's life since early infancy." Obviously, in the latter instances we were dealing with advanced gliosis, which precluded all hope of cure. Yet, as Pierce Clark says, "all seemed to be benefited for the time being." Even when there is marked gliosis, small doses of thyroid, by preventing the formation of the tidal waves of spasmogenic wastes, will greatly reduce the number of paroxysms if the diet is carefully adjusted to the particular needs of the case. But the best results are obtained, as shown in my own practice, when we have reason to believe that little or no sclerosis is present, and when there is evidence that the underlying cause is hypothyroidia.

Obesity.—The fact that thyroid preparations in sufficient doses promote the rapid combustion of fats has caused them to be used extensively in this disorder. Given indiscriminately and empirically, in excessive doses, their use has often been attended by distressing after-effects, including asthenia and disorders of vision. When thyroid preparations are employed with due discernment in properly diagnosticated cases, they not only procured marked loss of weight, but also improvement in the patient's general well-being and health.

The cases in which thyroid gland is scientifically indicated are those in which some degree of hypothyroidia exists, and in women in whom panhysterectomy, by removing two organs rich in adrenal rests, the ovaries, has greatly reduced the oxidative power of the blood—a deficiency which affects morbidly the thyroid apparatus as it does all other tissues. In the latter class of cases, therefore, hypothyroidia is also the foundation of the obesity. This may be said also of destructive disorders of the pituitary body which, by depriving the thyroid of its functional impulses, reduce its functional activity. Briefly, in all cases of obesity in which thyroid gland is rationally indicated, the feature to determine is whether directly or indirectly hypothyroidia underlies the adiposis.

In very mild cases, the underlying cause is sometimes difficult to determine; but as a rule, some, very few perhaps, of the typical signs of hypothyroidia may usually be discerned on close



CRETINIC OBESITY.

Case of cretinism aged 21. Effects of four months' thyroid treatment. [Sanderson.]

inquiry. These are chilliness and subnormal temperature, coldness of the extremities and sensitiveness to cold; fatigue on slight exertion; constipation with tendency to tenesmus; more or less frequent attacks of migraine, "sick headaches" with nausea, vomiting, etc., and other periodic manifestations of auto-intoxication—due to inadequate reduction of waste-products and their retention in the blood. The skin taking part in the process of elimination, urticaria and eczema may be found in the history of the case, while transitory œdemas of the brow, around the eyes, and sometimes of the face, even in the absence of albuminuria or casts, may also have occurred. Enuresis is commonly observed in fat, pasty children of this type and may persist to adult age. The patient may be subject to frequent catarrhal disorders of the respiratory passages, usually ascribed to colds, but due mainly to vascular and glandular relaxation. A tendency to early alopecia, including the eyebrows (especially their outer third), is also noticeable in some instances—a sign of deficient general nutrition which coincides with a marked proclivity to early senility. The supraclavicular pads are sometimes discernible when the adiposis is not excessive. Even in the latter case sometimes the pads project beyond the general level.

In women, the menstruation appears late owing to retarded development, and there is a proclivity to metrorrhagia due to laxity of the muscular coats of the uterine arterioles, while pelvic disorders are apt to occur owing to deficient support of the uterus, lack of tone in its muscular elements. Leucorrhœa is also frequent owing to relaxation of the glandular elements of the whole genital tract. Such women conceive readily, but abortion is very frequent among them; if the fœtus is carried to the normal period, they have little or no milk. If the obesity is marked, sterility is the rule; but when such patients are given thyroid gland and their obesity is reduced, they readily become pregnant, as observed by Hertoghe, Montgomery, and others.

Cases of obesity due to hypothyroidia also afford, as a rule, quite a clue as to the presence of this condition, by the statement that none of the dietetic "cures" seemed to improve their condition. Indeed, most of them complain of having been made worse. This is readily explained by the fact that their hypo-

thyroidia could only be aggravated by deficiency of food and forced exercise.

Contraindications to the use of thyroid preparations in obesity have been elaborated by various observers; but perusal of their work indicates clearly that they have been administering excessive doses. Several lives have been lost under these conditions, and many others have been lost by self-drugging. Large doses are always dangerous in the obese, since the heart is itself invariably fatty, while, conversely, small doses are always helpful because they very gradually rid the heart of the fat which compromises its functions and eventually causes death—when the patient has not been carried off by some intercurrent disorders. Even moderate doses have not proven harmful when the patient was under medical surveillance.

The *dose* of desiccated thyroid need not exceed 1 grain (0.066 Gm.) three times daily in any case. This suffices to cause a decrease of weight of from 1 to 3 pounds a week, and sometimes more, Anders[42] having observed in 2 cases under this dose "a progressive loss of weight at the rate of 4 to 6 pounds per week, respectively, without injury to the general health." Such doses do not impose upon the patient the need of modifying his usual mode of living and his diet need not, unless excessive, be altered. Occasionally, the dose must be gradually increased to 2 grains (0.13 Gm.) three times daily, but this is seldom necessary.

When the obesity is accompanied by weakness, the appetite is usually increased, especially when, as is my custom, $^1/_{50}$ grain (0.0013 Gm.) of strychnine is given with each dose of desiccated thyroid. The patient does best under these conditions, when lean meats, plainly broiled, roasted, or stewed, constitute the increase of his dietary. This treatment is valuable in another direction: it tends to counteract any tendency to constipation that may be present.

The *untoward effects* most frequently met with in obese subjects are of cardiac origin: marked discomfort in the precordia; dyspnœa, with tendency to heart-failure. In some instances this has been followed by death, when marked fatty degeneration happened to be present. But, as stated, these do not

[42] Anders: "Practice," 8th ed., p. 1276.

occur when small doses—1 grain (0.066 Gm.) of the desiccated thyroid—are used. Even the greatest watchfulness will not prevent toxic effects when large doses are administered, since the accumulation of the thyroid principle proceeds at a rapid rate and the milder symptoms of thyroidism are almost at once followed by its acute manifestations—those previously described.

Adiposis Dolorosa; Dercum's Disease.—Having had no personal experience in the treatment of this rare disease, the following quotation from a comprehensive article by Professor Dercum, soon to appear, is presented:—

"In the treatment of adiposis dolorosa one remedy has in a few cases proved of value, and that is thyroid substance. This should be given in doses of from 2½ to 5 grains (0.165 to 0.33 Gm.) three times daily, for a very long time. The salicylates, notably aspirin, are of decided value in relieving the pain. The best plan of procedure, as a matter of course, is to place the patient in bed, and to institute a systematic course of treatment. The rest should be absolute and should extend over several months of time.

"The patient should be weighed when treatment is begun and thyroid substance given at first in small and then in somewhat larger doses. At the same time a diet should be instituted that is largely free from carbohydrates and fats. It should be remembered, however, that a diet, no matter how rigid, will of itself make no impression in adiposis dolorosa; it will fail absolutely. It is, of course, wise to institute a careful diet, but patients do better when the diet is not too strict. Inasmuch as the affection is attended by a marked asthenia, the diet should be nutritious. It should consist of the red meats in moderation, the white meats freely, the succulent vegetables, eggs, and skimmed milk. The latter can be used between meals, and, if necessary, also at mealtimes.

"The pains are not infrequently controlled or, at least; made better by aspirin or salophen in full doses, 10 or 15 grains (0.66 or 1.0 Gm.) three times daily after meals. Sometimes the tenderness and soreness are better borne when the limb or part affected is gently supported by a flannel roller; if the tenderness be extreme a layer of cotton-wool may first be applied.

"Just as soon as the tenderness permits, gentle massage should be instituted; sometimes this can never be employed; in other cases, again, it can be instituted comparatively early, and there can be no doubt that in a measure it favors the diminution of the swellings, especially if the patient can bear deep kneading. Bathing between blankets, as in ordinary rest treatment, should also be carried out, but of themselves baths accomplish nothing in adiposis dolorosa; indeed, the physical exertion and manipulation attendant upon the application of ordinary hydrotherapeutic measures in these cases exhausts the patient.

"It is a good plan to keep a record of the pulse and temperature during thyroid administration, although the writer has never observed any fluctuations of moment in these cases, even when the thyroid was pushed. The patient should, of course, be weighed from time to time, and the dose of thyroid modified according to the impression made. In some cases no impression whatever can be made; in other cases, again, the impression is decided. In 3 cases of the writer the result was most satisfactory; 2 of these were treated systematically by rest in bed; the third could not, for certain reasons, be put to bed. In all 3 the improvement in the size of the swellings and in the lessening of pain was very great. Treatment was carried out six months to a year. In 1 case the affection recurred at the end of two years, but was again controlled. In the second, improvement and practically good health has persisted for four years. The third was greatly improved, and has disappeared from observation."

Goiter.—As Rogers[43] states: "Simple goiter, or hypertrophy of the thyroid gland, is usually considered to be a disorder which is entirely distinct from Graves's disease, and to represent a totally different pathological process; but there are many reasons for doubting this conclusion and for suggesting something of the same pathological physiology, at least, in the origin of both exophthalmic goiter and simple goiter." Yet we are confronted with the fact that thyroid preparations are often useful in goiter, whereas in the active or erethic stage of exophthalmic goiter it is harmful. This is explained,

[43] Rogers: Annals of Surgery, Dec., 1909.

from my viewpoint, however, by the fact that we are dealing in goiter with a compensative reaction very similar to that which occurs in cases of exophthalmic goiter, as previously stated. The presence of some toxic in the blood (goiters are now generally ascribed to the presence of some unknown toxic in the drinking water of the regions in which they occur endemically) creating a demand for an increase of thyroiodase as one of the antitoxic constituents of the blood, the organ is unable to furnish it. Being subjected to undue stimulation, the local expression of which is excessive vasodilation, it becomes enlarged, *i.e.*, goitrous. Briefly, in those cases in which thyroid preparations are effective, the goiter is the result of a toxæmia which the added thyroid substance helps to counteract as one of the physiological antitoxic agents.

In some of these cases, however, both iodine and thyroid gland seem to produce pernicious effects. Even minute doses, as observed in one of my cases, suffice sometimes to produce distressing symptoms. It is always advisable to begin with fractions of doses and to increase gradually until the beneficial dose. Beginning with ½ grain (0.033 Gm.) three times a day, the dose can be raised gradually to 2 grains (0.13 Gm.), but in most cases 1 grain (0.066 Gm.) suffices to compensate for the inability of the organ to supply the volume of thyroparathyroid secretion required by the organism at large.

The dietetic and other measures indicated in these cases have been reviewed in full in the article on goiter, to which the reader is referred (page 243, this volume). Surgical intervention may become necessary when pressure symptoms appear. In competent hands the post-operative mortality has been practically reduced to *nil*, and when we consider that a simple goiter may assume the more formidable type of exophthalmic goiter our duty is to afford the patient this, the surest, guarantee against it when medical treatment, including the use of thyroid, fails to turn the tide toward recovery.

Chronic Rheumatism.—In the treatment of this disease we owe much to the patient labors of Léopold-Lévi and H. de Rothschild.[44]

[44] Léopold-Lévi and Henri de Rothschild: "Etude sur la physio-pathologie du Corps Thyroide et de l'Hypophyse," 1908; "Nouvelles études sur la physio-pathologie du Corps Thyroide et des autres Glands Endocrines," 1911.

These leave no room for doubt that thyroid gland is of great value. In a series of 39 cases ranging from the ages of 12 to 75 years, 32 were greatly improved, cure being obtained in 2 severe cases. All the concomitant symptoms, such as œdema, neuralgia, etc., were favorably influenced; it increased the appetite, caused the cardiac anginas and all neural phenomena to disappear.

Two examples of the results obtained will serve to illustrate both the treatment resorted to and the doses employed. Both were cases of chronic rheumatism with hydrarthrosis. In one of these the hydrarthrosis followed a fall from a bicycle, and was the precursor of attacks of muscular rheumatism, all the joints being gradually involved in the morbid process. Notwithstanding seasons at Aix-les-Bains, Dax, and other stations, the patient became quite impotent, having even to be fed. The usual remedies proved unavailing, though aspirin and iodine seemed, at least for a while, to be of some benefit. The patient's condition becoming steadily worse, thyroid extract was tried, beginning with 1½ grains (0.1 Gm.) every other day during ten days, followed, after five days, by resumption of the remedy; then giving again only 1½ grains (0.1 Gm.) every other day. This dose was gradually increased until, eleven months later, the patient was taking 7½ grains (0.5 Gm.), in divided doses, daily. Good results have also been recorded by Revilliod, Lancereaux, and others.

The interpretation of the pathogenesis of rheumatism I submit elsewhere in this work affords an explanation of the manner in which these results are obtained. Briefly, from my point of view, rheumatism is due to the presence in the blood of any toxin, or toxic, especially toxic wastes derived from excessive tissue metabolism, capable of exciting violently the adreno-thyroid center, and of increasing to an abnormal degree, therefore, the functional activity of the adrenal system. The proportion of adrenoxidase in the blood being very greatly increased, as shown by the tendency to hyperthermia and the anæmia (due to hæmolysis), there occur (1) hyperconstriction of all vessels owing to excessive metabolism in their muscular coats, and, as a result, hyperæmia of all capillaries (which are not provided with such a coat), including those of

the serous membranes, especially those of the joints, and also, (2) as a result of hyperoxygenation of the pancreas and leucocytogenic tissues and hyperstimulation of the thyroid apparatus, an accumulation of autotoxic bodies in the blood-plasma, and effusion into the joints, serous membranes, glandular elements, etc. Hence the swelling, heat, severe pain, accumulation of fluid, and the inflammatory lesions, including erosion in the joints; hence also the marked predilection of serous membranes, the pericardium and endocardium, the myocardium, the tonsils, etc., to inflammation; hence, finally, the fibrous adhesions in the joints and around the neighboring structures which provoke ankylosis.

While the toxins of various bacteria, the staphylococcus citreus, the micrococcus lanceolatus, the gonococcus, may stimulate the test-organ sufficiently—especially in individuals in whom this organ is hypersensitive—to provoke acute rheumatism, it is caused in most cases by intermediate toxic waste-products which appear in the blood as a result of exposure to cold and the resulting hypocatabolism—the cellular trypsin failing, when the local temperature is below normal, to break down adequately wornout cell material.

Chronic rheumatism differs from the foregoing, in that the cause of the disease is inadequate catabolism of tissue wastes and excitation, by the toxic products formed, of the vasomotor center, while the pathogenesis of the joint lesions includes more or less increase of the vascular tension, as in the acute form.

Under these conditions, it is obvious that thyroid gland, by increasing the proteolytic activity of the blood, promotes destruction of the toxic wastes which underlie the disease.

Analyzing Lévi and de Rothschild's results from this viewpoint, the manner in which they were produced by their *small doses* becomes self-evident. Thus, increase of appetite was the first effect noted; this is a normal result, since the greater cellular activity and catabolism created a greater demand for foodstuffs. Increased heat production soon replaced the marked and constant chilliness from which the patient suffered—an effect due to the marked increase of oxidation the thyroid extract engendered throughout the body. The dose

was increased to 1½ grains (0.1 Gm.) one day, then to 3 grains (0.2 Gm.) the next, this being continued ten days. After a period of rest of five days, 3 grains (0.2 Gm.) were again given daily. The pain became less—a fact due to decrease of the vascular tension, owing to increased destruction of the toxic wastes which excite the vasomotor center, thus causing constriction of all arteries. The sensory nerve-terminals being relieved of the hyperæmia which caused the pain, the latter became less marked in proportion. Closely connected with this beneficial action was the effect on the joints, viz.: the *hydrarthrosis became reduced.* Being also due to excessive vascular tension, it is plain that, by causing vasodilation in the manner just explained, thyroid extract caused the excess of fluid to leave the joints. The dose being still further increased until 7½ grains (0.5 Gm.) were taken daily, *emaciation* occurred —a well-known effect due to excessive catabolism provoked by large doses of thyroid extract.

Eleven months' treatment brought Léopold-Lévi and Rothschild's case back to a condition of comfort, the joints having resumed their shape and flexibility—with the exception of one knee, which remained ankylosed—owing doubtless to fibrosis, a condition beyond the reach of the remedy. This does not militate against its use, however; it simply shows that the treatment was resorted to too late to avoid irremediable organic lesions. Rheumatism with eczema and epilepsy in the child also disappeared under thyroid treatment in a case of Léopold-Lévi's.[44a]

In a case treated by Parhon and Papinian[45] thyroid extract produced, though the disease was of twenty-four years' standing, "a true regeneration." When 7½ grains (0.5 Gm.) in five divided doses daily had been given some time, palpitations, tachycardia, and arrhythmia appeared. On withdrawing the remedy these untoward effects ceased, but recurred as soon as its use was resumed. This affords additional evidence in support of a fact I have often urged, viz.: that the best effects of thyroid extract are obtained with *small* doses.

These results have been confirmed by other observers,

[44a] Léopold-Lévi: Soc. de Méd. Paris, Oct. 28, 1911.
[45] Parhon and Papinian: Presse méd., No. 1, p. 3, 1905.

notably by Combe, F. Claisse,[46] Souques,[47] Ménard,[48] Claisse and Vincent,[49] and more recently by Steele-Perkins[49a] and Wilson.[49b] Though thyroid products act very gradually, and require patience and careful watching, the method is a very promising one.

Enuresis.—In many instances this condition is due to general asthenia, and the muscular debility which attends this state carries along with it inability of the sphincters to perform their functions at all times, especially when, during sleep, general relaxation prevails. The influence of thyroid on general metabolism and nutrition and the resulting increase of functional power in all organs affect equally both the cystic and urethral sphincters and thus overcome the trouble.

According to Hertoghe,[50] nocturnal incontinence of urine in young children and adolescents is due to thyroid insufficiency. He observed a number of cases in which the use of thyroid extract was followed by improvement or cure. Children who suffer from incontinence are often undersized, and they present the infantile habitus in varying degrees—improperly placed teeth, nasopharyngeal adenoids, flat chests, and emaciated and slender extremities. Such patients—those in which thyroid gland will prove beneficial—are often flat-footed and their feet have an offensive odor, their gait is stiff, they suffer from pains in the thighs and from sciatica produced by the cold and moist surroundings in which they lie at night. The systematic examination of the urine in these cases shows an abundant deposition of the cells covering the free surface of the cystic mucosa. In children beyond 2 years of age Hertoghe gives 2 grains (0.13 Gm.) daily with 3 to 5 grains (0.2 to 0.33 Gm.) of potassium iodide and the bromides on retiring.

Additional signs are subnormal temperature, deficiency of hair in the external third of the eyebrows, as observed by Léopold-Lévi and de Rothschild; scaphoid scapulæ, delayed epiphysial development, as determined by the X-rays, and adenoid vegetations. In such cases removal of the latter fails to benefit the patient. Thus, Leonard Williams[51] reported a case

[46] Claisse: Klinisch-therapeutische Woch., S. 979, 1899.
[47] Souques: *Ibid.*, p. 1003, 1908.
[48] Ménard: Tribune médicale, No. 9, 1908; Rev. intern. med., p. 326, 1908.
[49] Claisse and Vincent: Münch. med. Woch., S. 1667, 1908.
[49a] Steele-Perkins: London Lancet, March 5, 1910.
[49b] Wilson: British Medical Journal, Dec. 10, 1910.
[50] Hertoghe: Bull. de l'Acad. Roy. de Méd. de Belgique, vol. xxi, No. 4, 1907.
[51] Williams: London Lancet, May 1, 1909.