

causing interstitial and parenchymatous lesions which lead to sclerosis and atrophy. The resulting phenomena are proportionate, of course, with the degree to which the functions of the thyroid are inhibited. These may occur in the midst of the disease, the child failing thereafter to grow physically and mentally at the normal rate and becoming flabby and pale, and showing the typical symptoms of functional hypothyroidia—if not its more advanced stage, cretinoid infantilism. Traumatism of the thyroid may also produce it. Amenorrhœa, as noted by Macfarlane<sup>7a</sup> may be the salient symptom of the disorder.

Old age stands apart perhaps from these two classes in that it is normal to all living things; but the thyroid apparatus stands pre-eminently, we have seen, as the underlying factor in this connection, according to Lorand,<sup>8</sup> who traces the cause of senility back to the thyroid, Victor Horsley, Hale White,<sup>9</sup> Erdheim, and others having found this organ atrophied, and containing connective tissue, in aged subjects. This was found to occur as early as the fiftieth year in the seventy thyroids examined by White. As noted by Erdheim, the same evidences of degeneration appear in the parathyroids. I look upon concomitant changes in all the organs of the adrenal system, the thyroid, adrenals, and pituitary, as the underlying cause of senility.

The symptomatology of senility and that of atrophy of the thyroid gland present considerable resemblance, as Léopold-Lévi<sup>10</sup> holds to hypothyroidia; the wrinkled, dry skin, the sub-normal temperature, the alopecia, the thinning of the eyebrows, the loss of teeth, the anorexia and constipation, the diurnal somnolence, the suppression of the menses and of the sexual function, the vague muscular pains, the enfeeblement of all functions, and the tendency to degeneration, particularly of the vessels, being common to both conditions.

TREATMENT.—Small doses of thyroid cause gradual disappearance of the morbid phenomena, while large doses may aggravate them. As emphasized by Hertoghe, the actual secretory activity of the thyroid apparatus is an unknown quantity, and large doses, by suddenly bringing on headache, pain over the

<sup>7a</sup> Macfarlane: Jour. of the Am. Med. Assoc., Feb. 3, 1912.

<sup>8</sup> Lorand: "Old Age Deferred," p. 91, 1910.

<sup>9</sup> White: Med. Chirur. Trans., vol. lxxi, p. 132.

<sup>10</sup> Léopold-Lévi: Jour. de méd. de Paris, No. 26, 1909.

kidneys, articular, muscular, and hepatic pains and anorexia—to which I would add a rapid pulse, fever, a tendency to faint, tremors, and increase of the existing dyspnœa—merely serve to frighten the patient and cause unjustified condemnation of the treatment. The treatment should be persisted in for years if need be, as emphasized by a case reported by G. E. Price.<sup>10a</sup>

One grain of the desiccated thyroid gland during meals is sufficient to begin with in an adult. This may be gradually increased until 2-grain (0.132 Gm.) doses are given. Patients seldom stand larger doses well, and these are only warranted when the prolonged use of the smaller fails to improve the patient. Often when improvement is not noticed the fault lies with the preparation administered; a change should then be made. In mild cases one-half of the above doses often suffice.

When the anæmia is profound, the effects of treatment are enhanced by giving desiccated adrenal gland, 2 grains (0.132 Gm.), and a small dose of iron, 1 grain (0.066 Gm.) of Bland's pill, with each dose of thyroid. Such a small dose of iron does not increase constipation, and contributes to the rapid building up of the hæmoglobin molecule. The three agents can be given in a capsule. The constipation should receive careful attention. High injections of saline solution two or three times a week are sometimes necessary in severe cases to evacuate completely the lower bowel. This measure may be resorted to the first three or four weeks if needed, and replaced by glycerin suppositories until a free motion occurs daily. Usually the fourth week of thyroid treatment is attended by considerable progress in this and all other directions. Saline aperients are to be preferred if purgation *per ora* becomes necessary. Opiates are harmful.

#### MYXEDEMA, OR PROGRESSIVE HYPOTHYROIDIA.

In this disease we have the maximum expression of progressive hypothyroidia, as it develops after the process of body growth has been accomplished, *i.e.*, in the adult. When the corresponding disorder occurs during childhood or adolescence, it stunts growth of body and mind and is then known as cretinism, treated under the next heading.

<sup>10a</sup> G. E. Price: American Medicine, Aug., 1911.

The marked inhibition of the thyro-parathyroid functions that characterizes this disease is graphically illustrated in its symptomatology when these functions are interpreted from my viewpoint. The great diminution of the thyro-parathyroid secretion correspondingly impairs the sensibility of all phosphorus-laden structures, particularly the nuclei of all cells, the nervous system, and the adrenals, to the oxidase of the blood. There results, therefore, general retardation of metabolism, particularly its catabolic phase; this is well exemplified by the hypothermal phenomena, the general functional torpor, the accumulation of fat, and the extravasation of fluids which constitute the cutaneous œdema, the latter being due mainly to passive relaxation of the peripheral blood-vessels. Wastes, detritus, etc., accumulate in the blood also as a result of defective catabolism, giving rise to "rheumatic" and cutaneous disorders. The dystrophies of various kinds with a marked tendency to degenerative processes invariably witnessed in this disorder are also normal results of defective metabolism. Considered in this light the disease may be defined as follows:—

*Myxœdema is a functional disease due to marked or complete hypothyroidia when the latter occurs after puberty. It is characterized by deficient oxidation and catabolism, the main symptoms of which are hypothermia, infiltration, and swelling of the cutaneous tissues, including those of the face, increase in weight, dryness of the skin, marked weakness, and mental torpor.*

**SYMPTOMATOLOGY AND PATHOGENESIS.**—The deficient oxygenation is well exemplified by the correspondingly depressed heat production. These patients suffer almost continuously from cold; their temperature, both oral and rectal, being always sub-normal—as low as 93° F. in some instances—unless some fever be present. In a case observed by Hun and Prudden, the temperature fell steadily until it reached 66° F., before death. The least exposure to cold causes the lips, nose, ears, and fingertips to become cyanotic; hence the abundance of covering with which these cases are found provided. The extremities are, as a rule, cold and often purple or livid. This is partly due, however, to the cardio-vascular weakness referred to below.

The deficient metabolism and functional activity is well exemplified by its influence on the cardio-vascular system, the

functional torpor of which (partly due to similar condition of the vaso-motor system) gives rise to the pre-eminent symptom of the disease: the peculiar œdema of the skin and mucous membranes. This phenomenon, which led Ord to designate it "myxœdema," is a "jelly-like swelling," as he termed it, which causes the body, particularly the face and suprascapular regions—commonly the seat of cushions or pads—to become irregularly swollen. The infiltrated tissues are elastic, firm, and resistant, but do not pit on pressure, as in true œdema, though they vibrate under lateral stroking. At first the swelling may disappear temporarily or change situation, but after a time it becomes permanent. The abdominal walls being likewise affected, the abdomen appears enlarged and pendulous, with more or less projection of the umbilicus, and sometimes ascites. The genitalia are similarly tumefied as a rule. The hands are also thickened and sometimes spade-like; the nails are brittle and thin, sometimes abnormally curved and ridged, and occasionally undergo atrophy. A similar condition may affect the toes. The forearms, legs, and feet are also the seat of swellings.

The skin, its glandular elements and the hair, all show clearly the effects of defective trophic conditions. The skin, mainly owing to the arrest of its sebaceous and sweat glands, is dry, rough, and scaly, though that of the face may be relatively smooth. It may desquamate in flakes or in the form of a fine powder. Patches of pigmentation varying from yellowish brown to the actual bronzing of Addison's disease (thus affording additional proof of the participation of the adrenals in the functional torpor) are occasionally witnessed.

The hair also changes in appearance; it becomes coarse, lusterless, and breaks easily. It is gradually lost, falling out in patches, at first where the traction attending the use of the comb is greatest, *i.e.*, where the hair is parted, the brow, and the occiput. The lashes and eyebrows are also lost in part, along with the hair of the rest of the body.

As a result of the cutaneous thickening and infiltration, the face becomes coarse, expressionless, and mask-like. The lips, greatly thickened, are usually cyanosed and cause the mouth to appear greatly enlarged. The color of the skin is yellowish or wax-like, a circumscribed patch of redness being present, as a

rule, below each cheek-bone. The nose is cold, the tip being sometimes cyanosed; it appears broad and flat through thickening of the nostrils. The ears, being in a similar condition, are likewise enlarged; the auditory meatus, however, is narrowed by its thickened walls, causing more or less deafness. The lids droop over the eyeballs—though exophthalmus may occur, due to primary exophthalmic goiter—causing the patient to appear sleepy, while an effort to raise the upper lid is manifested by elevation of the eyeballs. There is usually considerable lachrymation, due to glandular leakage.

The mucous membranes being involved, as is the skin, those of the mouth and naso-pharyngeal cavities appear pale and tumefied. That of the cheeks is indented by the teeth, against which it presses, and is sometimes bitten; this applies also to the tongue. The teeth tend to decay, and may become black within a comparatively short period, owing mainly to deficient calcium metabolism, or readily break off and fall out. This is greatly aggravated by the recession of the gums and the readiness with which these structures tend to ulcerate and bleed. Stubborn stomatitis, with free salivation, dribbling from the corners of the mouth, and erosions of the buccal, pharyngeal, and laryngo-tracheal membrane, may appear. Edema of the larynx is not infrequently a cause of death. In some cases, however, the whole oral cavity is uncomfortably dry. The entire alimentary canal, down to the rectum, is also more or less infiltrated, causing anorexia, gastro-intestinal disorders, and constipation, which may alternate with attacks of diarrhoea. There is, as a rule, a profound distaste for meat, which in fact is toxic in a measure to these cases—as it is in thyroidectomized animals—owing to their impaired antitoxic functions.

The tumefaction of the oral mucous membrane and of the palate, tongue, and lips renders enunciation very imperfect and jerky; this condition being aggravated by the narrowing of the naso-pharyngeal lumen, it gives what voice there is a "nasal" character. It is also rendered coarse and low, that of a woman being sometimes lowered sufficiently in pitch to recall that of a man. Approximation of the cords being rendered difficult by the tumefaction, speaking sometimes requires considerable effort. The slow intellection from which these cases suffer—owing to

difficult metabolism of the organ of mind—increases greatly the trouble they experience in understanding questions and expressing their wants and ideas, a fact which often renders them extremely irritable. Mental disorders are frequent in these cases. Total lack of interest in their surroundings, somnolence, and amnesia are commonly observed.

The deficient oxidation of all muscular elements entails a corresponding weakness. Great lassitude with exhaustion upon the slightest exertion is the rule. Some cases are unable to raise the head at all or to stand. Others lapse into paralysis. Fibrillary tremor and muscular quivering are often noticed. Locomotion is tentative, often waddling; missteps are frequent, being produced by a slight obstacle. The ataxic gait may prevail; the motions of the arm are also uncertain and unsteady in sufficiently advanced cases. Although the parathyroids have been found sclerosed along with the thyroid in these cases, tetany is very rarely observed—a fact which further suggests the functional unity of these organs.

Sensation being, as a rule, markedly impaired, while the finger-joints are stiffened, the usefulness of the hands is greatly compromised. Small objects are held with considerable difficulty, and easily dropped, while such diminutive articles as pins, needles, and even small buttons are not felt at all. Tingling, formication, and pruritus are often complained of. Although cutaneous sensibility is greatly impaired, pain in the muscles and joints, neuralgia, and marked headache localized in most instances in the occipital region occur in about one-half of the cases. These are due to the accumulation of toxic intermediate waste products in the blood, owing to the deficient antitoxic power of the latter.

The senses of smell and taste are commonly impaired or perverted, the patient complaining of foul odors, a bitter or acid taste, etc. Vertigo is a relatively frequent symptom. The vision is occasionally dimmed and optic atrophy has been observed. Tinnitus aurium is not uncommon, and the hearing is impaired in the majority of cases.

Hæmorrhages from one or more organs are common. Epistaxis, hæmoptysis; bleeding at the gums, which may prove severe on extracting a tooth; intestinal, uterine, and even cere-

bral hæmorrhages may occur. Probably the most common, however, is menorrhagia. Postpartum hæmorrhages are also common in these cases. The menstruation is irregular, as a rule, and often ceases altogether until appropriate treatment procures recovery. This condition is mainly due to the poverty of the blood in fibrin ferment, as shown by the prolonged coagulation time, and to the relaxation and pseudo-fatty changes ("pseudo" because they are temporary) throughout the cardiovascular system. It is aggravated by the weak heart action, especially in advanced cases, in which the heart is deprived of the aid the adrenal secretion affords its muscular elements. The pulse is slow and weak and sometimes quite difficult to locate. The *vis-a-tergo* motion of the blood in the peripheral capillaries is slowed to a marked degree as soon as the disease has reached beyond the initial stage. To this is mainly due, in fact, the dense œdema which is the most evident characteristic of the disease.

The specific gravity of the urine varies but little; on the whole, however, it is somewhat reduced; but the urea excretion is diminished in most cases, and markedly so when the disease is advanced. In the latter case, both albuminuria and glycosuria (probably alimentary) may occur, but disappear when the thyroid treatment is instituted. Casts are also found in advanced cases.

Myxœdema progresses slowly, a case lasting, as a rule, from six to twenty years, unless the patient is carried off through some intercurrent trouble, which is often the case. Tuberculosis and pneumonia are the infections to which they seem to be especially vulnerable—owing to the enfeebled condition of their auto-defensive resources. Nephritis, pericarditis, and cerebral hæmorrhage seem to be next in the order of frequency. Periods of amelioration sometimes occur, but sooner or later the patient relapses into his previous state, and gradually dies of exhaustion. Rarely, especially in young adults, the disease may run its course in less than six months.

Acute myxœdema with prompt death may occur as the result of sudden arrest of the functions of the thyroid. In a case reported by Lloyd, the disease proved fatal in a few days. In another instance it occurred as the result of an injury to the

thyroid. It may appear as a sudden complication of goiter; it is probable, however, that under these conditions we are dealing with some toxæmia of thyroid origin rather than with true myxœdema, since we know that even extirpation of the thyroid does not produce death rapidly.

The thyroid gland is distinctly reduced in size in about 75 per cent. of the cases of myxœdema, its outline being hardly discernible by palpation in some of these. Conversely, some are abnormally large at first, and may then gradually atrophy irregularly, the portion which fails to decrease in size being resistant to pressure.

ETIOLOGY.—Women are more liable to the disease to a considerable extent than men, *i.e.*, it occurs about six times in women to once in men, and it may develop at any time of life, though the period between the thirtieth and sixtieth years shows by far the largest proportion of cases. There is a marked familial influence, some families showing several cases. While hypothyroidia, alcoholism, and syphilis are likely to be the predominant parental factors in progressive hypothyroidia or true myxœdema, tuberculosis and neuroses are met with much more frequently in the family antecedents of the patient. The main causes appear to be rapid child-bearing, the menopause, worry, mental shocks, and injuries, especially to the head. Neoplasms, fungi, and entozoa capable of destroying or inhibiting a sufficient area of the gland have also been known to cause the disease.

PATHOLOGY.—The characteristic lesion in the thyroid is atrophy, due to the development of fibrous tissue, the glandular elements of the organ being reduced in proportion. It may follow local inflammatory lesions in connection with acute articular rheumatism, erysipelas, syphilis, actinomycosis, cancer, an acute thyroiditis, local injuries, etc., which serve to destroy a part of the glandular parenchyma, and annul in proportion its secretory functions. Excessive child-bearing, shock, and the menopause can hardly be regarded as causes of an inflammatory process, however, and it is probable that we are dealing, in this connection, rather with functional exhaustion of the organ, or with an endarteritis or periarteritis of its vascular supply.

TREATMENT.—The use of thyroid gland in this disease, introduced by Murray, is rightly considered one of the great steps in modern medicine. As in the case of hypothyroidia, however, large doses should not be used; this rule is all the more applicable to myxœdema in view of the marked relative weakness of the subjects. Again, exertion of any kind should be avoided while taking thyroid; two of Dr. Murray's cases died of syncope during active exercise taken too early after a prolonged treatment, though it must be said that he used larger doses than are now recommended. One grain (0.066 Gm.) of the desiccated thyroid, three times daily, suffices to begin with; this dose may be gradually increased  $\frac{1}{2}$  grain (0.033 Gm.) until 2 grains (0.132 Gm.) are given at each meal, and until the temperature is raised to normal. If this is exceeded the dose should be reduced to  $1\frac{1}{2}$  grains (0.099 Gm.) or less. The pulse should also be watched, an increase of fifteen beats indicating the need of reducing the dose. I prefer these divided doses to the single daily, but correspondingly larger, dose recommended by some observers, as the latter has seemed to me to increase the likelihood of untoward effects. Cases vary considerably in this respect, however, and the tolerance of each case should be carefully studied. The patient should spend his time in an arm-chair during the day, at first, if possible, in the open air, and begin to walk around only when his temperature and pulse become normal.

The effect of the remedy is to cause gradual disappearance of all the morbid symptoms, but if its use is discontinued they as surely return. Two grains (0.132 Gm.) daily suffice, however, to perpetuate the recovery in most instances. Before the introduction of the thyroid treatment, the disease was fatal in practically every instance. Grafting of thyroid is now used successfully to prevent the need of constantly taking thyroid gland. The measure is described on page 200.

When the asthenia is marked and the heart, as is usually the case under these conditions, is considerably dilated, a small dose of digitalin,  $\frac{1}{20}$  grain (0.0033 Gm.), three times daily, or the desiccated suprarenal gland of the U. S. P., or, better, the pituitary gland, 1 grain (0.066 Gm.) during meals, greatly hastens the curative process.

#### INFANTILE MYXŒDEMA, OR CRETINISM.

Although cretinism is, like myxœdema, due to loss or impairment of the functions of the thyroid apparatus, its symptomatology differs in many respects from that of myxœdema, because, as previously stated, it occurs during the period of life when growth and development, physical and mental, are most active, *i.e.*, between birth and puberty, whereas myxœdema includes only cases that occur after puberty. In cretinism we witness the results of defective oxidation and metabolism of cellular proteids and fats at a time when the building up or anabolic phase is exceptionally active, and, as a result, arrest of physical and mental growth. The following definition seems to me to include the main features of the disease:—

*Infantile myxœdema, or cretinism, is a functional disease due to marked or complete hypothyroidia during the period between birth and puberty. It is due to deficient oxidation and is characterized by retardation of physical and mental development, the main symptoms of which are: stunted growth, the cretinic facies with flattened nose, thickened lips and tongue, a harsh skin, and more or less advanced idiocy.*

SYMPTOMATOLOGY AND PATHOGENESIS.—The disease may develop *in utero*, but it is seldom recognized before the first month. The attention is drawn to the child through the fact that it fails to grow at the average rate either physically or mentally. Its tongue is then noticed to be unusually thick—sufficiently so, in some instances, to project beyond the lips at all times, fill the oral cavity, and interfere with the respiration when the child lies in the recumbent position.

Closer examination then reveals the symptoms witnessed in adult myxœdema. The “jelly-like swelling” of Ord, coupled with the yellowish, white, or waxy pallor, the rough, dry, and scaly skin, so unlike that of a normal child, is clearly defined, though the puffy face retains some of its smoothness. The fontanelles remain patent unusually long. The features of the cretin are, as a rule, repulsive, though pitiful. The swollen, often wrinkled brow; the puffy lids, which reduce the watery eyes to mere slits; the “saddle-back,” or depressed, nose with its wide and thick alæ; the swollen, erect ears; the large and drooling

tongue between thick lips, and the aged appearance constitute a picture which causes all cretins to resemble one another, and which one is not apt to forget.

Again do we meet the evidences of deficient metabolism and nutrition. The hair is thin, but coarse and brittle, the eyebrows and eyelashes being also scant and often absent. In some cases the hair may be thick, but likewise coarse and deprived of luster, resembling tow in texture rather than human hair. The nails are very short, thin, streaked, and brittle. The teeth, which may be represented by a few sharp points, as in a teething infant, are irregular and tend to early decay, the second dentition, which often fails to occur at all, being long delayed at best, the teeth being no less liable to caries, and no less ill-shaped, than their predecessors.

The body and extremities show not only arrested development, but the effects of irregularity in this morbid process, the different parts of the body, the bones especially, showing considerable disproportion. The trunk, though small as compared to the head, may be relatively massive, the back arched at the waistline and perhaps scoliotic, the abdomen, on the other hand, projecting forward considerably, with, often, an umbilical hernia. Conversely, the legs are short and more or less bowed; their cutaneous covering having developed to a greater degree and thickened, it forms folds which tend further to distort these members. The same perversions of local growth exist elsewhere, but to a less evident degree. The hands are broad, spade-like, and the fingers pudgy and stiff, a condition reproduced in the feet, the toes of which are kept apart by the thickened skin. The supraclavicular region is usually the seat of thick pads, which sometimes encircle the neck, filling the depression between the latter and the shoulders. When a goiter is present, as is usually the case in the endemic form—though the gland is practically functionless—the distortion of this region of the body is striking.

The defective oxidation due to the inhibited thyro-adrenal functions is well shown by the subnormal temperature, the cold surface, the extremities being sometimes livid, and the marked diminution of nitrogen excretion. The blood-pressure is correspondingly lowered both owing to the deficiency of the adrenal product, which deprives the blood-vessels of its direct tone-

sustaining effect, and because the rate of metabolism in the cardio-vascular muscles is slowed. Both these factors and the ever-present anæmia cause general vaso-dilation and low tension. All muscular elements in the body being influenced in the same way, the child is weak, walks in a wobbly, slow, inco-ordinate way, and, in some instances, is quite unable to stand or to sustain its head, which then droops on the chest.

A similar condition of the muscular coat of the intestines practically prevents peristalsis, with inveterate constipation as result, the bowels being relieved only by an occasional outburst of diarrhoea, unless appropriate measures, enemas, purgatives, etc., are resorted to periodically. This ultimately leads the patients to realize that semifluid or fluid food is alone well borne by the child, which has to be fed with a spoon, the whole alimentary canal from mouth to anus being much in the same condition as the skin—i.e., deprived of much of its normal fluids—another source of constipation.

The genital organs, both the ovaries and testes, remain imperfectly developed, though not necessarily infantile. Occasionally the genital organs are hypertrophied and the sexual instincts are enhanced. Their offspring tend to be feeble-minded, however, and are liable to excessive mortality. Menstruation often fails to appear, or is scanty; or it may be profuse, and even hæmorrhagic, owing, as in myxœdema, to deficiency of adrenoxidase in the blood and to the imperfect coagulating power this entails. Epistaxis and bleeding at the gums are also commonly observed.

The urine shows but little change, though the urea excreted is below normal. In very marked cases, albumin and hyaline casts have been found periodically, doubtless owing to the autointoxication resulting from retained excreta in the intestinal canal. The thoracic and abdominal organs do not seem to be involved in the morbid process.

The mental state of the child depends upon the severity of the case. In some it is not far removed from what Roesch has termed a "human plant," even the intelligence common to the higher animals being wanting. The child fails to recognize its parents or any person about it, or even a person from an object, and nothing, even toys, interests it in the least. It neither weeps