raising the arterial tension." In other words, it awakens all the typical phenomena, physiological and pathological, to which the adrenal product gives rise.

Twelve other general facts, covering a wide scope of research in the domain of various branches, submitted on page 510, also indicate that the pituitary is not a secreting organ.

Again, if the pituitary body were the source of an internal secretion its removal, as has been repeatedly done in recent years by Hochenegg, Cushing, and others for tumors, should prove harmful if not fatal, as is the case when the thyroid apparatus or the adrenals, which we *know* to be the source of internal secretions, are removed. But such is not the case. If, on the other hand, the pituitary is considered, with me, as a co-ordinating center supplied with subsidiary centers in the bulb, which centers could normally assume its functions gradually as the chief center is being destroyed, we can readily understand how a degenerated and useless pituitary can be removed with impunity.

Twenty-six years have elapsed since Pierre Marie identified acromegaly with the pituitary, and it must be admitted that the secretory theory has served but little if anything to elucidate its pathogenesis. Indeed, notwithstanding the painstaking labors of many distinguished observers, George Dock[68] could but write of it recently (1911): "Acromegaly is closely associated with disease of the pituitary body, but the alterations reported by various observers have been interpreted so differently that it is still uncertain just what the true relation is." The semeiology of the disease and its pathology have been raised quite to the high level of diseases that have had the benefit of centuries' analysis; but the relation between the seat of lesion and the clearly defined external phenomena of the disease still belong to the domain of conjecture. Will my interpretation of the functions of the pituitary body prove more fruitful in results? All that is claimed for it is that it offers a field for new lines of thought.

PATHOGENESIS AND SYMPTOMATOLOGY.—Tamburini[69] has shown, after an analysis of twenty-four cases in which autopsies

[68] Dock: Musser and Kelly: "Practical Treatment," p. 853, 1911.
[69] Tamburini: Riv. Sper. di Fren., p. 559, 1894, and p. 414, 1895.

had been made, that "in all *typical* cases of acromegaly a growth of the pituitary prevailed, but that there was, at first, hypertrophy of the gland, *with exaggeration of its functions,* and, later on, *abolition of these functions,*" a view in which Harlow Brooks,[70] after a painstaking study of the whole subject, concurs. These and other facts I will submit below have suggested the advisability of dividing the disease into two stages, the first representing the ascending period of the disease in the sense of exaggerated nutrition, terming it the *sthenic* stage, and to add thereto another stage representing the period of decline, as was done in other diseases of the ductless glands, namely, the *asthenic* stage. This will make it possible to identify the meaning of each symptom, and also, perhaps, to suggest more effective remedial measures than those now employed.

The characteristic phenomena of acromegaly have naturally established it as a disease of nutrition, as foundation for the many theories that have been advanced to explain its pathogenesis. To account for its symptoms, therefore, through organs such as the thyroid and adrenals, to which I have attributed such leading functions in oxidation and nutrition, must *a priori* seem, to say the least, reasonable. Again, the identity of the pituitary body as the starting point of the disease has been demonstrated by Marie and many other observers since. If, therefore, exaggeration of function is followed by abolition of function, another established fact, we have seen, we are brought to the logical conclusion that the diseased pituitary first excites the thyroid and adrenals, which, as I have shown, provoke hyperthyroidia and exophthalmic goiter, and also hyperadrenia, and that it subsequently depresses these same organs, bringing on, to a more or less marked degree, the opposite states: hypothyroidia, myxœdema, and Addison's disease or its milder prototype hypoadrenia. Interpreted from this viewpoint, then, the disease might be defined as follows:—

Acromegaly is a disease of nutrition, due to any condition, hyperplasia, neoplasm, etc., of, or any pressure upon, the pituitary body, capable of primarily exciting abnormally this organ, and then of progressively annulling its functions, and also, therefore, those of the organs it controls, viz., the adrenals and thyroid

[70] Harlow Brooks: Arch. of Neurol. and Psychopath., vol. i, No. 4, 1898.

apparatus, whose combined secretions sustain tissue oxidation, metabolism, and nutrition. Its symptoms are, during the first stage: excessive tissue growth, merged with those of hyperthyroidia and hyperadrenia, and, during the second stage, with those of hypothyroidia and hypoadrenia.

No reference is made here to the other functions of the pituitary in order to restrict the morbid process to its main general cause.

The *sthenic* stage is replete with clinical evidence of the participation of the thyroid apparatus in excessive development of the body. There are several cases of acromegaly on record which, by showing in an exaggerated manner the involvement of the pituitary,—to the point of bringing on all the prominent signs of exophthalmic goiter,—clearly indicate the participation of the thyroid even in those cases in which such prominent phenomena do not appear. Thus, Lediard[71] exhibited a case before the Clinical Society of London, in which the accompanying goiter was sufficiently large to require operation. Neal and Smyth[72] also witnessed a case in which a parenchymatous goiter was present. Sometimes swelling of the neck, which develops into a goiter, is the first symptom observed, as in a case reported by Grove.[73] In these cases, which but exemplify many others on record, the goiter might, however, occur as an independent condition. But in many instances the full syndrome of exophthalmic goiter is present. Lancereaux[74] reported 5 such cases, and Murray[75] 2 out of 4 cases of acromegaly he had witnessed. Exophthalmus, tremor of the hands, and glycosuria were prominent features. Hinsdale,[76] in fact, found exophthalmus in 23 out of 130 reported cases—evidence of the frequency with which the major symptoms of exophthalmic goiter are present, and of the important factor the thyroid apparatus must represent in the pathogenesis of acromegaly.

As to the adrenals, we must not lose sight of the fact that we are dealing with the sthenic stage of the disease, *i.e.*, that in which both the thyroid apparatus and the adrenals are rendered

[71] Lediard: Brit. Med. Jour., April 4, 1903.
[72] Neal and Smyth: London Lancet, July, 1898.
[73] Grove: Bulletin Johns Hopkins Hosp., Sept., 1910.
[74] Lancereaux: Semaine médicale, June 24, 1896.
[75] Murray: Edinburgh Medical Journal, p. 170, 1897.
[76] Hinsdale: "Acromegaly," p. 23, 1898.

CASE OF ACROMEGALY, EXOPHTHALMIC GOITER, PHTHISIS, AND GLYCOSURIA. [*Murray.*]

overactive by the irritated pituitary. Here, therefore, the connection is with excessive activity of the adrenals, such as adrenal hypernephromas furnish. Now, Owen Richards[77] describes such a case in a girl of 7 years, "who was as tall as a person of 20." Tileston and Wolbach,[78] referring to this type of cases, state that "they are obese and abnormally large for their age, a child of 5 years having the size and general appearance of a boy of 16 (Linser's case). Pigmentation of the skin may occur, but the color is more like that of a brunette than like the bronzing seen in Addison's disease. The intellect is dull and the disposition sullen. Appetite and sometimes thirst are increased, and vomiting is likely to be an obstinate feature" . . . As these phenomena occur as the result of an excess of an adrenal tissue, however, the body growth might only occur solely as an effect of such a surplus of adrenal secreting tissue; but that normal adrenals under stress—as they are in acromegaly—are capable of producing it, is well shown by the additional statement of Tileston and Wolbach's, that "in three instances (Otto,[79] Crecchio,[80] Marchand[81]) premature development has been associated with simple hyperplasia of the adrenal glands."

We thus have functionally overactive the two organs known to stimulate growth by their secretions: the adrenals, we have just seen, and the thyroid, as illustrated by its influence on body growth in the treatment of cretinism; and if, as Meige wrote: "Gigantism is the acromegaly of the growing period, while acromegaly is the gigantism of the period of completed development," these two organs, beyond doubt, account for the morbid growths. When to this we add the recognized fact that the thyroid apparatus influences calcium metabolism, we have all the factors necessary to trace the most characteristic phenomenon of the disease: the progressive enlargement of the bones and soft tissues, to its source. Marie restricted his conception of the disease to enlargement of the extremities (hence, ἄκρον, extremity, and μέγας, large), but, besides these, the bones of the skull, face, arms, and legs, the spinal column, scapulæ,

[77] Richards: Guy's Hospital Reports, vol. lix, p. 217, 1905.
[78] Tileston and Wolbach: Amer. Jour. Med. Sci., June, 1908.
[79] Otto: "Path. Anat.," p. 139, 1816. Cited by Tileston and Wolbach, *Ibid.*
[80] Crecchio: Wien. med. Presse, N. 30, p. 763. Cited by Tileston and Wolbach, *Ibid.*
[81] Marchand: Beitr. zur Wissensh. Med., B. i, 1891. Cited by Tileston and Wolbach, *Ibid.*

clavicles, and the ribs are also caused to grow, increasing the stature in the young and building upon giants, but causing deformities (projection anteriorly and posteriorly of the thoracic cage—of which the double hump of Punch or Punchinello is the type—in some) in adults. The soft tissues over the entire body are no less overnourished; the enormous hands and feet, the hypertrophied muscles, which, notwithstanding their great bulk, are weak, and the hypertrophied heart, scalp, face, lips, tongue, penis, etc., bear witness to this fact.

Side by side with this morbid growth we witness, more or less marked, the other phenomena of thyro-adrenal activity. There is abnormal demand for food; indeed, bulimia is considered by Hinsdale[82] as "one of the characteristic signs of acromegaly"—a fact which points to exaggerated metabolism. Thirst is also marked in some cases "out of all proportion to even the extraordinary size of the subjects," says the same writer, a symptom which he connects "with the glycosuria present in many cases." But here, also, we are dealing with a prominent symptom of exophthalmic goiter, and also of adrenal overactivity, since, as shown by Blum, Herter, Croftan, and others, injections of adrenalin produce it. So marked, in fact, is the connection between acromegaly and exophthalmic goiter and glycosuria that it has attracted attention. Lorand,[83] for instance, observed, independently of my views, that there was an intimate relationship between these disorders; that similar conditions: fevers, traumatisms, shock, etc., brought all three on; that polyuria, polydipsia, polyphagia were also met in all. In all three also more or less pronounced swelling of the thyroid occurred, having himself noted it in diabetes. Launois writes in this connection: "Whether we adopt the view of Loeb, involving pressure changes, or that of Sajous, relative to nervous irritation [transmitted to the thyroid, adrenals, etc.], however, the presence of an intermediary is further required for the production of glycosuria. According to some, this intermediary factor is the pancreas; in the opinion of Gilbert and his followers, it is the liver which, under these conditions, becomes functionally overactive; according to Sajous, it is the adrenals, to

[82] Hinsdale: *Loc. cit.*, p. 27.
[83] Lorand: La Presse médicale, Sept. 19, 1903.

which he traced nerves from the pituitary." Here, again, my views harmonize those of others: the adrenal secretion, by enhancing general metabolism, increases the functional activity of the pancreas and thereby the production of amylopsin; the hepatic glycogen is then converted by this ferment into glucose at an abnormal rate, producing glycæmia and glycosuria. Hence, it is by exciting the adrenals that the pituitary in acromegaly causes glycosuria. The circulatory phenomena include, we have seen, tachycardia where other signs of exophthalmic goiter prevailed. Others have noted a "paradoxical acceleration of the pulse." The "frequent and copious sweating," the tremors, the cramps, paræsthesias, tingling, shooting pains, due to circulatory disturbances in the neurons, sensory endings, etc.; dyspnœa, the anomalies of tastes, the tinnitus aurium, are all symptoms of acromegaly common to exophthalmic goiter. Both often give a history of rheumatic pains and occasionally symptoms of unbalanced mind, especially delusions of fear or maniacal excitement. Conversely, in both diseases the patient may lapse into a condition of melancholia. In both, also, are witnessed the brand of adrenal overactivity, a swarthiness, or dirty yellowish-brown hue of the skin, more marked in some parts than others.

Passing to the *asthenic* stage, the connection with myxœdema as to failure of thyroid functions, and with Addison's disease as to adrenal insufficiency, is quite as clearly defined. "Myxœdema may form part of the hypophysial syndrome," writes Launois. "From the observation of Norman Dalton[84] to that of Sainton and Rathery[85] a large number of cases have been reported which support the view that this combination can occur."

The functional relationship between the pituitary and the thyroid is well shown by the case of myxœdema reported by Sainton and Rathery, just referred to, in which the pituitary had been destroyed by a malignant growth, while the thyroid, adrenals, and ovaries were atrophied. Here the period of growth of the tumor had evidently caused excessive activity—hyperæmia—of the other organs and finally their functional destruction by atrophy, with myxœdema as a result. Other cases

[84] Dalton: Lancet, Nov. 6, 1897.
[85] Sainton and Rathery: Société médicale des Hôpitaux, May, 1898.

of the latter in which the pituitary was destroyed have been reported.

Strikingly suggestive in this connection is a case of myxœdema reported by Adami,[86] in which there was cancer of the pituitary, while the thyroid was normal. This shows plainly that it was to the absence of the impulses from the pituitary that the hypothyroidia was due. When, therefore, in acromegaly, the pituitary loses, by gradual degeneration, its power to excite the thyroid, hypothyroidia occurs, while the general tissue hypertrophy remains over from the sthenic period. The general signs of exophthalmic goiter are then gradually replaced by those of myxœdema, though the symptom-complex of the latter is somewhat obscured by the physical changes remaining over from the first stage; still, cases of acromegaly have been reported in which the myxœdematous symptoms were sufficiently marked to warrant the conclusion that the two diseases were associated. Lyman Greene,[87] Auerbach,[88] and others have reported such cases.

The phenomena of hypothyroidia and its progressive form myxœdema both include, we have seen, hypothermia. "A no less singular manifestation," writes Launois,[89] referring to acromegaly, "is lowering of the internal temperature, which, in a patient of Bartels, remained for weeks at a time between 34° and 36° C. ($93^1/_5$° and $96^4/_5$° F.) without the supervention of any sign of collapse. The same phenomenon has been witnessed by Petrina. In a case reported by Götzl and Erdheim,[90] the temperature fluctuated for three weeks between 35° and 36° C. (95° and $96^4/_5$° F.), later falling to 33° C. ($91^2/_5$° F.) It would be rather difficult at the present time to explain the origin of such disturbances," continues Launois; "we shall merely point out their similarity to the phenomena observed in myxœdema, in which disorder the temperature often fluctuates between 33° and 35^9 C. ($92^4/_{10}$° to 95° F.) and sometimes even falls below these figures." This symptom is no paradox when interpreted from my viewpoint, since, as I have shown, the pituitary governs

[86] Adami: Trans. Cong. of Amer. Phys. and Surg., p. 114, 1897.
[87] Lyman Greene: N. Y. Med. Jour., Oct. 21, 1905.
[88] Auerbach: Wiener klin. Woch., Feb. 10, 1907.
[89] Launois: Monthly Cyclopædia and Medical Bulletin, Jan. and March, 1911.
[90] Götzl and Erdheim: Zeitschr. f. Heilkunde, vol. xxvi; Intern. Med., p. 372, 1905.

the thyroid apparatus, while the adrenals, in turn, sustain tissue oxidation, and therefore the body heat.

"Unusual sensitiveness to cold," mental and physical torpor, and marked asthenia are also typical signs of hypothyroidia and hypoadrenia approximating Addison's disease. Facial œdema and even the moon face of hypothyroidal infantilism may be witnessed, as in Glaser's case,[91] though the deformities of the face, the prognathism, the projecting brows, mainly due to the osseous overgrowth of the sthenic stage, tend to conceal the myxœdematous signs in this region. There is often marked accumulation of fat, giving no œdematous pitting, and presenting the resistance to pressure as in myxœdema. This can evidently be of pituitaral origin; in a case reported by Madelung,[92] for example, a shot in the infundibulum was followed by marked obesity. Indeed, Fröhlich and Launois have elaborated syndromes, since sustained by numerous cases, in which adipose overgrowth is directly connected with neoplasms of the pituitary. There is good ground for the belief also that Dercum's disease, adiposis dolorosa, is primarily due to disorders of the pituitary. That thyroid gland is used as a remedy for obesity is known to every one; that obesity should occur when the thyroid apparatus is rendered deficient through inhibition of its center—the pituitary—by disease is self-evident.

Dilated veins, as in the infantilism of hypothyroidia, are commonly observed in acromegaly, though these may occur as a remnant of the sthenic stage. Suppression of sexual desire and impotence and amenorrhœa, rheumatic pains, neuralgia, are also common, as in hypothyroidia. A painful form has been identified which "may assume," says Launois, "the rheumatoid type when it becomes localized in a certain group of joints"—a sentence which reminds us vividly of the labors of Léopold-Lévi and de Rothschild, referred to under hypothyroidia. As in myxœdema we may also meet with various forms of delirium, delusions of persecution, mystery, and the manic depressive psychoses, and even with epileptic seizures. These are mainly due, as I have shown, to the accumulation of toxic wastes in the blood incident upon the inhibition of the antitoxic functions—

[91] Glaser: Virchow's Archiv, B. cxxii, p. 389, 1890.
[92] Madelung: Langenbeck's Archiv für klin. Chir., lxxiii, p. 1066, 1904.

a result, in turn, of the deficient activity of the three organs which, from my viewpoint, take an active part in the process, the pituitary, the thyroid apparatus, and the adrenals.

The implication of the adrenals in acromegaly has been referred to in connection with the sthenic stage—that of overgrowth. In the asthenic stage we witness the effects of their functional decadence. "Small freckles are frequent," writes Pirie,[93] referring to a personal case; "patches of a yellowish bronzing occur on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) . . . The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse. Palpitation and fainting fits occur often. Dyspnœa and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath," attesting to marked insufficiency of the adrenals in the respiratory process. Harlow Brooks[94] also writes, "macroscopically, the skin in these areas is considerably thickened; the surface is rough and often fissured. A general brownish pigmentation is present in the average case, which, at times, strongly resembles that found in Addison's disease." But the signs of myxœdema are again apparent in the remark by Pirie, that the skin of the eyelids was "thickened and puffy," there being also increased lachrymation and "a colloid secretion between the eyelids"—the typical "watery eyes" of myxœdema.

The symptoms that belong to the domain of the pituitary proper, *i.e.*, those which are not brought about through the agency of the thyroid and adrenals, are the ophthalmic disorders, including progressive amblyopia, amaurosis, hemianopsia, etc., the result in turn of pressure by the enlarged pituitary upon the optic tracts, the chiasm, optic nerves, etc. That the headache, sometimes extremely severe, from which these patients may suffer is also due to pressure is probable, though we must remember that it may also occur during the early or sthenic stage of the disease, and may then be due to increased intracranial tension.

PATHOLOGY.—The prevailing view, at the present time, is that of Marie, which ascribes the disease to a secretion of the

[93] Pirie: London Lancet, Oct. 5, 1901.
[94] Brooks: Archives of Neurology and Psychopathology, vol. i, No. 4, 1898.

gland. We have now seen, however, that there is considerable evidence to the contrary, *i.e.*, in favor of my own view, that it is through the adrenals and thyroid mainly that the characteristic phenomena of the disease are produced. Marie's original idea that the disease is due to disease of the pituitary is strongly sustained by my views, however, though still a matter of doubt among a few observers.

An important feature of the whole question is the predilection of the pituitary body for sarcoma, though, as suggested by Tamburini, Benda, Mendel, and others, many of these sarcoma-like tumors, on close histological differentiation by means of appropriate stains, proved to be examples of hyperplasia or adenoma, in which the destructive process does not proceed with as great rapidity unless the adenoma be malignant, which is frequently the case. This accounts for the fact that in many cases, particularly in women, the progress of the disease seems to be rapid, the asthenic stage, that characterized by hypothyroidia and hypoadrenia, coming on before the typical acromegalic changes and overgrowths have had time to advance materially. This probably corresponds with Parona's figures, which indicate that sarcoma or adenosarcoma is present in 64.5 per cent. of all cases.

That adenoma of the pituitary frequently occurs without giving rise to signs of acromegaly, or in fact to any symptoms, has been shown by Lowenstein. But we must not overlook the fact that many faces among the multitudes show marked evidences of overactivity of the pituitary at a given time of their existence. I have had occasion to treat a young man 6 feet 2 inches tall, in whom the prominent orbits, nose, and chin clearly indicate temporary hyperactivity of the pituitary. The same phenomena, though far more marked as to facial deformities than in the preceding case, were also observed in an average-sized woman by Léopold-Lévi, who pointed her out to me at the Rothschild clinic in Paris.

That children's diseases are frequently the source of temporary hyperplasia of the anterior lobe of the pituitary, I have no doubt. This sustains the personal view, treated at length in the second volume, that this lobe and the pars intermedia are mainly concerned, as a sensory organ, with the defense of the organism at large against disease.

TREATMENT.—Launois, referring to the cases in which Hochenegg removed the pituitary, states that "the progressive retrogression of the manifestations of acromegaly witnessed after excision of hypophysial tumors affords an argument of the first importance in favor of the theory of glandular hypersecretion." From my viewpoint, it affords a no less strong argument in favor of my view, since by removing the pituitary Hochenegg arrested the cause of the overstimulation of the thyroid apparatus and adrenals, to which the disease is due. Indeed, the latter view is the stronger, since the actual existence of a secretion from the pituitary is still a matter of conjecture, while the existence of the thyroparathyroid and adrenal secretions is beyond question.

The treatment of the disease has been necessarily restricted to symptomatic measures, and to the promiscuous use of organic preparations. The foregoing pages indicate that such should not be the case, and that, whatever use is made of the latter, they should always be carefully adjusted to the *stage* in which they are indicated. As stated by Dock,[95] "pituitary glands and extract have not produced definite improvement. The same may be said of thyroid treatment which has often appeared to make the symptoms worse." It is self-evident that in cases in the sthenic stage with the hyperthyroidia approximating, if not actually reproducing, exophthalmic goiter, and the blood already replete with thyroid secretion, the addition of thyroid gland to it cannot but prove harmful. But in a case such as Sears's,[96] in which the asthenic stage—which may appear early in women—was present, with signs of hypoadrenia, a puffy and mask-like face, dry and coarse hair, etc., with brown patches and asthenia denoting hypoadrenia, especially where, as the author specifies, "the thyroid could not be felt," considerable benefit can be obtained under thyroid treatment. In the sthenic or first stage, especially where the signs of exophthalmic goiter are marked, the treatment for that disease (see page 229) is indicated. The use of coal-tar products, it includes, is known in fact to afford considerable relief of the most distressing symptom of acromegaly, intense headache. Acetanilid and antipyrin, and also aspirin, have been considerably used for this purpose.

[95] Dock: *Loc. cit.*, p. 854.
[96] Sears: Boston Med. and Surg. Jour., July 2, 1896.

With respect to the therapeutic value of pituitary extract a case reported by Rolleston was greatly improved by pituitary and thyroid extracts combined. But the author observed that the superficial resemblance of acromegaly to myxœdema seemed to justify the administration of thyroid extract, pituitary extract alone having failed to effect any improvement. The patient neglecting the treatment, ultimately died, the autopsy revealing a sarcoma of the pituitary—a type of growth which rapidly brings on the asthenic stage.

As to the use of pituitary alone in the asthenic stage, it has been found of value in some cases as a palliative for headache,[97] but Rénon and Delille[98] found, in a woman who showed clear symptoms of hypothyroidia, that it aggravated the acromegalic signs, including the deformities of the face, hands, feet, etc. Yet, in similar cases, the simultaneous use of thyroid has proven of value. The solution of this enigma was furnished by Rolleston[99] when he said that "the apparent success obtained from the administration of the combined extracts was in reality due to the thyroid extract." On the whole, all this indicates that, as soon as any sign of hypothyroidia or myxœdema appears, the treatment for the latter disease (see page 192) should be instituted.

In the light of the facts submitted under the heading of pathology, particularly those which refer to arrest of the morbid process, there is ground for the hope that appropriate remedies may further such a result. Until our hopes are fulfilled, however, operative measures, such as those introduced by Hochenegg in Europe and admirably developed by Cushing in this country (see his recent volume[100]), should be resorted to where remedies do not check the lethal trend.

[97] See chapter xii, this volume; article "Pituitary Organotherapy."
[98] Rénon and Delille: Le Bulletin médical, June 24, 1908.
[99] Rolleston: Brit. Med. Jour., April 17, 1897.
[100] Cushing: "The Pituitary Body and its Disorders," Philadelphia and London, 1913.