temperature to 104° or 105° F. (40° or 40.5° C.) when reaction occurs, with marked intensification of the knee-jerk and bilateral paralysis.

William Browning[114] states that in children the chances of partial recovery are good; that in adults the recovery depends upon the severity of the apoplectic attack; and that in old age, when the arteries are tortuous or calcified, but limited recovery is to be expected. Barrs[115] concludes that if either renal disease, Cheyne-Stokes respiration or hyperpyrexia be present, the patient will probably not recover.

Pathogenesis and Pathology.—Whether we ascribe the rupture of the artery to miliary aneurisms, to endarteritis, to the so-called "fatty erosion" or to "diffuse degeneration," we are always brought back in cerebral hæmorrhages that are not due to traumatism or to an acute infection, leukæmia, etc., to a common cause: arteriosclerosis, the lesions being similar to those of that disease (*q.v.*). The multiple causes of arteriosclerosis: overeating (gout), alcohol, syphilis, senility, excessive exertion, excitement, starvation, lead, etc., are likewise those of arteriosclerosis. This applies as well to the renal lesions of this disease. On the whole, the relations of cerebral hæmorrhage to the adrenal system are those of the latter to arteriosclerosis.*

The reader is referred to the article on Arteriosclerosis for the details of the process. Whittaker[116] writes in this connection: "In all cases the process depends upon arteriosclerosis, which runs a slow and insidious course for months and years, and usually eludes all discovery. The catastrophe is sudden, but the disease process which leads up to it is very slow." Allen Starr,[117] in a study of 200 cases of apoplexy, found that 80 per cent. presented prodromal symptoms which he regarded as probably due to arteriosclerosis. Broadbent,[118] in a study of the vascular changes in 16 cases, found senile degeneration of the vessels in 2, while 7 were associated with granular kidney, and 7 with a type of kidney in which the main changes were thickening and hyaline degeneration of the vascular intima. The cerebral vessels were *dilated*, thinned and hyaline or studded with white patches, which, on microscopic examination, were found to consist of localized thickening and degeneration of the subendothelial tissues, over which the muscular coat, thin and atrophied in some instances, could not, as a rule, be traced. These are, we have seen, precisely the lesions found in the arteries of the body at large in arteriosclerosis. Stein[119] observed the typical loss of elasticity, and states that miliary aneurisms are far less frequent than is generally believed, the lesion being atheromatous.

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* *Author's conclusion.*

[114] William Browning: Sajous's "Analyt. Cyclo. of Pract. Med." vol. ii, p. 127, 1898.

[115] Barrs: Brit. Med. Jour., May 18, 1895.

[116] Whittaker: Indiana Med. Jour., May, 1896.

[117] Allen Starr: Med. Record, July 4, 1903.

[118] Broadbent: Lancet, Feb. 20, 1904.

[119] Stein: Deut. Zeit. f. Nerv., Bd. vii, S. 313, 1895.

Unfortunately the phenomena which make it possible to recognize the presence of arteriosclerosis, hardening of the radial and temporal arteries, the arcus senilis, etc., are not always present. The arterial lesion being present, coughing, sneezing, straining, etc., may suddenly increase the general vascular tension and cause rupture of the vessel, a mass of blood varying in size from that of a small cherry to that of an orange or more being suddenly projected under a pressure varying from 100 to 200 mm. Hg. upon the brain. As it coagulates at once, it forms a relatively dense body which may forcibly compress or disintegrate more or less the brain-substance, and as this substance is not renewed in the latter case, permanent lesions remain. The "stroke" is the result of shock, which reacts upon the entire cerebrospinal system, while the loss of consciousness is due to the suddenly-induced cerebral anæmia.

The hæmorrhage is derived either from a meningeal or central artery, but rupture of a meningeal branch is often due to traumatism. In most cases it occurs within the field of the central branches of the circle of Willis rather than in the cortical branches of this circle. The branches of the middle cerebral artery, which penetrates the brain by way of the anterior perforated space, are especially prone to rupture; this applies particularly to a branch that passes to the internal capsule and the lenticular nucleus and which has been named by Charcot the artery of "cerebral hæmorrhage."

Though any portion of the brain may become the seat of the hæmorrhage, certain regions suffer more frequently than others. The principal among these are, in the order of diminishing frequency: the internal capsule, the corpora striata, the thalami optici, the corona radiata, the convolutions and the pons Varolii.

The pressure in the central vessels is very great, owing to their proximity to the great channels, the carotids. Hence the predisposing influence of a short neck, especially in massive, full-blooded individuals. Stein[120] showed that the pressure of the blood projected into the cerebral tissues was 100 to 200 mm. Hg. The destructive action becomes obvious in view of the fact that the same tissues under normal conditions are subjected to a pressure of only 10 mm. Hg. Boudet[121] reported a case in which three-fourths of the right hemisphere was destroyed. Norbury[122] emphasized the importance of the great pressure in the basilar

[120] Stein: *Loc. cit.*

[121] Boudet: Cited by Whittaker: *Loc. cit.*

[122] Norbury: Medicine, July, 1897.

arteries as well as in the median cerebral arteries and the thinness of the walls of the cerebral vessels which predispose them, when they are the seat of atheromatous or miliary aneurisms, to hæmorrhage. Zapinsky[123] in 15 autopsies found degenerative lesions in the vessels of the base in every instance, the atheromatous plates being sufficiently marked to be seen with the naked eye.

Treatment.—Measures to Prevent the Development of an Attack.—In some cases some of the prodromal symptoms, slight thickness of speech, torpor, or numbness of an extremity, headache, vertigo, fullness in the head, etc., occur several days before an attack. When there is any evidence or likelihood of arteriosclerosis, measures should at once be instituted to prevent the stroke. If the arterial tension is high, the pulse tense and hard, an attack may occur at any moment; agents which cause immediate relaxation of the vessels by obtunding directly the vasomotor centers* are necessary. Among these are *nitroglycerin,* which acts on the pulse in two minutes, and the effects of which have entirely passed off in three hours; *sodium nitrite,* the action of which shows itself in about five minutes and lasts the same length of time; *erythrol tetranitrate,* in the solid form, acts in from twenty to thirty minutes, and its effects continue from seven to eight hours. To thwart the attack, therefore, either of the two first agents should be given every two hours and the third every six hours. An immediate result may be obtained with *amyl nitrite,* 5 drops, inhaled from a handkerchief; or a slight degree of help may be derived from *sweet spirits of niter,* two teaspoonfuls in a little water, pending the arrival of a stronger vasodilator.

The period of onset and the duration of the effects of nitroglycerin are those given by C. R. Marshall,[124] those of sodium nitrite by Leech,[125] and those of erythrol trinitrate by Bradbury,[126] both cited by Marshall.

Important in this connection is the avoidance of any effort or excitement and of agents which tend to stimulate the patient and cause a rise of the blood-pressure: stimulants, emetics, digitalis and strychnine are particularly harmful in this connection. Strophanthus and potassium iodide, casually mentioned by some authors among the useful drugs, are also contraindicated in threatened apoplexy. Saline injections may also prove harmful

* *Author's conclusion.*
[123] Zapinsky: Wratch, No. 4, p. 95, 1896.
[124] C. R. Marshall: Brit. Med. Jour., Dec. 11, 1897.
[125] Leech: *Ibid.*, July 1, 1893.
[126] Bradbury: *Ibid.*, Nov. 16, 1895.

by increasing the body fluids and the blood-pressure. The bowels should be kept free, to avoid autointoxication.

As attacks sometimes come on at night owing to the recumbent position, vasomotor depressants should be taken on retiring. To those mentioned may be added *sodium or potassium bromide, chloral hydrate* and *veratrum viride.* These three agents may be advantageously combined.

The patient's diet should be light, and coffee, tea, and other stimulating beverages should be dispensed with.

Preston[127] rightly holds that more could be done in the prodromal stage if this condition were carefully studied.

Measures to Prevent Extension of the Cerebral Lesions During the Attack.—After the first outpour of blood, the hæmorrhage almost always continues some time, and if steps be taken to decrease the cerebral blood-supply, the extension of the lesions may be, to a certain extent, curtailed, provided the patient be seen sufficiently early.

The patient is usually found lying on his back; his trunk and head should be gently raised until he is in a semirecumbent posture; the back and head being supported by the back of an overturned chair, made comfortable with pillows if these are available. If the face is dusky or cyanotic and the pulse is hard, incompressible, inhalations of *amyl nitrite,* 6 to 8 drops or more, should be resorted to, the handkerchief upon which the drug is poured being held in front of the patient's mouth and nose. This causes immediate relaxation of all arteries and the patient is bled, as it were, into the large trunks of the splanchnic area. In the meantime, the necessary preparations for *venesection* having been made, the patient should be bled. The brain is thus relieved instantly by the drug, and kept in that condition by the bleeding; the destructive process is thus necessarily counteracted. To prevent recurrence of the high vascular tension *veratrum viride,* 10 drops or more, if need be, of the tincture (1905 U. S. P.), should be given every two hours.

Browning[128] writes in this connection: "Some cases are promptly fatal, meningeal and ventricular forms being usually of this kind. Nearly always, however, the effusion progresses for some time. It is here that the physician can be of great service." Some clinicians having advocated the recumbent position, Heidenhain[129] refers to several

[127] Preston: Maryland Med. Jour., July 29, 1903.
[128] Browning: *Loc. cit.*
[129] Heidenhain: Berl. klin. Woch., Bd. xxvii, S. 126, 1890.

instances in which the placing of this position had been followed immediately by aggravation. Osler, Tyson, Bramwell[130] and others all recommend venesection, the latter stating that it is contraindicated when the pulse is feeble, rapid or irregular, the heart dilated and weak, and the patient very old and debilitated. As illustrated by a case reported by Benham,[131] it tends furthermore to arrest convulsions, which, owing to the intense vascular tension accompanying them, must increase greatly the cerebral effusion. The value of the measures outlined above are further suggested by the fact emphasized by Grasset[132] that "whatever may be the pathogenic theory regarding apoplexy, it is essentially characterized by a congestive condition of the head and by circulatory erethism."

A purgative aids the remedial process by further depleting the vascular system. By causing, moreover, congestion of the intestinal vessels, it acts as a derivative besides insuring the elimination of substances capable of causing autointoxication. Two drops of *croton oil* mixed with a little glycerin or olive oil, dropped on the back of the tongue, or $^1/_4$ grain (0.016 gm.) of *elaterium* dissolved in a little water in the same manner are usually employed with advantage. An *enema* of lukewarm water is also useful. A hot *foot-bath* also serves a good purpose as a derivative.

By this time the patient has received all the truly useful attention he requires. Counterirritation to the neck serves only to irritate him by increasing his discomfort. The ice-bag placed on his head to meet the popular notion on the subject only serves to contract the peripheral vessels and increase in proportion the internal pressure—while affording a second source of discomfort.

As in the premonitory stage, all stimulants and tonics, including particularly strychnine, digitalis and the iodides, should be avoided, as they all tend to raise the blood-pressure.

It is often necessary to relieve the bladder by means of the catheter.

Measures to Aid the Process of Resolution.—When the *reaction* sets in, the fever is a protective phenomenon—an effort of the organism to rid the brain of the hæmorrhagic coagulum and of what detritus has accumulated around it. *Trephining* has been used with success to remove a meningeal clot, but a clot in the deeper tissues is usually beyond reach. *Potassium iodide* is usually given at this stage in the hope of hastening the absorption of the clot, but, like digitalis, it increases the vascular tension in the usual therapeutic doses, and, therefore, exposes

[130] Bramwell: Treatment, July, 1897.
[131] Benham: Brit. Med. Jour., Mar. 21, 1896.
[132] Grasset: Méd. moderne, vol. ix, p. 1, 1898.

the patient to another stroke. It is preferable to allow the physiological resources of the body to act without interference on our part.*

Whittaker[133] writes in this connection: "Certain lymph cells, phagocytes, begin at once to remove the obstruction, and cells which incorporate blood-corpuscles are seen as early as the third day. Dürck found on the eighteenth day free pigment, and nothing but pigment on the sixteenth day."

When the period of *resolution* has set in, however, much may be done to prevent the development of paralysis.

We have seen that the cerebral lesions are located in the brain proper, the source, therefore, of voluntary impulses, the spinal system *per se,* governed by the pituitary body and the source of involuntary, *i.e.,* automatic impulses, remaining whole.* The loss of voluntary stimuli does not mean, however, that the spinal system has lost its control over the muscles of the paralyzed side, or that the vasomotor supply through which the muscles are nourished is the least impaired.* It only means that the strictodilator nerves which incite function in certain muscles no longer receive *one* of the two kinds of stimuli which they are in the habit of receiving through the intermediary of the cord, *i.e.,* the *voluntary* from the impaired area of the organ of mind, in contradistinction to the *automatic* from the somatic brain, the pituitary body.* Even this may be reduced to a mere question of quantity as far as the vasa vasorum (which, when constricted, cause the arterioles they nourish to dilate and admit more blood into the muscular elements) are concerned, since all impulses to them, whether originally derived from the brain or from the spinal cord, serve but one purpose, namely, to provoke their constriction.*

Such being the case, paralysis finally occurs, merely because the muscles are *allowed* to degenerate through deficient use.* It would be prevented to a great extent, and perhaps altogether in some cases, were measures to do so initiated as soon as the patient has recovered from the immediate effects of the paralytic stroke.

The reader is referred to the sixteenth chapter for evidence to the effect that all somatic functions, including intricate muscular movements, can be performed independently of the brain. Not only do extensive injuries of the hemispheres—the crow-bar case, for instance—fail

* *Author's conclusion.*
[133] Whittaker: *Loc. cit.*

to impair muscular activity, but even their entire removal as in so high a mammal as the dog, will fail to do so. This has been shown by Goltz's animal, which lived eighteen months after both lobes and a part of the optic thalami had been removed. That timely measures are useful is shown by the following lines of Browning's:[134] "Recently a German writer has done good service by calling attention to the importance, in these cases, of doing everything to bring activity again into the patient's nerve tracts. He shows that by rousing these persons, lifting them—when not too feeble—into a sitting position, getting them once more interested in life; further by *exercising actively* and *semi-passively* the *paretic muscles*, we can save the patient from *further degeneration* that so often ensues and may effect great gain. To the value of this principle I can heartily subscribe. Ere beginning this plan, however, we must wait until the danger of immediate relapse is past—say, usually until the end of the first week or ten days." The practical side of the question thus sustains the explanation I submit.

An important practical point in this connection is that the vitality of muscles can be preserved reflexly, and enhanced when defective, by massage. The latter should be begun as soon as possible, therefore, avoiding much pressure. The muscles of the trunk, especially the trapezius, should not be overlooked in this connection. Passive movements should follow the massage, taking care to give each member exercise in the line of its usual functions. Thus, the fingers should be gently flexed and unflexed upon the hand, and separated and approximated; the arm likewise at each joint, and rotated, etc. After the massage and passive motion, the patient should attempt to repeat the same motions voluntarily. He will be aided in this not only by the temporary increase of nutrition which the previous procedures will have brought about, but also by the fact that the *somatic* brain is able to supply, when movements are alone in order, impulses which strikingly recall those projected by the organ of mind.*

Interpreted from my standpoint, manipulations such as those practiced by osteopaths and masseurs promote nutrition of the structures thus treated by enhancing reflexly the propulsive activity of the arterioles through the sympathetic, and aid materially thereby the restoration of function.

When the patient is able to go about, he should be treated as a case of arteriosclerosis—a condition quite amenable to treatment in a large proportion of cases.

Many highly accomplished men, including Samuel Johnson, have lived many years of usefulness after an attack of apoplexy. As to disability, Whittaker refers to the fact that Schmidt "described 39

* *Author's conclusion.*
[134] Browning: *Loc. cit.*

cases of cerebral lesion in which no sign of brain affection could be demonstrated during life," these cases constituting one-third of all of local lesions which came to autopsy during eight years in Eichhorst's clinic.

DIABETES MELLITUS.

SYNONYM.—*Glycosuria.*

Definition.—There are two forms of glycosuria: (1) *Diabetes Mellitus,* due to hyperactivity of the adrenal system, and (2) *Asthenic Glycosuria,* due to hypoactivity of the adrenal system.*

Diabetes mellitus, an excessive excretion of sugar and urine, is due to hypersensitiveness of the test-organ, and to the presence in the blood of waste-products or other irritating substances which keep this organ, and through it the adrenals, overactive. An excess of adrenoxidase is thus produced, and the intrinsic metabolism of all tissues is correspondingly activated. The pancreas being thus caused to secrete, besides its other ferments, an excess of amylopsin, the hepatic and muscular glycogens are converted into sugar with unusual rapidity, and the surplus of sugar formed is eliminated by the kidneys.*

Symptoms.—The onset of diabetes mellitus is insidious, and any one of its symptoms may appear first. As a rule, however, the earliest phenomena observed are unusual thirst and dryness of the mouth and pharynx, and viscidity of the saliva. Polyuria may either appear concurrently or be the first symptom observed, the excretion of urine being increased to a daily quantity varying from 6 to 30 pints or more, the urine itself being pale and acid, and having a specific gravity varying from 1020 to 1040, or even higher. It contains from $^1/_2$ to 5 per cent. or more of sugar (glucose), the daily excretion of which may vary from one ounce to as much as two pounds. Stains on the linen or on the shoes or clothing, where drops of urine happen to fall, prove on analysis to be sugar.

The patient may sweat profusely under the influence of slight exertion or during moderately warm weather, or his skin may be dry or more or less harsh owing to deficient perspiration. Pruritus may cause considerable suffering, especially in women, owing to involvement of the meatus urinarius and the labia.

* *Author's definition.*

The gums may become spongy and the teeth show an unusual proclivity to caries; recession of the gums is also apt to occur in these cases and render the teeth liable to fall out. The tongue is often red, dry and glazed; the breath may have a peculiar odor recalling that of apples. Excessive appetite is a common symptom, though the patient gain no weight or even lose flesh and grow weaker.

These symptoms may appear in rapid succession and the case remain a benign one—at least for a time—or they may develop very slowly, constituting a chronic case.

As the disease progresses, *complications* may occur. Neuritis, especially of the brachial and crural nerves, is frequently observed. Gangrene may be readily produced by what under normal conditions would prove to be trifling injury or disorder, an abrasion, a boil, etc.; it is apt to begin in an extremity, especially the toes, and to extend upward. Gastrointestinal disorders are frequently observed, consisting of indigestion with pyrosis and gastralgia, constipation and flatulence, or diarrhœa. The odor of the breath changes to an unpleasant one, suggesting that of vinegar or stale beer. The patient at this stage is especially prone to intercurrent diseases, especially those of the respiratory tract, tuberculosis, pneumonia, bronchitis, etc. Carbuncles are frequently observed in the course of the disease and promptly assume an alarming aspect.

In *advanced cases* the temperature, though not materially affected early in the disease, may become subnormal. The tendon reflexes are, as a rule, diminished. Symptoms recalling those of tabes, the so-called "diabetic tabes," may occur, with "steppage" gait and paralysis of the extensors. Atrophy of the optic nerve, cataract and other disorders of vision may appear, both eyes being affected simultaneously. The other organs of special sense may likewise become impaired. Impotence, sterility and abortion are common complications, as is also interstitial nephritis.

Diabetic coma occurs in advanced cases, usually as a fatal complication. It is often preceded by general malaise, irritability, vertigo, anxiety, constipation with abdominal and muscular cramps. Conversely, it may occur suddenly with special premonitory symptoms, the patient lapsing into unconsciousness,

with the eyes half closed, the respiration sighing, the pulse rapid and weak. The temperature, at first somewhat above normal, gradually declines, cyanosis appears, the precursor of death, which ensues usually between twenty-four and forty-eight hours after the onset of the coma. Death from coma occurs, however, in less than half of the cases of diabetes.

Diabetes mellitus, as here understood, begins in sthenic and more or less vigorous subjects.*

Pathogenesis and Pathology.—Diabetes mellitus is due to excessive irritability of the test-organ and to the presence in the blood of waste-products, stimulating drugs, poisons, toxins, etc., which cause this organ to react inordinately owing to its oversensitive condition. By thus provoking an excessive production of adrenal secretion, these agents excite hyperoxygenation of all organs, including the pancreas.* As this organ (its islands of Langerhans) supplies a ferment, amylopsin, which on reaching the muscles through the intermediary of the leucocytes,* and the liver by way of the splenic vein,* converts the glycogen of all these organs into sugar, a larger quantity of the latter is produced than usual, and the excess is promptly excreted by the kidneys.* Hence the presence of a more or less great quantity of sugar in the urine, the excess voided over and above the normal ratio being proportionate with the degree of hyperactivity of the adrenal system.*

In the first volume of this work (Jan., 1903)[135] I concluded, after submitting evidence to that effect, that toxic glycosuria was "primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar." In the present volume[136] I pointed out that diseases of the anterior lobe of the pituitary body (the seat of the adrenal center) attended by hyperæmia or hypernutrition provoked glycosuria, and that the adrenal center was the so-called "glycogenic center." This term applies, interpreted from my standpoint, only in connection with the *abnormal* production of sugar, for I regard the vagus center as the true "glycogenic center" in the sense that it adjusts the conversion of glycogen to the physiological needs of the body at large, by regulating simultaneously the functions of the pancreas and the liver. The production of glycosuria by stimulation of the adrenal center accounts (1) for the fact that Blum, Herter, Croftan and others produced this symptom by injecting adrenal extract; (2) for the cessation of toxic glycosuria when, as observed by Claude Bernard, Kauffmann and others, the splanchnics—which contain the nerves from the adrenal center to the adrenals—were severed; (3) for

* *Author's conclusion.*
[135] *Cf.* vol. i, p. 366
[136] *Cf.* this vol., p. 1021.

the recent observation of André Mayer[137] that after extirpation of the adrenals Claude Bernard's puncture no longer provoked glycosuria; and (4) for the rapid diminution of sugar both in normal glycæmia and glycosuria, when, as observed by Kauffmann, the inferior vena cava—to which the adrenal secretion is carried by the adrenal veins—was ligated. As all these observations had remained unexplained before I had shown the functional relationship between the pituitary body and the adrenals, they now stand as evidence of the correctness of my interpretation.

As the adrenal system includes the thyroid gland, thyroid extract should also cause glycosuria. This fact was not only observed by Ewald in 1894 and by many observers since, as we have seen in the seventeenth chapter and as shown below, but Lorand found that it was even more active than adrenal extract in this particular.

The "internal secretion" referred to in the text only means, according to the current view, the substance secreted by the islands of Langerhans as distinguished from the pancreatic juice secreted externally, *i.e.*, in the intestinal canal. The manner in which this substance reaches the liver, however, has not been shown. In the first volume[138] I suggested that the sugar-forming ferment passed out of the pancreas with its venous blood *into the splenic vein;* that it met in the latter the internal secretion (nucleo-proteid derived from broken-down leucocytes) of the spleen, which rendered it active, and then passed to the portal system, where it converted glycogen into sugar. Additional evidence to this effect is available in the literature on the pathogenesis of glycosuria; a small part of which only can be submitted here.

We owe to Mering and Minkowski[139] the view that the pancreas produces an internal secretion which governs carbohydrate metabolism and to Laguesse[140] the demonstration that the islands of Langerhans were the source of this secretion—both of which conclusions have been repeatedly sustained, especially by Schäfer's[141] independent researches. But Laguesse[142] concluded, moreover, that the secretion-granules of the islands, at least in the embryo, were carried away by the blood-vessels. This applies to the developed islands as well, since they also are deprived of ducts. My own conclusion that it is carried to the splenic vein not only affords the only normal path for the internal secretion to the liver, but it explains also why ligation of the pancreatic duct, while causing disuse-atrophy of the rest of the pancreatic parenchyma, leaves the islands of Langerhans practically unharmed, thus showing that their functions are not arrested. Indeed, as shown by Ssobolew[143] in the guinea-pig, rabbit, cat and dog, the islands persisted 400 days, *i.e.*, until all the vital activity of the glands had ceased. Moreover, the atrophy of the gland elements did not modify carbohydrate metabolism; it only became impaired when the entire gland, including therefore the islands of Langerhans, had been extirpated.

Conversely, Arthaud and Butte[144] arrested glycosuria by ligating the veins of the pancreas, which open, as is well known, into the mesenteric and splenic veins. This result (although the observers mentioned in no way refer to the possibility of an internal secretion such as that suggested by myself twelve years later) proves conclusively that it is through its veins that the internal secretion which provokes glycosuria enters the circulation and through it the liver.

[137] André Mayer: Arch. gén. de méd., July 17, 1906.
[138] *Cf.* vol. i, pp. 367 *et seq.*
[139] Mering and Minkowski: Arch. f. exp. Pathol., Bd. xxvi, S. 371, 1889.
[140] Laguesse: C. r. de la Soc. de biol., 9 série, vol. v, p. 819, 1893.
[141] Schäfer: Lancet, Aug. 10, 1895.
[142] Laguesse: *Loc. cit.*
[143] Ssobolew: Virchow's Archiv, Bd. clxviii, S. 91, 1902.
[144] Arthaud and Butte: C. r. de la Soc. de biol., 9 série, vol. ii, p. 59, 1890.

As to the participation of a splenic internal secretion in the glycogenic process, I must refer the reader to the first volume[145] for details, in which its action upon trypsinogen is studied, and which applies to the carbohydrates as well. Referring to the investigators and the researches I mention therein, Hammarsten[146] says: "Such a 'charging' of the pancreas by the spleen has been repeatedly suggested by Schiff, and his statements have not only been confirmed by these recent investigations, but in part also explained." He also states, however, that this is caused "in a still unknown manner by a body whose nature is unknown."

We thus have for the conversion of glycogen into sugar a triad composed of the blood's adrenoxidase and nucleo-proteid from the spleen which, by their interaction, supply the heat-energy required to activate the pancreatic proferment amylopsinogen, to which the conversion is due, the three forming, in reality, the compound* now known as amylopsin.

Several drugs in common use are capable, in sufficiently large doses, of provoking glycosuria: adrenal extract, which causes it indirectly by enhancing the oxygenation of the pancreas; thyroid extract, which initiates the same process by stimulating the adrenal center; strychnine, mercury and other drugs, which also stimulate the adrenal center, but less vigorously.*

Various diseases, the pathogenic agents of which cause marked stimulation of the adrenal center,* may also provoke glycosuria. These include pertussis, measles, varicella, diphtheria, enteric fever, epilepsy, convulsions and malaria, and diseases such as gout and rheumatism, but only during exacerbations of adrenal activity caused by an accumulation of toxic wastes in the blood.

We have seen that adrenal extract readily provokes glycosuria. Thyroid extract, which acts much as does the thyroid secretion itself, by stimulating the adrenal center, was found to produce marked glycosuria by W. Dale James[147] in the case of a physician who had taken thyroid for a psoriasis of old standing. The sugar disappeared when the use of the drug was discontinued. Similar cases have been observed by Ewald,[148] Lorand and other clinicians. Georgiewsky[149] found that in dogs the use of fresh thyroid gland as food, or of the expressed juice by injection, produced a glycosuria which sometimes reached as much as 17 per cent., and which disappeared when the thyroid was no longer given. Strychnine was found to cause glycosuria by Claude Bernard, Schiff and many others; Demant[150] showed that it caused the hepatic glycogen to be rapidly reduced. Langendorff[151] observed, moreover, that extirpation of the liver prevented strychnine glycosuria. The clinical use of mercury was also found to bring on glycosuria by Reynoso, Rosen-

* *Author's conclusion.*
[145] *Cf.* vol. i, pp. 367 *et seq.*
[146] Hammarsten: "T. B. of Physiol.," p. 323, 1904.
[147] W. Dale James: Brit. Jour. of Dermat., June, 1894.
[148] Ewald: Deut. medizinal Zeitung, S. 669, 1894.
[149] Georgiewsky: Centralbl. f. b. med. Wissen., Bd. xxxiii, S. 465, 1895.
[150] Demant: Zeit. f. physiol. Chemie, Bd. x, S. 441, 1886.
[151] Langendorff: Arch. f. Physiol., Suppl. Bd., S. 269, 1886.

bach, Bouchard and others. Handfield Jones[152] noted, moreover, that mercury caused marked hepatic hyperæmia. Phloridzin glycosuria is likewise due to marked stimulation of the adrenal center. The fact that it is accompanied by excessive metabolism is shown by Cartier's[153] statement that "all authors who have studied phloridzin unite in saying that the animal experimented upon becomes voracious, and, if not overfed, rapidly wastes."

As to the causative influence of various diseases, Charrin and Carnot[154] produced diabetes by injecting diluted culture of bacillus pyocyaneus. Thomson, of Glasgow,[155] in a study of a large number of cases, found a large excess of sugar in children suffering from pertussis, epilepsy and convulsions, and a slignt increase in cases of varicella, variola, enteric fever and peritonitis. Teschemacher[156] observed a case of measles in which the urine contained 4 per cent. of sugar. Mossé, Charles Blanc and others[157] observed it in cases of intermittent fever. Strümpell,[158] Dyce Duckworth[159] and many others refer to gout as a cause of transitory glycosuria.

In a large proportion of the cases met with, the glycosuria is due to the presence in the blood of an excess of normal physiological waste-products. These, by overstimulating the adrenal center, produce glycosuria in the same manner as thyroid extract and the other agents referred to above.*

The accumulation of these poisons is principally due to the ingestion of food in excess of the body's needs; excessive work is thus imposed upon the adrenal system and through it upon the pancreas.* Overeating becomes more active as a cause of glycosuria when, in addition, the blood is simultaneously being deprived, by the free use of alcohol, of some of the excess of oxygen the immunizing overactivity of the adrenal system is providing.* Hence, the fact that diabetes is usually observed in vigorous subjects who are large eaters, many of whom partake freely of alcohol.

All conditions which impose excessive wear and tear upon the body, prolonged overexertion, mental or physical, worry, anger,—which are all attended by an excessive production of toxic wastes—may also provoke diabetes through the same morbid process.*

This involves the conclusion that in this class of cases general metabolism must be correspondingly excessive. Lépine[160] states that it

* *Author's conclusion.*

[152] Handfield Jones: Cited by F. Cartier: Thèse de Paris, 1891.
[153] Cartier: *Ibid.*, p. 15.
[154] Charrin and Carnot: C. r. hebd. des séances de la Soc. de biologie., 10 série, vol. i, p. 438, 1894.
[155] Thomson: Glasgow Hosp. Rep., vol. ii, p. 324, 1900.
[156] Teschemacher: Berl. klin. Woch., Bd. xxix, S. 33, 1892.
[157] Mossé, Charles Blanc, and others: Cited by Verneuil: Semaine méd., vol. viii, p. 386, 1888.
[158] Strümpell: Berl. klin. Woch., Bd. xxxiii, S. 1017, 1896.
[159] Dyce Duckworth: Lancet, Aug. 5, 1893.
[160] Lépine: Semaine médical, vol. xvii, p. 279, 1897.

is a positive fact that in many cases of diabetes there is exaggerated destruction of nitrogen, a fact now generally recognized. Tyson[161] also says that the "urea is almost invariably increased," and considers as one of the causes of this symptom "the ingestion of large amounts of nitrogenous food, whether to appease the appetite or by the physician's advice."

A. Lorand, of Carlsbad,[162] also holds that diabetes is due to the fact that "people are taking more food, especially carbohydrate food, into their bodies than they can burn." As interpreted from my standpoint, it is the attempt to destroy the excess of wastes that this entails which causes glycosuria, the conversion of glycogen into sugar, glycosuria being in reality but one of the phenomena indicating that excessive metabolism is in progress.

The morbid influence of alcohol is illustrated by cases studied by Strauss of von Noorden's clinic[163] in which glycosuria followed the use of a mixed diet after a drinking bout. In one patient, who had lost the tendency to glycosuria after a carbohydrate diet without sugar, the glycosuria could be made to return by administering alcohol. Strümpell had already shown that alcohol favored the appearance of alimentary glycosuria.

The influence of physical strain, such as that caused by long tramping, is shown by five cases reported by Hoppe-Seyler,[164] in which rest caused the glycosuria to disappear. Gobbi[165] made a similar observation in eight runners who, before the race, had no sugar in their urine. Other instances of this kind have been reported. Mitra[166] states that diabetes is four times more prevalent in Bengal than elsewhere, and that it is practically limited to hard-worked professional men, officials and students. Bolye Chunder Sen[167] had already emphasized that while the country Hindoos were comparatively free from the disease, the proportion was large among the brain workers. Worms[168] found that among scientists and others leading intellectual pursuits, the proportion of diabetics was 10 per cent. in Paris, where, as shown by Bertillon, the mortality from diabetes had almost doubled between 1883 and 1892. Worms observed that the condition of diabetics was aggravated by worry.

The development of pathological changes in the organ which bears the brunt of the morbid process, the pancreas, occurs late in the history of the case. It is merely overworked, and is able to meet the needs of the stress imposed upon it. Glycosuria cannot, therefore, be attributed primarily to disease of the pancreas in this form of diabetes.* After a more or less prolonged period of overwork,* however, this organ begins to show morbid changes, though previously, and notwithstanding the presence of considerable sugar in the urine, and all the typical symptoms of diabetes, it had shown none whatever.

The general trend of the pathological process is a general

* *Author's conclusion.*

[161] Tyson: "Practice of Medicine," third edition, p. 804, 1903.
[162] A. Lorand: Vermont Med. Monthly, Feb. 15, 1906.
[163] Strauss: Berl. klin. Woch., Bd. xxxvi, S. 276, 1899.
[164] Hoppe-Seyler: Münch. med. Woch., Bd. xlvii, S. 521, 1900.
[165] Gobbi: Riforma medica, Apr. 29, 1905.
[166] Mitra: Indian Med. Record, May 20, 1903.
[167] Bolye Chunder Sen: Indian Med. Gazette, July, 1893.
[168] Worms: Bull. de l'Acad. de méd., 3 série, vol. xxxiv, p. 109, 1895.