degeneration of the pancreas, and more particularly as regards the glycosuria of the islands of Langerhans.

The first step is a general engorgement of the capillaries, which may be sufficiently marked in the more advanced cases to be accompanied by hæmorrhage, especially in the islands of Langerhans, in which these small vessels are extremely thin. The capillary walls then undergo hyaline degeneration, which gradually invades the islands and destroys them. In some cases, however, these structures become granular and undergo necrobiosis. Both these morbid processes may proceed to an advanced stage in the islands of Langerhans without involving the rest of the gland, or the latter may undergo atrophy and be replaced by fatty tissue. The local changes may also lead to a cirrhosis in which the secreting structures of the gland, as well as the islands of Langerhans, are gradually enmeshed in a fibrous network and obliterated.

The islands of Langerhans are the structures of the pancreas which yield first under the excessive stimulation to which the latter organ is subjected. Thus, a case of diabetes may proceed to a fatal termination through gradual degeneration of the islands and the other glandular elements be found normal after death. Moreover, these glandular elements may be profoundly diseased and no glycosuria occur.

Important in this connection is the fact that disease of the pancreas is not the cause of diabetes, as believed by many, and that the pancreatic lesions are due to overstimulation of this organ.*

As stated by R. H. Fitz,[169] the existence of pancreatic diabetes is established, but disease of the pancreas does not necessarily cause diabetes. Of 29 cases from the Massachusetts General Hospital that showed lesions of the pancreas, glycosuria was found in but 2, although in 12 cases there were no records of tests for sugar. The investigations of E. L. Opie[170] have thrown considerable light upon this problem. He not only pointed out that extensive lesions of the ordinary secretory structure with escape of the islands of Langerhans are unattended by diabetes, but also that destruction of the latter structures alone concurred with this disease. This is emphasized by the following details of an autopsy of a diabetic negress aged 54 years. The pancreas weighed 80 grammes, was soft and of a gray-yellow color. Almost every island of Langerhans showed microscopically a homogeneous material that stained with eosin. This substance at times lay in the midst of groups of cells, but was usually in contact with the walls of the capillaries penetrating the island, or next the peripheral fibrous tissue, and was, therefore, usually between the remaining cells and the capillary walls. The cells of the island were, in large part, replaced, so that between the hyaline particles only an occasional compressed fusiform or irregular nucleus could be seen. The hyaline metamorphosis was strictly limited to the islands of Langerhans, the glandular acini remaining intact. In this pancreas, therefore, a lesion of obscure etiology had destroyed the islands of Langerhans, while those of the secreting acini, as well as those of other organs, were unaffected. The association of diabetes mellitus affords convincing proof that the islands of Langerhans are intimately connected with the glycogenic metabolism.

The fact that the pancreatic lesions are not the *original* cause of glycosuria, however, is shown by the many cases observed in which pancreatic lesions were either slight or absent. Thus, M. B. Schmidt[171] in 23 autopsies of diabetics found the pancreas entirely normal in 8 instances. It showed evidences of slight inflammation in 7, while in the rest there was either: *acute* interstitial inflammation, *chronic* interstitial inflammation or *hyaline* degeneration, which—from my viewpoint—represent steps of the degenerative process, followed in sufficiently vigorous cases by a reparative fibrosis. A. E. Finney[172] was also led to conclude, by a comprehensive study of the subject, that "diabetes may occur in the absence of demonstrable lesion in the islands of Langerhans." He also found that the injection of adrenalin chloride in the guinea-pig produced—besides general phenomena and hyperæmia of other organs—a peri-acinous engorgement of the pancreatic capillaries, the typical lesion to be expected in a condition brought about through excessive activity of the adrenal system.

* *Author's conclusion.*
[169] R. H. Fitz: Yale Med. Jour., Mar., 1898.
[170] E. L. Opie: Jour. of Exper. Med., Mar. 25, 1901.

There is, in the light of my views, as previously stated, another form of glycosuria, *asthenic* glycosuria, due to insufficiency of the adrenal system caused by poisons and diseases that *depress* the functional activity of either of its three organs, and thus lower oxygenation in the body at large.* The functions of the pancreas being inhibited thereby, overactivity of the islands of Langerhans plays no rôle in the pathogenesis of this stage.* This subject is treated below under a separate heading.

Treatment.—AGENTS WHICH REDUCE THE HYPERSENSITIVENESS OF THE ADRENAL CENTER.—If, as I would urge, diabetes mellitus is clearly differentiated from the form I describe below as pathogenically a totally different disease, it may be said that we possess a specific for each of these two affections.* Indeed, the test-organ and the adrenal center being overactive in diabetes mellitus, the remedy which suggests itself is that which serves physiologically in the body to subdue the functional activity of these organs,* namely, *arsenic.* That this remedy has proven of great value in a large proportion of cases

* *Author's conclusion.*
[171] M. B. Schmidt: Münch. med. Woch., Bd. xlix, S. 51, 1902.
[172] A. E. Finney: Med. Chronicle, June, 1903.

is well known. The cause of its failure and of the harmful effects occasionally observed are accounted for, on the other hand, by the fact that it was given in cases of asthenic glycosuria, in which, as shown under the next heading, the adrenal mechanism is already markedly depressed.* In what might be termed sthenic diabetes, the form described above, however, it is of great value;* *Fowler's solution* may be given in 3-drop doses in a glassful of water during each meal, the dose being gradually increased until the first signs of the physiological effects of the drug appear, when it should be somewhat reduced. The object should be to keep the test-organ depressed until the excess of sugar disappears from the urine, and then to adjust the subsequent use of the remedy to this end.*

Louis Lewis[173] ascribes the origin of the arsenic treatment of diabetes to Salkowski, who discovered that in animals poisoned by arsenic no artificial diabetes could be produced, either by puncture of the fourth ventricle or curare. Here the arsenic had evidently paralyzed the adrenal system and thereby the pancreatic functions. No amylopsin being produced, glycosuria failed to occur. Arsenic has been highly recommended by Dujardin-Beaumetz,[174] Jaccoud[175] and other authorities. Tyson[176] states that "after opium, arsenic has longest maintained its reputation as a remedy in diabetes," and that it seems to him that "there is something more than a simple tonic action in it."

Unfortunately, the patients become rapidly accustomed to the use of arsenic, and to offset this drawback, other agents having the same physiological action are indicated for a time. In some cases, the use of a different preparation of arsenic, the *bromide of arsenic, i.e.,* Clemens's solution, (administered in the same way as Fowler's, the dose being, on the whole, reduced one-third) suffices.* In others, the change does not affect the situation. The *sodium* or *strontium bromide* in 15-grain (1 gm.) doses on retiring, increased if necessary, and taken in a glassful of water, may then be used for a time—not more than a couple of weeks—then gradually reduced, while simultaneously the course of arsenic, beginning with 5 drops of Fowler's solution, is resumed.* When it becomes necessary again to withdraw the arsenic, *chloral hydrate* or *chloralamid* may be employed instead of the bromides or in conjunction with these salts, reducing the dose of each in proportion.* If the sugar in the urine can be

* *Author's conclusion.*
[173] Louis Lewis: Med. World, Oct., 1888.
[174] Dujardin-Beaumetz: Bull. gén. de thérap., vol. cxvi, p. 241, 1889.
[175] Jaccoud: Méd. moderne, vol. ix, p. 108, 1898.
[176] Tyson: *Loc. cit.*, p. 815, 1903.

kept down with smaller doses of these depressants, such doses should, of course, be used.*

It is obvious that the administration of any "tonic," "alterative," or "chalybeate," as recommended by some authors, must compromise the results.*

All these remedies have been used empirically for some time, as is well known. That they have been highly recommended by some and condemned by others is not strange, in view of the fact that while beneficial in sthenic glycosuria (diabetes), they are harmful in the asthenic form.

Drugs which Tend to Reduce Excessive Tissue Metabolism.—Remedies which, by exciting the sympathetic center only, but sufficiently to cause constriction of the arterioles, naturally reduce the volume of the blood supplied to all organs through their capillaries, and the intrinsic metabolism of these organs.* It is to this property that *opium* and *morphine* owe their beneficial effects.* A small dose of morphine, $^1/_8$ grain (0.008 gm.), may be given twice daily, then three times daily. The dose is then increased to $^1/_6$ grain (0.01 gm.) once in the day instead of the corresponding dose, then twice in the day, etc., the dose being increased and regulated according to the proportion of sugar in the urine. The danger of morphinism may, to a certain extent, be reduced by substituting *codeine* for a time, beginning with $^1/_4$ grain (0.016 gm.) of the sulphate (not the phosphate, the preparation most used) three times daily. Opium or morphine, which are well borne by diabetics, are preferable, however; they diminish hunger because they reduce tissue waste by lessening the quantity of adrenoxidase admitted to the tissue-cells; they also cause a marked reduction of the sugar excreted, because the tissue carbohydrates, especially those of the muscular elements, are not as rapidly consumed.* The bowels should be kept open by means of *saline aperients;* the simultaneous free use of *Carlsbad water,* which contains sodium sulphate, bicarbonate and chloride, often suffices for this purpose, besides tending to preserve the blood's alkalinity.

Tyson states that "the only drug that can be relied upon to produce an effect in diminishing glycosuria is opium." Shoemaker[177] writes: "Opium is, perhaps, the most efficient drug which we possess in the treatment of this disorder. It diminishes hunger and thirst, the quan-

* *Author's conclusion.*
[177] Shoemaker: "Materia Medica and Therapeutics," sixth edition, p. 691, 1906.

tity of urine excreted, and the amount of sugar eliminated. The progress of the disease is checked and the condition of the patient ameliorated. Large doses are required and well-borne in diabetes mellitus."

If, for some reason, opium or its preparations cannot be continued, or given at all, *antipyrin and acetanilid* may be used instead, the initial dose being 10 grains (0.6 gm.)—with equal parts of sodium bicarbonate, three times daily, gradually increased if the sugar does not show a marked fall. We have seen that the effects of these coal-tar products are similar to those of opium, *e.g.*, they stimulate the sympathetic center and provoke constriction of all arterioles.* Another remedy which acts similarly is the *sodium salicylate* in doses varying from 10 to 15 grains (0.6 to 1 gm.) three times daily, but this remedy presents a drawback: it excites the test-organ sufficiently to counteract, at least partly, its beneficial effects.*

Antipyrin has been highly recommended by Dujardin-Beaumetz, Huchard, Robin and others. The first-named clinician noted that omission of the drug caused prompt recurrence of the sugar of the urine, both of which had been greatly reduced. Opitz[178] found antipyrin of great value also in cases of long standing. He gave 10 grains (0.6 gm.) t.i.d. and increased the dose by 5 grains (0.3 gm.) daily until 30 grains (2 gms.) were taken t.i.d., if necessary. The latter dose seems excessive, but it is generally recognized that these patients, as a rule, require large doses. The sodium salicylate introduced by Ebstein is mentioned because it has been found beneficial in some instances. I have never used it.

Agents which Increase the Alkalinity of the Blood.—An important feature of this disease is the steady loss of the mineral constituents. Hence the fact that the blood's alkalinity is always low. When this condition is allowed to proceed, the acetone bodies accumulate in the blood, acetone, diacetic and oxybutyric acids appearing in the order named, according to the stage of the disease. Appearance of the two latter means that the patient is exposed to diabetic coma, owing mainly to the irritating influence of these two acids upon the kidneys. Now, sodium bicarbonate is known to offset and prevent coma, especially when given with large quantities of fluid. This is due mainly to the fact that, besides neutralizing the acids, the osmotic properties of the body fluids are restored to their normal condition, and that the catabolism of sugars and fats, as well as that of proteids, can be carried to a finish.* We should not wait,

* *Author's conclusion.*
[178] Opitz: Deut. med. Woch., Bd. xv, S. 646, 1889.

therefore, until these acids accumulate in the blood to utilize alkaline salts.

In the early stages, the use of an alkaline *mineral water* as a usual beverage (of which the patient usually partakes in large quantities), and the addition of an extra amount of *common salt* in his food suffice to preserve the normal osmotic properties of his blood—and, therefore, to insure adequate catabolism of sugars and fats,—thus preventing the formation of the pathogenic acids.* This process is aided materially by the free use of *green vegetables,* which are rich in potassium salts. In more advanced cases the addition of *sodium bicarbonate,* 20 grains (1.3 gms.) twice daily, dissolved in one glassful of the mineral water used, affords the additional alkalinity required. Or, *Vichy water,* the chief constituent of which is sodium bicarbonate, may be used as usual beverage.

The marked loss of mineral constituents by diabetics has been emphasized by Robin,[179] who found that the coefficient of demineralization sometimes attained 30 to 40 per cent. He found, as I have, that the patient fares better if encouraged to drink alkaline waters. Orlowsky[180] ascertained that the administration of alkalies increased the alkalinity of the blood and of its plasma to an appreciably higher degree than in healthy individuals.

Diet.—With hyperactivity of the test-organ and its adrenothyroid center as the direct factor in the overproduction of sugar, the prevailing method of depriving the patient of starches and sugars is unscientific.* The morbid process being an *excessive* consumption of these substances in the body at large, including the hepatic glycogen, their withdrawal from the food can have but one effect, viz., to place at the mercy of the amylolytic triad of the blood what carbohydrates remain in the tissues.* The body is thus depleted, as far as possible, of physiological components of the highest importance to its welfare. The sugar in the urine naturally diminishes, and may even disappear, but this does not prove in the least that the disease is counteracted; it only shows that the patient has been drained effectively of his main sources of muscular energy and heat. Nor does the meat diet to which the patient is relegated even protect him against the renal complications feared, since glycosuria is known frequently to persist under such a diet and to promote the appear-

* *Author's conclusion.*
[179] Robin: Revue de thérap. méd-chir., vol. lxx, p. 397, 1903.
[180] Orlowsky: Vratch, vol. xxxii, pp. 1193, 1222, 1901.

ance of acetonuria and acidosis. That abstention from starches, sugar, etc., is harmful under such conditions is shown by the fact that the restoration of carbohydrates often causes both acetonuria and acidosis to disappear.

But one carbohydrate, *usually wheat flour,* need, as a rule, be abstained from. Again, a large excretion of sugar occurs because the test-organ and its adrenothyroid center are hypersensitive.* The indications, therefore, in sthenic diabetes, are to seek the offending carbohydrate, forbid it, and reduce the total diet, in order to diminish as much as possible formation of *wastes which sustain the irritability of the test-organ.** Moreover, the diet should be varied, to avoid the presence in the blood of a relatively large proportion of any one waste. It is important to watch the urine for acetone and diacetic acid, which tend to bring on diabetic coma. Reduction of fats, the addition of a little bread, and sodium bicarbonate 15 grains three times daily, will, as a rule, cause the danger signals to disappear.

The true position of the dietetic measures usually recommended is well exemplified by Croftan's statement[181] that "with the introduction of calorimetric methods into the treatment of diabetes a new danger has arisen, viz., the substitution of a modern ultrascientific routine for the old-fashioned and venerable, but altogether unscientific, routine of feeding every diabetic on a diet containing no starches or sugars." Stark[182] also wrote recently: "A rigid exclusion of sugars and starches in the treatment of diabetes is a thing of the past, nor do we often find it necessary to exclude them permanently from the menu of diabetes. On the contrary, we often substitute carbohydrates for fats in cases of marked acetonuria. . . . . As a matter of fact, the organism actually requires for its maintenance carbohydrates for the repair and growth of its tissues, and for the production of heat and muscular force. This necessity for carbohydrates is so emphatic that directly they are prescribed the system draws upon the nitrogenous element of food to supply the missing component." As to the influence of meat, Croftan states that "in many cases it is well known that the sugar excretion only stops when the amount of meat is considerably reduced. Further, it can be shown that withdrawal or reduction of meat appreciably increases the tolerance of carbohydrates." He urges, moreover, that "the chief danger incident to complete withdrawal of carbohydrates is . . . *acidosis and coma,*" and also that "it is surprising how often the administration of a little carbohydrate in cases that are on a rigid diet, or of some more carbohydrate in cases that are receiving only small quantities of carbohydrate will cause all these dangerous phenomena to disappear." A lugubrious commentary upon the true meaning of all these facts is suggested by the case of a man in the last stages of the disease observed by Lépine, to whom sugar was granted owing to his hopeless condition, and who . . . . . began to improve. This suggested honey as an

* *Author's conclusion.*
[181] Croftan: Therap. Gaz., Apr. 15, 1906.
[182] Stark: Med. Record, Sept. 23, 1905.

appropriate food, *i.e., mel* in diabetes *mellitus.* The fallaciousness of the whole dietetic treatment based on old lines is emphasized by another method of which Hare[183] says: "Although potatoes are *eminently a starchy food,* recent investigations indicate that it is perhaps the best form of starch which can be taken by the diabetic." Mossé, who advocated this method, recommends that 2 or 3 *pounds* daily of this "eminently starchy food" be taken by the patient.

Finally, the Hindoos and all vegetarians should show an enormous proportion of diabetics were the prevailing doctrine true. A Hindoo physician of wide experience, Bose,[184] states that the Jams, who are great starch and sugar eaters, and the Sadhoos, Jogees, and Chowbays of Muttra, who live upon sweets, do not suffer from diabetes. This does not mean that diabetes is not observed in India. A suggestive fact asserts itself in this connection, however: the patients live much longer in India, because, owing to their aversion for meat, they *cannot* be placed upon the "sugar- and starch-free diet."[185]

In the treatment of these cases, the following course is recommended: (1) Forbiddance of the offending carbohydrate, with reduction of diet and use of some plain alkaline mineral water: Ballardvale, Londonderry Lithia, etc.; (2) second week, arsenic added. If at the end of the third week the sugar is not reduced very considerably, acetanilid on retiring (besides preceding indications) and Vichy adopted as usual beverage.*

ASTHENIC GLYCOSURIA.

SYNONYMS.—*"Toxic" Glycosuria,* but only as to depressing poisons (arsenic, chloral, etc.); *"Traumatic," "Shock"* and *"Fright" Glycosurias; "Diabetes Decipiens;" "Conjugal Glycosuria;" "Diabète Bronzé"* of the adrenal type; *"Diabète Maigre"* or *"Emaciating Diabetes."*

Definition.—A form of glycosuria due to poisons, diseases, traumatisms, shock, fright and other conditions which depress the functional activity of the test-organ or of the adrenothyroid and sympathetic centers of the pituitary body, and, therefore, the functional activity of all organs, including the pancreas. The secretory functions of this organ being inhibited, the formation of glycogen is correspondingly reduced, and the food carbohydrates which should be utilized in this function are directly converted into sugar in the alimentary canal and absorbed as such. Being unsuited for utilization by the tissues, this sugar is eliminated by the kidneys.**

* *Author's conclusion.*
** *Author's definition.*
[183] Hare: "Practice of Medicine," p. 810, 1905.
[184] Bose: Brit. Med. Jour., Feb. 2, 1895.
[185] Editorial: The Antiseptic (Madras), Dec., 1905.

I find it impossible to avoid introducing the name "asthenic glycosuria." The term "toxic glycosuria" is sometimes employed to distinguish the form due to poisons from true diabetes mellitus. In the light of my views, however, it is faulty, since it includes two pathological processes which are not only distinct, but antagonistic. Thus, while strychnine and mercury provoke toxic glycosuria, by *stimulating* the adrenal system, arsenic, antimony, etc., bring it on by *depressing* the same system. Again, while the drugs which stimulate this system ultimately give rise to lesions similar to those observed in diabetes mellitus, those which depress it lead to organic changes of a special character, *i.e.*, those of arrested nutrition and atrophy. The term "asthenic" glycosuria seems to me not only to embody the essential feature of an autonomous morbid process, but also to suggest the appropriate line of treatment.

Aliméntary glycosuria is not included in this form, since it may be produced through both hyper- and hypoactivity of the adrenal system.

Symptoms and Etiology.—While in the sthenic form, *i.e.*, diabetes mellitus, described in the preceding section, the type of patient is usually one indicating vigor and overactivity, in the asthenic form the opposite is the case.* The patient may be bulky and *obese,* but of the type denoting clearly general torpor and low vital activity. He may also be *thin,* delicate and anæmic, a class in which hypochondria and melancholia sometimes occur concurrently.

In the first volume[186] I advanced the view that there was also a form of diabetes due to insufficiency of the adrenal system and concluded[187] that "the glycosuria following extirpation of the pancreas is due to the action of the ptyalin upon food-starches." The latter conclusion was based on experiments by Aldehoff, Minkowski, Chittenden and Griswold, and von Mering and the well-known fact that, as stated by Howell,[188] "saliva or preparations of ptyalin act readily on boiled starch, converting it into sugar and dextrin." That amylopsin carries on, both in the intestine and elsewhere, the conversion of starches and glycogen into sugar is well known. The sugar produced, therefore, may be derived from that produced through the action of ptyalin and amylopsin, or directly—and mainly in asthenic glycosuria—from sugars ingested.

Howell also says,[189] referring to diabetes: "In severe forms of this disease, all the carbohydrate material of the food appears in the urine." That leucocytes take up food-stuffs from the intestine has been emphasized both in the first volume and the present one. In a recent paper, Pavy[190] states that he had[191] "adduced evidence to show that at the seat of absorption in the alimentary canal the carbohydrate is assimilated by synthesis into proteid through the instrumentality of the lymphocytes of the villi."

* *Author's conclusion.*
[186] *Cf.* vol. i, p. 365.
[187] *Cf.* vol. i, p. 418.
[188] Howell: "T. B. of Physiol.," p. 679, 1905.
[189] Howell: *Ibid.*, p. 733.
[190] Pavy: Lancet, May 5, 1906.
[191] Pavy: "Carboh. Metab. and Diabetes," London, 1906.

Further evidence to the effect that the explanation I furnish of the pathogenesis of the asthenic form of glycosuria is sound, is afforded by the manner in which it harmonizes with the results of experimental observation, Lépine,[192] Bédart,[193] Thiroloix[194] and others having found that glycosuria did not follow removal of the pancreas in dogs deprived of food several days. The cause of this becomes obvious when the sugar is derived directly from the food-stuffs, as removal of the organ typifies, in the pathology of the disease, advanced organic changes in the pancreas. Lancereaux first pointed out in 1877 that the *diabète maigre* with which the asthenic type corresponds is invariably accompanied by pancreatic lesions. Saundby in his Bradshaw lecture[195] states that "in all typical cases of emaciating diabetes," the pancreas was in a shrunken state, and that they showed microscopically hyaline change and fibrosis. That general nutrition should be impaired under these conditions is self-evident. As de Dominici[196] says: "Destruction of the pancreas inevitably induces dystrophy of the organism in virtue of the absence of the very important functions of this organ in digestion, and in virtue of the absence of the substances that the pancreas produces, which regulates the equilibrium of metabolism."

That when the functions of the pancreas are inhibited by removal of this organ, glycosuria is produced, is well known. Minkowski found, and his results were confirmed by Hédon,[197] that when a fixed quantity of sugar was administered to animals after their pancreas had been removed, the sugar obtained from the urine was increased precisely in proportion with the quantity ingested. These and other experiments of a similar kind, clearly show that, as in the advanced stage of diabetes, the sugar eliminated is derived from the food and not from hepatic or tissue glycogen.

Adapting these facts to the forms I include under the term "asthenic glycosuria," we are brought to realize that hypoactivity of the adrenal system, *i.e.*, of the test-organ and the center through which it influences the adrenals and the thyroid—the adrenothyroid center—or of the thyroid and parathyroid glands; or of the adrenals or of the nerve-paths connecting any of these organs with one another—and whether due to organic lesions or to functional impairment of any of these structures—must, in turn, depress the secretory activity of the pancreas through the deficiency of adrenoxidase, and produce asthenic glycosuria by materially reducing the volume of amylopsin formed.

The diabetes ascribed to *syphilis* belongs to this group, and is apt to appear during the first four years, and in the course of the secondary and tertiary periods.* The so-called conjugal diabetes is, in reality, due to sexual transmission of the disease; the glycosuria of hereditary syphilis is also to be regarded as asthenic glycosuria.*

The glycosuria of alcoholism and influenza is essentially asthenic in character.* This applies as forcibly to the form observed in *neurasthenia* and after *cerebral hæmorrhage,* and,

* *Author's conclusion.*
[192] Lépine: Lyon médical, vol. lxxvii, p. 335, 1894.
[193] Bédart: Le midi médical, Aug. 12, 1894.
[194] Thiroloix: C. r. hebd. des séances et mém. de la Soc. de biol., 10 série, vol. i, p. 297, 1894.
[195] Saundby: Birmingham Med. Rev., vol. xxviii, p. 129, 1890.
[196] De Dominici: Gazz. d. Osped., vol. xxiv, Pt. i, p. 620, 1903.
[197] Hédon: Arch. de physiol. norm. et pathol., 5 série, vol. v,, p. 154, 1893.

obviously to the glycosuria of *senility*, and that due to excessive or too prolonged *lactation*.* In individuals who, in one way or another, show the landmarks of *gout*, glycosuria is also asthenic in character, while this fact becomes self-evident in the *diabète bronzé* in which more or less advanced adrenal lesions are found, and which present many of the symptoms of Addison's disease.* *Shock* is another cause of this form of glycosuria, which may be attended by all the phenomena of diabetes, including a more or less rapid loss of flesh. *Grief, worry* and *exhaustion* may engender asthenic glycosuria, while anger and violent excitement may incite the sthenic type.*

An important form of asthenic glycosuria is that due to *traumatism*. In this class of cases sugar may appear as early as six hours after the receipt of the injury; but, as a rule, it begins in from eight to twelve hours. If it appears soon it is apt to be temporary, *i.e.*, to disappear within ten days. The interval between the accident and the appearance of sugar usually includes shock phenomena, more or less weakness, pallor, hypothermia, etc. This is followed by somnolence in some and insomnia in other cases, and leading at times to melancholia and other psychical disorders, especially in head injuries, which give rise to glycosuria oftener than others. Acetone and acetic acid are very rarely found in traumatic glycosuria except when it becomes permanent, and even then only when the case is advanced. Albumin, however, is always present.

The principal poisons which produce asthenic glycosuria in the same way are arsenic, antimony, curare, nicotine and the salts of uranium nitrate.*

A number of agents provoke the same functional inefficiency of the pancreas, and, therefore, asthenic glycosuria, indirectly.* Thus alcohol produces it by deoxidizing the blood; chloroform, ether and other anæsthetics, by reducing the intake of oxygen; amyl nitrite, chloral and chloralamid, by relaxing the arterial system and depleting the capillaries, including those of the pancreas; and, finally, morphine—a frequent cause of glycosuria—and caffeine, which, by causing marked constriction of the arterioles, reduce the quantity of blood admitted to all organs, including the pancreas.*

* *Author's conclusion.*

That syphilis is a cause of glycosuria is familiar to every one. Ord[198] and Trollet,[199] however, emphasized the fact that it occurred with relative frequency during the third stage—that attended by the greatest adynamia. Tchistiakoff[200] found also that the urine presented no other abnormal constituent. This serves to differentiate asthenic glycosuria from that of diabetes in which phosphoric acid, etc., and other evidences of exaggerated metabolism are present.* Again, as suggested by Trollet, such cases account for the so-called "conjugal diabetes," which thus becomes conjugal syphilis with diabetes as a normal consequence. Schnee,[201] moreover, has traced it to inherited syphilis. Suggestive also is the fact that this form of diabetes promptly yields to antisyphilitic treatment, *i.e.*, to mercury and the iodides—both most powerful adrenal stimulants, and which, therefore, most vigorously counteract the asthenia.* Stress was not only laid on this fact by Seegen, Servantie, Tchistiakoff, Decker[202] and others, but the last-named observer found that recovery ensued without modifying the diet.

As stated by Ebstein,[203] obesity, gout and diabetes are closely related, and any two or all three of them may be present in the same person. Hirschfeld[204] not only observed this close relation between obesity and diabetes, but also that obese people showed sugar after a meal containing a fairly large quantity of sugar. In the concomitant presence of obesity and gout we have evidence of deficient metabolism, and in the post-prandial glycosuria a strong probability that the sugar is derived directly from the food-starches.

The concurrence of glycosuria with neurasthenia has been frequently observed by Landon Carter Gray.[205] Influenza, a disease in which general neurasthenia is marked, may also be followed by severe glycosuria, as observed by Magelson,[206] Holsti,[207] Broadbent[208] and others. In the latter observer's case, which was already of three years' standing when reported, there was weakness and abolition of the knee reflex.

As to drugs, arsenic, which, we have seen, is an efficient remedy in true diabetes, is a pernicious agent in asthenic glycosuria. Claude Bernard, Saikowski, Quinquaud and Masoin[209] all found that it was even capable of preventing the glycosuria produced by puncture of the bulb. Latham[210] first reported cases of glycosuria caused by arsenic. The reason for this is plain, when we recall that arsenic is the physiological antagonist of the thyroid secretion. That alcohol can cause glycosuria is generally recognized. As emphasized by Sandras and Bouchardat, however, large doses are required. Von Noorden[211] considers chronic alcoholism a prominent cause. Chloroform was found by Winterstein[212] to reduce in animals the intake of oxygen; Ebstein[213] observed a very great aggravation in a practically cured case through the use of chloroform as an anæsthetic. Bendix gave dogs large quantities of grape

* *Author's conclusion.*

198 Ord: Brit. Med. Jour., Nov. 2, 1889.
199 Trollet: Thèse de Paris, 1905.
200 Tchistiakoff: Wratch, Nos. 4, 5, 1894.
201 Schnee: Inter. klin. Rundschau, Sept. 20, 1888.
202 Decker: Deut. med. Woch., Bd. xv, S. 944, 1889.
203 Ebstein: *Ibid.*, Bd. xxiv, S. 693, 1898.
204 Hirschfeld: Med. News, Jan. 28, 1898.
205 Gray: Med. Record, May 12, 1894.
206 Magelson: Med. News, Oct. 10, 1891.
207 Holsti: Zeit. f. klin. Med., Bd. xx, S. 272, 1892.
208 Broadbent: Lancet, Sept. 15, 1894.
209 Claude Bernard, Saikowski, Quinquaud and Masoin: Cited by Cartier: *Loc. cit.*
210 Latham: "Facts and Opinions Concerning Diabetes," London, 1811.
211 Von Noorden: Berl. klin. Woch., Bd. xxxvii, S. 1117, 1900.
212 Winterstein: Cited by Bendix: Centralbl. f. Stoffw. u. Verd. Krankh., Bd. iii, S. 149, 1902.
213 Ebstein: *Ibid.*

sugar, but found none in their urine; a similar experiment followed by chloroform anæsthesia, caused the appearance of glycosuria in all the animals. Similar experiments with morphine led to identical results. This agent was found by Eckhardt[214] to readily provoke glycosuria; F. Cartier[215] states that from 0.03 to 0.06 gm. (½ to 1 gr.) never fails to produce it in the rabbit; he refers to a case of Gilbert's in which morphinomania gave rise to continuous glycosuria. The other drugs mentioned as causes are represented by desultory cases in literature.

Pathogenesis and Pathology.—The disorders, diseases or poisons which provoke asthenic glycosuria include those which greatly depress the functional activity of the test-organ, the adrenothyroid center, or any of the organs of the adrenal system; or those of the vascular centers: the sympathetic and vasomotor.* The oxygenation of the blood or the access of the blood to the various organs being impaired, their functions and nutrition are correspondingly inhibited.* The pancreas being included among the organs thus affected, its output in ferments—including the active agent in the conversion of glycogen to sugar, amylopsin—is greatly diminished.* The pancreas is reduced, therefore, as far as its functions are concerned, to the condition which prevails in the advanced stage of diabetes mellitus.* While in the latter disease the pancreas is destroyed organically through excessive intrinsic metabolism, in asthenic glycosuria it may be only functionally paralyzed, owing to inadequate oxygenation and local hypometabolism.*

The sugar originates, therefore, as may be the case in advanced diabetes, directly from the sugar ingested or from food-starches, the conversion occurring in the alimentary canal. This sugar, being taken up by the digestive leucocytes, is unloaded by these cells in the intercellular spaces, but being in excess of the needs of the tissues, the surplus is carried by the lymph-stream to the blood.* The glycolytic property of this fluid enables it to destroy a part of this sugar, but the bulk of it, to prevent hyperglycæmia, is promptly excreted by the kidney.

The presence in some cases of bronzing, as in Addison's disease, *i.e.*, the diabète bronzé of Hanot and Chauffard (1882), clearly points to adrenal insufficiency. Their opinion that cirrhosis of the liver is always present has been invalidated in recent years, Abbott,[216] Murri,[217] Rabé[218] and others having reported cases in which it did not prevail.

* *Author's conclusion.*
[214] Eckhardt: Beiträge z. Anat. u. Physiol., 1877.
[215] F. Cartier: *Loc. cit.*
[216] Abbott: Jour. of Path. and Bact., Dec., 1900.
[217] Murri: Med. Woche, Mar. 24, 1902.
[218] Rabé: Presse méd., vol. ix, p. 183, 1902.

Auscher, Gilbert, Opie, Chauveau and Kauffmann and others have met the issue by considering the glycæmia as a simple complication of hæmochromatosis. But the cause of the latter phenomenon was left unanswered. This answer is afforded, however, by inhibition of the adrenal functions. Not only is bronzing caused, as is well known, by such a condition in Addison's disease, but we have seen that removal of these organs produced hæmochromatosis, and as shown by the experiments of Boinet, a general invasion of the whole organism by bronze pigment. The adrenals themselves may be involved in the process, as shown by cases reported by various observers. In a case of diabetes reported by Kuhn[219] coinciding with cancer of the breast, the right adrenal was found to be the seat of metastasis. Barth,[220] de Massary[221] and many other observers have reported cases of glycosuria in which bronzing was present. Lépine[222] observed a marked case of diabetes and hyperglycæmia in which the right adrenal was the seat of a large sarcoma. Mimi[223] observed a typical case in a woman whose entire body, except the soles and palms, was bronzed.

In keeping with this class of cases are the many in which lesions of the sympathetic paths and ganglia are present, thus interrupting the impulses from the pituitary body to the adrenals. Thus, Saundby[224] refers to 4 cases in which the semilunar ganglia were found diseased. Thiroloix, Sandmeyer,[225] Cavazanni[226] and others have since reported cases in which the sympathetic structures were deeply involved.

Myxœdema, interpreted from my standpoint,[227] is the typical syndrome of failure of the adrenal system. Talbot Jones,[228] in a clinical paper, concluded over ten years ago, that "there are striking pathological analogies between true diabetes and myxœdema," and that "in the latter disease, success has also attended both injections and thyroid grafting—a success achieved not only in animals, but also in man." That the two conditions may occur simultaneously is shown by 2 cases reported by A. Gordon[229] in brothers, in both of which thyroid extract proved highly beneficial. Conversely, we have seen by the cases of Ewald and Strasser that when glycosuria does not exist in such cases it may be brought on by giving thyroid extract, *i.e.*, by stimulating too vigorously a torpid adrenal center.* This involves an important distinction when treatment is to be instituted. We will see that it is only in the asthenic type that thyroid extract is indicated, and that as observed by Murrell[230] "its administration should be maintained just as in myxœdema."

The asthenic glycosuria due to traumatism is the result of concussion of the *sensorium commune, i.e.*, the aggregate of highly differentiated centers of the posterior pituitary, of which the sympathetic center is the most sensitive.* As a result of this concussion and the general shock it entails, the vessels are

* *Author's conclusion.*
[219] Kuhn: Münch. med. Woch., Bd. xlix, S. 103, 1902.
[220] Barth: Bull. de la Soc. anat., vol. lxii, p. 560, 1888.
[221] de Massary: *Ibid.*, vol. lxx, p. 594, 1895.
[222] Lépine: Revue de méd., vol. xxvi, p. 537, 1906.
[223] Mimi: Rev. crit. de clin. méd., Mar. 16, 1901.
[224] Saundby: *Loc. cit.*
[225] Sandmeyer: Münch. med. Woch., vol. xxxviii, p. 309, 1891.
[226] Cavazanni: Centralbl. f. allg. Pathol. u. pathol. Anat., Bd. iv, S. 501, 1893.
[227] *Cf.* vol. i, p. 174 *et seq.*
[228] Talbot Jones: Med. Record, May 23, 1896.
[229] A. Gordon: Amer. Medicine, Feb. 6, 1904.
[230] Murrell: Med. Press and Circular, Dec. 14, 1898.

relaxed, and, blood accumulating in the larger vessels and depleting the capillary system, the functions of the pancreas and liver, among other organs, are inhibited.* Traumatic glycosuria may be temporary, but it may also persist and ultimately terminate the patient's life, owing mainly to gradual atrophic degeneration of the pancreas similar to that observed in asthenic glycosuria due to other causes.*

Injuries may also, by causing concussion of the pituitary body and inhibition of what functional activity a diseased pancreas may still retain in an advanced case of diabetes,* hasten the fatal termination of that case.

That general concussion—including the most delicate centers of the organism, those of the pituitary body—should attend traumatisms is suggested by the general asthenia observed in such cases. The prominence of nervous phenomena, which has caused this form of glycosuria to be included among the traumatic neuroses, points in the same direction. Ebstein,[231] in reporting a case of fatal diabetes due to a general concussion received during a railway accident, concluded after a comprehensive study of the subject, that "numerous cases recorded in medical literature show that between trauma and diabetes, as well as between trauma and functional disturbances of the nervous system, there exists a causal relation." If we were dealing with cerebral concussion, mental phenomena should develop at once in every instance; but such is not the case. The unconsciousness of shock is due to depletion of the cerebral vessels, somnolence likewise, melancholia to hyponutrition—all conditions which bring us back to the sympathetic center. We have seen also that in acromegaly all disorders of sensibility are traceable to the neural lobe of the pituitary body. As stated by Bernstein-Kohan,[232] after a study of 45 cases, disturbances of sensibility are frequently observed in cases of diabetes following injury. That fatal diabetes may occur without injury of the bulbar centers is illustrated by a case of Vogel's mentioned while discussing a paper by Ziemssen[233] in which it followed the fall of a beam on the neck. The glycosuria which appeared a few weeks after the injury was ascribed to concussion of the spinal cord, though no lesions were found in this organ or in the medulla. That its governing center, the pituitary body, should have borne the brunt of the shock seems logical in view of the fact that the slightest irritation of this organ, as shown by the experiments of Cyon and Masay,[234] will bring about widespread vascular phenomena.

It is generally impossible to assert that sugar was not present in the urine before the injury was received. Loisnel[235] reported a case, however, in which the urine had been examined—owing to a slight gastric disorder—with negative result, two months before the injury, a fall on the back, was received. Within a few weeks after the latter, glycosuria developed and the patient died of diabetic coma two months later. In such a case the slow—and many of the same kind are available in literature—process of hyaline degeneration and fibrosis of true diabetes has no time to occur.

* *Author's conclusion.*

[231] Ebstein: Deut. Archiv f. klin. Med., Bd. liv, S. 305, 1895.
[232] Bernstein-Kohan: Thèse de Paris, 1891.
[233] Ziemssen: Münch. med. Woch., Bd. xxxvi, S. 17, 1889.
[234] Cyon and Masay: *Cf.* this vol., p. 983.
[235] Loisnel: La normandie médicale, vol. vii, p. 145, 1891.

The entire history of such cases points to shock and inhibited function and nutrition. Suggestive in this connection is the fact that traumatisms of the head are more frequently followed by glycosuria than when located elsewhere. In Bernstein-Kohan's series of 45 cases, 25 were due to head injuries. Higgins and Ogden,[236] in a study of 212 reported cases of traumatism of the head, found that glycosuria had been present in 20.

Asher[237] and other authors place the spine and sacral region immediately after the head. Shock, asthenic and inhibited function are well exemplified by one of von Gadden's[238] cases, a fall on the head—there was extreme weakness and emaciation. Immediately after the fall, the patient suffered from intense thirst, and his urine contained 7 per cent. of sugar.

That shock and inhibited function are also the pathogenic factor in true diabetes is also shown by recorded cases. Spitzer,[239] for example, instances a woman who had suffered from diabetes for five years, and who developed coma three hours after fracturing her clavicle; sodium bicarbonate administered in large doses did not prevent a fatal issue. Litten[240] reported the case of a diabetic who fell and bruised his testicle; some days afterward he developed acute digestive symptoms, and died of coma ten days after the accident.

Fright usually causes but a temporary glycosuria. Lorand,[241] however, reported two cases which proved fatal: one in a woman of 35 years, who had been well before the fright was experienced. Weakness appeared the same day; polyuria and glycosuria (7 per cent.) five days later, followed by death in one year. The second occurred in a girl of 16 years, also in perfect health before the fright. Soon afterward gastric disorders and emaciation occurred and her urine ultimately showed 8 per cent. of sugar. The case proved fatal in a few months.

The history of these cases clearly points to the nature of the morbid process. As stated by Herter[242] in respect to the glycosuria following head injuries, it must be assumed either that the pancreas is also involved, or that the circulation in the liver has been permanently changed in such a way that no carbohydrate can be stored. Interpreted from my standpoint, the *central* shock impairs the nutrition of the pancreas, and its functions being inhibited, the alimentary starches are directly converted into sugar and eliminated precisely as is the case after removal of the pancreas.

It is in this form of glycosuria that the pancreas is often found free from lesions post-mortem, while in the cases of relatively prolonged duration, the organ presents all the evidences of atrophy.

The absence of lesions of the pancreas in cases of diabetes has led Hansemann[243] to classify them separately. As such a group would contain cases of incipient diabetes as well as cases of asthenic glycosuria, such a subdivision is not desirable. Nevertheless, it emphasizes the fact that glycosuria is often unaccompanied by pancreatic lesions. William-

[236] Higgins and Ogden: Boston Med. and Surg. Jour., Feb. 28, 1895.
[237] Asher: Vierteljahresschrift f. gericht. Med. u. Sanitätswesen, Bd. viii, S. 219; Bd. ix, S. 1, 1895.
[238] von Gadden: Friedreich's Blätter f. gerichtl. Med. u. Sanitäts-Polizei, Bd. 1, Hft. 1, 1899.
[239] Spitzer: Deut. med. Woch., Bd. xxvi, S. 756, 1900.
[240] Litten: Soc. méd intern. de Berlin, Apr. 29, 1901.
[241] Lorand: St. Petersb. med. Woch., Jahrg. xxviii, S. 223, 1903.
[242] Herter: Med. Record, Feb. 9, 1901.
[243] Hansemann: Zeit. f. klin. Med., Bd. xxvi, S. 191, 1894.

son[244] in a series of 15 cases in which autopsy was performed with especial care, macroscopically and microscopically found the pancreas normal in 7 instances and the seat of simple atrophy in 2. In 23 autopsies mentioned by M. B. Schmidt[245] the pancreas was normal in 8 and markedly atrophied in only 1 instance. Mollard[246] also reported a case of wasting diabetes in which the pancreas was found in a perfectly healthy condition.

Treatment.—That the indications in asthenic glycosuria should be precisely the converse of those of the sthenic type, diabetes mellitus, is now self-evident.* We have, therefore, practically a specific in *thyroid gland* irrespective of the cause of the asthenia.* Even the concussion of the delicate centers of the sensorium commune is counteracted by this agent, since the increase of thyroidase it insures promptly increases sensibility, while by stimulating the test-organ and the adrenal center, it promotes general oxygenation, including that of the depressed centers.* It may be given in 1 grain (0.06 gm.) doses of the desiccated gland, three times daily, increased to 2 grains (0.13 gm.) doses if necessary, whatever be the cause of the asthenia.*

The use of thyroid gland in glycosuria has been practically abandoned, owing to the fact that it increased the excretion of sugar in many instances. The reason for this is self-evident in the light of my views: it was used empirically, and as the majority of cases of glycosuria are of the sthenic type, the trouble was aggravated. In true asthenic cases, however, it is quite effective. Thus, Lépine[247] obtained marked improvement in the case of an obese patient, although at first the sugar increased. In a case due to shock, in which considerable loss of flesh and the typical symptoms of diabetes were present, Murrell[248] obtained marked benefit from thyroid, but its use had to be persisted in as in myxœdema. Under its use health was maintained, though the patient "did not diet herself." J. McNamara[249] found that thyroid extract was able to cause disappearance of the sugar in such cases, several of which he had had occasion to treat. He concluded that, inasmuch as there was diminution of fat, the thyroid produced its beneficial effects by promoting metabolism.

A striking confirmation of the value of adrenal stimulants in a class of cases which can only be of the asthenic type* is afforded by the recognized efficiency of *potassium iodide* in some cases, especially those clearly traceable to syphilis. An important distinction is necessary here, however. We have seen that large doses, by sensitizing the depressor nerve, inhibit the functions of the pituitary body and of the thyroid apparatus.* The

* *Author's conclusion.*

[244] Williamson: Lancet, Apr. 14, 1894.
[245] M. B. Schmidt: *Loc. cit.*
[246] Mollard: Lyon médical, vol. lxvi, p. 239, 1891.
[247] Lépine: Semaine médical, vol. xviii, p. 497, 1898.
[248] Murrell: Med. Press and Circular, Dec. 14, 1898.
[249] J. McNamara: Lancet, July 18, 1903.

best effects are obtained in asthenic glycosuria by giving small doses of iodide, namely 5 grains (0.3 gm.) in a glassful of water after meals, and gradually increasing the dose until 10 grains (0.6 gm.) are administered in the same manner.* The *biniodide of mercury* is preferable when the centers require more active stimulation, $^1/_{16}$ grain (0.004 gm.) three times daily, carefully watched, to prevent salivation.*

The statement in text-books that iodine or the iodides should not be given after meals because it forms an iodide of starch with that contained in bread, vegetables, etc., is not sustained clinically. I have seen iodism caused by one-drop doses of pure iodine thus given. The value of the iodides in the syphilitic form of diabetics requires no evidence. This applies as well to the use of mercury, which, as is well known, increases promptly the functional activity of the pancreas (by increasing general metabolism, I would add), the end in view.

The diet should in no way be reduced in such cases, unless some carbohydrate, whether starch or sugar, be found to sustain the glycosuria, the aim being to enhance the vital process. Tonics are in order, especially *strychnine* and *quinine*, which stimulate both the vascular and adrenal centers.* The *desiccated adrenal gland* (*glandulæ suprarenales siccæ* of the U. S. P.) is very effective in these cases. The best results are obtained when the diagnosis of asthenic glycosuria has been carefully established, by giving the *thyroid gland*, 1 grain (0.06 gm.) *adrenal gland*, 2 grains (0.13 gm.) and *strychnine*, $^1/_{40}$ grain (0.00165) together in a capsule, during, *i.e.*, in the middle of each meal.

* *Author's conclusion.*