temperature rises more rapidly and to a higher point than the rectal temperature." Obviously the bath inhibits for a time the elimination of heat and thus provokes a temporary fever, which, like all febrile processes, serves to destroy the pathogenic element.*

Buisson's own case hardly warrants the diagnosis of rabies; but instances of unmistakable rabies in which the Buisson method was successfully employed were observed by Leon Petit, Hermance, Cameron, Gray and others.[325] Some of these used the Turkish bath; but as Kellogg says: "The temperature of both the rectum and the axilla rises much more quickly in the vapor-bath than in the Turkish or dry hot air bath." Others apply the cold-sheet after the vapor-bath; but this imposes upon the patient an unnecessary hardship, and drives the blood into the deeper vessels, including neural capillaries. The longer blood is kept in the peripheral capillaries, the longer, of course, the virus and the spasmogenic autotoxins will be exposed to the blood's proteolytic action.

Measures Which Control Spasm.—Here, again, the measures recommended for the corresponding stage of tetanus are indicated, but only when their use is necessary to arrest the spasms or reduce their violence while the blood's auto-antitoxin, augmented by either of the remedies mentioned, is counteracting the paralyzing influence of the virus.* The latter is in reality the death-dealing agent in rabies, and to destroy it should be our aim.* The bromides, chloral and kindred drugs being themselves paralysants,* *amyl nitrite* inhalations are preferable, though the former cannot be dispensed with, as a rule.

A ten-per-cent. solution of *cocaine hydrochlorate* sprayed, not into the mouth, where it is wasted owing to great amount of saliva secreted, but into the nasal cavities as far back as possible, suggests itself as a valuable adjuvant to prevent paroxysms.* It trickles down the post-nasal cavities and the pharyngeal wall and by anæsthetizing the superficial sensory terminals of the latter, inhibits the intense reflex irritability so manifest in this region.*

Osler[326] recommends the local application of cocaine, but the quantity of saliva in the mouth and the irritability of the pharynx render this measure very difficult. Free spraying into the nose while the patient is in the recumbent position is readily accomplished.

* *Author's conclusion.*
[325] Cited by Shepard: *Loc. cit.*
[326] Osler: "Practice of Medicine," third edition, p. 229, 1898.

CHAPTER XXV.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

PAIN-CAUSING DISORDERS DUE TO HYPOACTIVITY OF THE ADRENAL SYSTEM.

Balfour[1] wrote a few years ago, referring to the pathogenesis of gout: "With all our increased accuracy in details, it does not appear that our ideas of what gout really is are any clearer or any better defined than those of our forefathers." If anything, the obscurity surrounding this question may be said to have become greater, more recent investigations having overthrown those which ten years ago seemed of great promise. Even these modern products of the laboratory evidently rest upon a very weak foundation, for Graham Lusk in a recently published work[2] (1906), closes a review of purin metabolism in gout with the suggestive remark that "present-day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries." In truth, the labor that physiological chemists have devoted to this subject, though fruitful as to valuable experimental facts, has remained sterile as to final results, and will continue to do so because they persist in ignoring the cardinal functions of the adrenal secretions in metabolism and in the life process itself, where their work has proven as futile. Indeed, Lusk also writes[3] in this connection: "However clearly formulated the laws of metabolism may be, and many of them are as fixed and definite as are any laws of physics and chemistry, still the primary cause of metabolism remains a hidden secret of the living bioplasm." It is only by a broad and generous conception of all available lines of knowledge that we can ever hope to solve these great problems which, as we have already seen, involve several of the scourges of mankind.

[1] Balfour: Edinburgh Med. Jour., June, 1898.
[2] Graham Lusk: "The Elements of the Science of Nutrition," p. 287, 1906.
[3] Graham Lusk: *Ibid.*, p. 297.

In the present chapter I propose to show, not only that the internal secretions, as I interpret their functions, play a dominant rôle in the pathogenesis of gout, but also in two other painful disorders closely allied to this disease, migraine and neuritis, including neuralgia.

GOUT AND GOUTY DIATHESIS.

SYNONYMS.—As to GOUT: *Podagra.* As to the GOUTY DIATHESIS: *the Gouty Habit; Uricæmia; Lithæmia.*

Definition.—The *"gouty diathesis"* is a chronic disorder of metabolism, due to inability of the adrenal system to insure, through its active agent, the auto-antitoxin (leucocytic and plasmatic), the conversion of food nuclein into harmless, eliminable end-products. This inability may be actual, *i.e.,* due to hypoactivity of either of the organs of the adrenal system; or passive, these organs, though normal, being unable to provoke the formation of sufficient auto-antitoxin to insure catabolism of the excess of wastes with which the lymph and blood are burdened when overeating is indulged in. In either case the blood contains more or less toxic wastes of the purin type, which incite the various disorders usually ascribed to the gouty diathesis.*

Acute gout is the indirect result of an exacerbation of chronic interstitial nephritis due, in turn, to the presence in the blood of wastes which aggravate this renal disease. The free excretion of the sodium salt of uric acid, sodium biurate, being prevented, its crystals accumulate in great part in the joints, owing to the absence in their synovia, under normal conditions, of auto-antitoxin and phagocytes. The acute attack is incited by a local inflammatory process which entails the presence of these defensive agents and the conversion of sodium biurate into simpler products, especially urea, to facilitate their excretion. If this process is imperfectly carried out, the sodium biurate accumulates about the joints, forming tophi.*

Symptoms and Pathology.—An attack of acute gout is generally preceded by *premonitory symptoms, i.e.,* disorders of digestion, anorexia, flatulence, foulness of the tongue, vertigo, irritability—or the converse, mental torpor and drowsiness—palpitations with a tense, hard and sometimes irregular pulse,

*Author's definition.

obstinate constipation, irritative cough, tinnitus aurium, muscular cramps, neuralgia, perversions of sensation, especially at the extremities, chilliness, etc. Any of these symptoms may occur in groups which may be said to vary with each case, each sufferer having, so to say, his own set of precursory signs. These usually cease, however, immediately before the onset of the acute attack; in fact, the patient may feel unusually well.

These phenomena do not always culminate in an attack of gout; they are the expression of a condition which has been termed *lithæmia, uratæmia, uricacidæmia, uricæmia,* etc., which may appear as readily in subjects who have never suffered from acute gout, as in those who have. In the former, however, the symptoms are less marked: the tense, hard pulse is replaced by a slow pulse, and irritability with depression of spirits, gastric disorders with marked acidity and nausea, constipation, vertigo and throbbing headache, constitute the symptom-complex in the average case. Eczema and other cutaneous disorders, hay-fever, migraine, asthma, pharyngitis, and many other disorders have been ascribed to lithæmia.

The onset of the *acute attack* usually occurs at night, the patient being awakened by a very intense pain in the metatarsophalangeal joint of the great toe. Other articulations, those of the great toe of the other foot, the fingers, knees, elbows, etc., may then become involved in the morbid process. Any of these joints may be the seat of the initial attack, especially if previously injured. The affected joint becomes the seat of great tension and throbbing, and the excruciating pain is still further intensified by the slightest touch or motion. After a few hours, *i.e.,* towards dawn, relief is experienced, and the patient, after perspiring freely, is able to sleep. Some pain is experienced during the succeeding day, when the affected joint is found swollen, shining, tense and very tender. The acute pain only recurs the following night and thereafter each succeeding night, with daily remissions, until the attack passes off.

During the acute attack, the temperature is somewhat raised, *i.e.,* 100° to 102° F. (37.8° to 38.9° C.) and the pulse likewise from 80 to 100. In the affected joint, however, the opposite is the case, the temperature being considerably lower than that of the body at large, sometimes as much as 6° F.

(3.3° C.). Though thirst is usually marked, anorexia and even aversion for solid foods are often correspondingly great. There is nausea, rarely accompanied by vomiting, and, as a rule, constipation. The urine presents almost typical changes: it is scanty, acid and highly colored, its specific gravity being high. Uric acid and urates are precipitated on standing. The urine of subjects suffering from "lithæmia" or "uricacidæmia"—the so-called gouty diathesis—presents precisely the same characteristics. Albumin and sugar are also present during acute attacks of gout.

As the attack progresses, the affected joint or joints become somewhat œdematous—a symptom especially noticeable when large joints are involved. About the fourth or fifth day, all the acute symptoms begin to recede; the inflamed joint gradually becomes less painful, and desquamation occurs, the pain being replaced by tenderness, itching—sometimes quite severe—and stiffness.

Such an attack usually lasts from six to ten days, but remission may appear and greatly prolong it. This is apt to occur in cases of long standing. When complete recovery is reached, the patient may be in better health than before the attack.

Recurrence of a seizure may at first take place only after a year, but the intervals usually become shorter as time progresses until the attacks recur repeatedly in a twelve-month. As they become more frequent, the pain loses its severity, but the patient steadily becomes weaker, the joints do not as readily resume their freedom of action, and may remain, in fact, swollen and sensitive, the case lapsing into one of chronic gout.

In asthenic cases of long duration metastasis sometimes occurs, the so-called *metastatic* or *retrocedent gout,* the symptoms, including the pain, in a joint suddenly disappearing, to reappear abruptly in some internal organ, the heart, brain, stomach, testicles, bladder or parotid gland. When the heart receives the brunt of the attack, its action becomes irregular and there is severe præcordial pain and dyspnœa. The most prominent cerebral manifestations are violent excitement with severe headache, or, conversely, hebetude; these may be associated with the gastric metastatic symptoms, namely, vomiting and diarrhœa, with severe gastro-intestinal pain and marked weakness. In the

other organs named the phenomena are those of acute inflammation, *viz.,* cystitis, orchitis and parotitis. Metastatic gout of the heart and brain has been attended by sudden death.

Chronic gout generally occurs, as already stated, in cases weakened by repeated attacks, particularly in those of long standing, and in aged subjects. The affected joints then fail to undergo resolution and remain stiff and swollen. Tophi or hard masses of urates then form over them, causing them to become nodulated and greatly deformed. So great are these accumulations in some instances that dislocation of the joint is caused. The skin may also be stretched to such a degree that it sometimes breaks, allowing the chalky masses to fall out or to remain exposed. When the large joints are the seat of these accumulations, they become rigid, and the patient is gradually transformed into a cripple. Especially is this the case when the softer structures, the periosteum, tendons, bursæ, etc., are invaded by the morbid process. Almost any portion of the body, in fact, may become the seat of deposits, the eyelids, the cornea, the crystalline lens, the cartilages of the ear, nose, the skin, etc.

Pathogenesis.—The cause of the symptoms attributed to a "gouty diathesis" and of those witnessed in acute gout, is inadequate catabolism of certain food-products. As the efficiency of all catabolic (*i.e.,* digestive) processes in the body is dependent upon the adrenal system, it is primarily to the inability of this system to provoke the formation of enough adrenoxidase, nuclein and trypsin—auto-antitoxin—that the morbid process is due.*

The inadequacy of the adrenal system is only *relative, i.e.,* is not due to actual functional debility of the adrenal center and other organs of the adrenal system, in most cases of "lithæmia" or gout caused by excessive indulgence in animal food and wines containing considerable alcohol, etc.* Even the excessive stimulation to which the adrenal center is submitted in such cases, as shown by the resulting arterial tension, the peripheral hyperæmia, the congested face, etc., is inadequate to free the blood of toxic wastes by breaking them down to simpler and benign end-products.*

* *Author's conclusion.*

In the majority of cases, however: those in which hereditary predisposition is present, those due to insufficient food and squalor ("poor man's gout") or to overwork, physical or mental, or to chronic lead-poisoning, both "lithæmia" and gout, acute or chronic, are the result of *actual* functional weakness of the adrenal system, and to the imperfect catabolism of waste-products which this entails.

This relegates the primary cause of gout to a nerve-center, that of the adrenals, which governs all nutritional processes. Cullen, over thirty years ago, attributed to the nervous system the primary rôle in the pathogenesis of gout. Leven, of Paris,[4] Mortimer Granville,[5] Sir Dyce Duckworth and others have strongly urged the same view, *i.e.*, that the accumulation of the pathogenic elements was the result of a neurosis. Vindevogel, of Brussels,[6] more clearly defined the nature of the central disorders, *i.e.*, "an *enfeeblement* or lessened activity of the *trophic* nervous centers, and a loss of equilibrium between the processes of assimilation and disassimilation, by which the products of disintegration are rendered incomplete or toxic to the economy."

The pathogenic influence of debility of the adrenal center may be illustrated by the connection between lead and gout, urged by Garrod (1859), Dickinson, Lancereaux, Rosenstein, Leyden and others. Nobécourt,[7] in a comprehensive study of the subject, found that it followed slow intoxication, that it appeared at about the same age as ordinary gout, *i.e.*, during the fourth decade, and that the gouty diathesis evoked by lead could be transmitted by heredity. Now, Lemoine and Joire[8] had previously ascertained that the metal *interfered with catabolism*, thus favoring the formation of uric acid and urates. Lüthje[9] found the blood loaded with uric acid in saturnine gout—a fact which available knowledge could not explain. It is clearly accounted for, however, by the fact that lead markedly depresses the functional activity of the adrenal center, and, therefore, the production of adrenoxidase. The paralytic phenomena, the wrist-drop, the wasting, etc., also show that it reduces nutrition, *i.e.*, that its action is a debilitating one. Bouchard has pointed out that gout is a result of "slowed" nutrition, *i.e.*, of inhibited metabolism. "Poor man's gout" likewise exemplifies the influence of impaired nutrition in the pathogenesis of the disease.

The gastro-intestinal disorders observed in uricæmic or gouty subjects are the normal outcome of the imperfect gastric juice and auto-antitoxin produced, since the gastric glands, as well as the pancreas, are themselves inadequately nourished when the supply of adrenoxidase in the blood is subnormal.* This applies likewise to the muscular coats of the stomach and intestines; hence the gastric dilation and constipation, the post-

* *Author's conclusion.*

[4] Leven: Med. Record, May 26, 1888.

[5] Mortimer Granville: Med. Press and Circular, Feb. 15-22, Mar. 1, 1893.

[6] Vindevogel: "Nature, Causes, and Conditions of Gout," Brussels, 1892.

[7] Nobécourt: Semaine méd., Apr. 23, 1897.

[8] Lemoine and Joire: Gazette médicale de Paris, 8 série, T. i, pp. 1, 13, 25, 1892.

[9] Lüthje: Zeit. f. klin. Med., Bd. xxix, S. 266, 1896.

prandial discomfort, the nausea, the acidity, the flatulence, etc., observed in such cases.* These are not manifestations of gout: they are the expression of the debilitated condition of the governing center of nutritional processes, *i.e.*, the adrenal center.*

The gastro-intestinal digestive functions being imperfect, the products of digestion are correspondingly unfitted for absorption. As it is this material which the digestive leucocytes take up in the intestinal canal for conversion into nucleoproteid granules, *i.e.*, into living tissue-chromatin, they become laden not only with what products of digestion are suitable for assimilation, but also with products that have been imperfectly digested.* The leucocytes thus garner in the alimentary canal materials which are foreign to their own intrinsic functions and which ultimately become the pathogenic elements of gout.*

That broken-down leucocytes can be the source of the pathogenic elements of gout was suggested by Horbaczewski,[10] who held, however, that there was a constant proportion between the number of white corpuscles and the amount of uric acid excreted. The latter conclusion was refuted by Kolisch[11] and others, and is likewise defective from my standpoint, since we are dealing with a physiological—and therefore momentary—leucocytosis which invariably attends digestion, and not with the leucocytosis that occurs during disease, though Chalmers Watson[12] found myelocytes in the blood in the interval and during an acute attack. The fact remains, however, that leucocytes are now the recognized source of the pathogenic elements of acute gout, especially since the investigations of Burian and Schur[13] and Marès[14]. The latter observer found, moreover, that an increase of uric acid excretion occurred immediately after meals. This coincides with clinical observation. A. Robin,[15] for instance, considers "the leucocytic origin of uric acid as definitely settled" and says, referring to great meat-eaters: "The blood contains an enormous quantity of leucocytes. This is what is termed digestive leucocytosis."

On reaching the tissues, or rather the pericellular lymph-spaces, the leucocytes deal out their nucleo-proteid granules, and these are absorbed normally by the tissue-cells, and converted into living substance, *i.e.*, chromatin.* In addition to these physiologically normal elements, however, the leucocytes simultaneously secrete products of disintegration formed in these cells

* *Author's conclusion.*

[10] Horbaczewski: Sitz. d. Wiener Acad. d. Wissen., Bd. c, Abth. iii, S. 13, 1891.

[11] Kolisch: "Ueber Wesen u. Behandlung der uratischen Diathese," Stuttgart, 1895.

[12] Chalmers Watson: Brit. Med. Jour., Jan. 6, 1900.

[13] Burian and Schur: Archiv f. d. ges. Physiol., Bd. lxxx, S. 241, 1900; Bd. lxxxvii, S. 239, 1901.

[14] Marès: Monats. f. Chemie, Bd. xiii, S. 101, 1892.

[15] A. Robin: Rev. de thérap. méd.-chir., vol. lxix, p. 37, 1902.

out of the imperfectly digested food-stuffs absorbed by them in the alimentary canal.* Their two products differ totally, therefore, in that the granules are useful bodies built up by the leucocyte, while the abnormal substances are products of disintegration ejected by the cell as unfit for the elaboration of living substance.*

The identity of these wastes depends upon the stage of disintegration they have reached when excreted by the cell, and this, in turn, depends upon the digestive activity of the intraleucocytic ferment: (1) When the adrenal system is debilitated and the production of adrenoxidase is deficient, the cell is itself poorly supplied with this substance and the heat-energy liberated through its reaction with the cellular nuclein is inadequate to raise the proteolytic activity of the cytase, *i.e.*, the cell's own proteolytic ferment, to its full potency.* As a result, imperfect disintegration occurs, and the materials ejected by the leucocyte* are intermediate waste-products, *i.e.*, alloxuric or purin compounds: xanthin, hypoxanthin, purin, adenin, etc.,—all derived from nucleins (and not from proteids). Several of these bodies, especially xanthin and hypoxanthin, are poisonous; they are not only the pathogenic elements of the so-called "gouty diathesis," "uricæmia," "lithæmia," etc., but they also play an important rôle in the pathogenesis of migraine and other disorders. (2) When, conversely, the adrenal system is adequate and an ample supply of adrenoxidase is available,* the proteolytic process is carried on further, and instead of the toxic intermediate wastes just referred to, the leucocytes excrete a substance which, though not poisonous in itself, may, under certain conditions, provoke acute gout, namely, uric acid.

The fact that, as I pointed out in the fifteenth chapter, leucocytes ingest food-products to convert them into tissue elements, harmonizes various discordant views. Horbaczewski believed that nucleins were not the direct source of uric acid; he concluded, however, that they provoked leucocytosis, and that these leucocytes, when broken up, were the source of the uric acid. Since the latter has been known to originate directly from nucleins, this interpretation has been generally discarded. Still, the prevailing view, as stated by Hammarsten, is that "the uric acid, in so far as it is produced from nuclein bases, is in part derived from the nucleins of the destroyed cells of the body [tissue cells] and in part from the nucleins or free bases introduced with the food." If, however, as I have pointed out, it is the function of the leucocytes to *ingest* all food-products, uric acid is, as was suggested by Horbaczewski,

* *Author's conclusion.*

derived from these cells (mainly secreted by them with their granules in the lymph-spaces, according to my interpretation), though derived from nucleins, in accord with his opponents. Even his belief that leucocytosis played a part in the process is warranted, provided we consider it a digestion leucocytosis. Horbaczewski can be said to have been radically wrong only in believing that uric acid was not derived directly from nucleins.

Another important feature of the problem is the identity of the process through which the nucleins are converted into xanthin, uric acid and other purin compounds. Contrary to the prevailing belief that "oxidation" is the direct agent, I attribute this rôle, in keeping with the views advanced in the fifteenth chapter, to a trypsin-like enzyme whose nucleolytic activity is sustained by heat-energy liberated by the interaction of adrenoxidase and nuclein secreted by leucocytes. This view harmonizes with modern experimental evidence in the present connection as it did when studied in its relations to the digestive process in the alimentary canal, the leucocytes and the tissue cells, as may be shown by a few salient facts.

The process of uric acid formation described by Kossel and Fischer was reviewed in the first volume.[11] Briefly, they showed that the alloxuric or purin compounds, including xanthin, hypoxanthin, etc., and uric acid, were disintegration-products of the nucleins, nucleo-proteids or nucleic acid of many articles of food. Horbaczewski then found that the purin compounds could be converted into uric acid, and, moreover, that when spleen pulp, which is rich in nuclein, was fed to man or animals, the output of uric acid was increased. Krüger and Schmid[17] then found that when xanthin, hypoxanthin, guanin or adenin was administered to men, the output of uric acid was likewise augmented. These facts clearly point to food-nucleins as the source of uric acid and to the latter as an advanced disintegration-product.

That a digestive ferment is the active factor in the process is sustained by recent research. Mendel,[18] for example, says in a recent (1906) paper: "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism"—a fact fully in accord with the functions I have ascribed to the "digestive triad." On page 139 of the first volume I wrote: "Horbaczewski, in a series of experiments, observed that splenic pulp, allowed to digest several hours with blood at the body temperature, gave rise to a marked increase of uric acid and nuclein bases, but that the relative amounts of these products depended entirely upon the degree of oxidation." In other words, simple digestion —and therefore a limited supply of oxygen—gave xanthin and hypoxanthin; the addition of oxygen, on the other hand, caused the formation of uric acid. Now, the constituents of the triad were obviously present: the phosphorus-laden nuclein in the splenic pulp; the adrenoxidase, rendered very active by an artificial supply of oxygen, in the red corpuscles and plasma; and the trypsin in the leucocytes and plasma.

It now becomes a question whether the tissues contain a ferment capable of converting purin bases into uric acid. Such was found to be the case recently by Schittenhelm.[19] Alcohol inhibited the action of this ferment—precisely as it does, we have seen, that of adrenoxidase. More to the point, however, was the observation of Burian,[20] that muscles, and particularly the liver and spleen, contain an *oxidase* which can convert *hypoxanthin* into uric acid. This process also requires a free supply

[16] *Cf.* vol. i, p. 137 *et seq.*
[17] Krüger and Schmid: Zeit. f. physiol. Chemie, Bd. xxxiv, S. 549, 1902.
[18] Mendel: Jour. Amer. Med. Assoc., Mar. 24, 1906.
[19] Schittenhelm: Zeit. f. physiol. Chemie, Bd. xlii, S. 251, 1904.
[20] Burian: *Ibid.*, Bd. xliii, S. 494, 297, 532, 1905.

of oxygen. That, in view of these experimental facts, a deficient supply of adrenoxidase should entail an accumulation of these toxic wastes in the body is self-evident.

Uric acid, though itself harmless, becomes pathogenic when, owing to imperfect elimination, from any cause, it is allowed to accumulate in the body. It may then give rise to acute gout.

An important pathogenic factor in this connection is granular atrophy of the kidneys, a condition in which the permeability of these organs is more or less reduced. It occurs in individuals who have suffered during a prolonged period from the so-called "uric acid diathesis," *i.e.*, individuals in whom, owing to insufficiency of the adrenal system, the blood is more or less laden with purin compounds.* These bodies, xanthin, paraxanthin, adenin, guanin, etc., are not only toxic, but they irritate sufficiently the renal epithelial elements, while being eliminated, to provoke after a given time the local organic lesions which interfere with the free excretion of uric acid.

A temporary accumulation of these poisons in the blood during an exacerbation of lithæmia may also cause a sufficiently marked renal congestion to interfere with the free elimination of uric acid and thus provoke an access of gout.

As is well known, considerable uric acid is found in the blood in leukæmia; and yet these cases do not suffer from gout. In these cases the kidneys are permeable. Conversely, Levison,[21] who first drew attention to the pathological importance of renal lesions in gout, writes: "In all described cases of gout in which the *post-mortem* examination is mentioned, the kidneys have been found diseased, and in almost all cases they were suffering from granular atrophy." Luff, moreover, found uratic deposits in 41 cases out of 77 cases of granular kidney. Levison also states that in all such cases, "the power of elimination of the kidneys as regards uric acid, as well as various other substances, is diminished," and that "the consequence of this defective elimination of uric acid is its retention in the blood (von Jaksch)." Since these lines were written cases of gout and lithæmia have been reported in which no renal lesions were found after death, but if we take into account the well-known fact that the kidneys readily become congested under chemical irritation, it is evident that their permeability may readily be composed during life, though no lesions be discernible *post-mortem*.

That purin compounds, xanthin, hypoxanthin, adenin and guanin, are the renal irritants, while uric acid *per se* is not, was first shown by Gaucher, in 1884. This was fully confirmed by Kolisch,[22] whose conclusion was based on observations which included experiments by Tandler. The renal lesions thus produced artificially were found by Paltauf and Albrecht to be identical with those found in gout. Croftan[23] also found that both xanthin and hypoxanthin, when injected hypodermically in the

* *Author's conclusion.*
[21] Levison: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. iii, p. 350, 1899.
[22] Kolisch: Med. Press and Circular, Dec. 18, 1895.
[23] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.

strength of 0.3 to 0.7 per cent. watery solution, for a period of several months, produced granular degeneration of the epithelial cells lining the convoluted tubules and a proliferation of the endothelium of the intertubular capillaries.

If renal lesions—or inflammatory impermeability—are necessary to provoke gout, lead-gout should likewise be attended with such lesions. Levison, referring to the experiments of Charcot, Binet, Coen and d'Ajutolo, and to clinical observations "in persons exposed to lead-poisoning," says that "one of the earliest and most constant symptoms of this disease is a pathological change of the renal tubuli conducive in rather a short time to granular atrophy of the kidneys." Moreover, Garrod,[24] and others since, found uric acid in the blood of cases of chronic lead-poisoning. As lead depresses the functional activity of the adrenal center, and inhibits, therefore, the formation of adrenoxidase, the cause of the renal lesions is the same as in gout, *i.e.*, inadequate cleavage of ingested nucleins and the production of xanthin, hypoxanthin, etc. Again does it become evident, therefore, that gout is primarily due to any toxic capable of causing adrenal insufficiency.

In the *"gouty diathesis"* or *"lithæmia"* some of the symptoms are due to the primary depression of the adrenal system, namely, the gastro-intestinal disorders, as already stated, the vertigo, the depression of spirits and the slow pulse—all manifestations of inadequate oxygenation.* Other symptoms, however, are the result of the imperfect catabolism which this inadequate oxygenation entails, the pathogenic agents thus formed being poisonous intermediate wastes of undetermined nature, but which include xanthin, paraxanthin and other purin bases. They do not include uric acid, however, since this substance is the normal end-product of nuclein catabolism, which is as harmless in itself and as readily eliminated by the kidneys as is the normal end-product of proteid catabolism, urea. Among the symptoms produced by these toxic subcatabolic wastes are those due to the penetration of the poisons into the axis-cylinders, cell-bodies, dendrites, and other nervous elements, along with the adrenoxidase circulating through them.* Hence the migrainous headache, the neuralgia, the shooting pains, or the opposite states: anæsthesia and other paræsthesias, and also the extreme nervous irritability so frequently observed in these cases.

The symptoms of the so-called *"irregular"* or *"atypical gout"* observed in lithæmic subjects, and which sometimes alternate with attacks of true gout, are due to the same subcatabolic poisons, including also xanthin and other purin compounds, but not to uric acid. In addition to the lithæmic symptoms just

* *Author's conclusion.*
[24] Garrod: Med. Chir. Trans., vol. xxxi, p. 83, 1848.

enumerated, these poisons give rise to eruptions and pruritus (as excretion products), flushes of heat, sometimes limited to the palms and soles, muscular pains, especially in the back, and inflammatory phenomena in various organs, *i.e.*, the bronchi, pericardium, bladder, gums, etc., and also in the vascular walls, leading to arteriosclerosis. Many other disorders, migraine, epilepsy, tetanus, eclampsia, etc., in which these subcatabolic poisons play the leading rôle are reviewed in this chapter.

In both of the above syndromes—which in reality differ only in name—certain of the phenomena are due to a direct action of the subcatabolic poisons upon the centers in the pituitary.* The flushes of heat and a febrile process in which the temperature is raised two or three degrees F. are often concomitant general phenomena which point to excitation of both the adrenal center and the sympathetic center, and to increase of the propulsive activity of all arterioles.* Fever denotes here an effort to raise the nucleolytic activity of the blood, *i.e.*, its asset in auto-antitoxin, and thus to convert the subcatabolic poisons into uric acid, *i.e.*, into a benign eliminable end-product.*

Uric acid is found in the urine of man and other carnivorous mammalia, and abundantly in that of birds. In the latter and in the scaly amphibians, in fact, "the greater part of the nitrogen of the urine," as stated by Hammarsten, "occurs in this form." It is evident that in these animals it occurs as a terminal waste-product, that as such it is itself non-toxic, and, finally, that it is eliminated physiologically, that is to say, without injuring the kidneys or any other organ. That uric acid is non-toxic even in large doses was shown experimentally by Bouchard.[25] This was fully confirmed by Croftan,[26] both as to large quantities, and as to small quantities given hypodermically a long time, *i.e.*, three months. Microscopical examination of the kidneys in the animals of the latter series revealed no abnormalities. Deposits of urates were found in none of the structures examined, including the synovial membranes and joints.

We have seen that xanthin, paraxanthin, etc., produced marked irritation of the kidneys; Salomon,[27] Filehne,[28] Pachkis and Pal[29] and Rachford,[30] have shown that these substances can provoke various nervous disorders, including migraine, muscular rigidity, tonic spasms, and also marked arterial tension, arteriosclerosis, dyspnœa, cyanosis and rigor mortis. Paraxanthin obtained from the urine of a case of migraine which lapsed into "epileptoid" tonic spasms, described by Rachford, reproduced the latter—"almost a tetanus"—in mice. Salomon found that 0.0005 gm. ($^1/_{120}$ gr.) sufficed to tetanize a mouse fatally.

* *Author's conclusion.*

[25] Bouchard: "Lectures on Auto-Intoxication in Disease," transl. by Oliver, p. 51, 1894.

[26] Croftan: N. Y. Med. Jour., Aug. 11, 1900.

[27] Salomon: Archiv f. Physiol., S. 426, 1882, and other papers.

[28] Filehne: DuBois-Reymond's Archiv., S. 72, 1886.

[29] Pachkis and Pal: Wien. med. Jahr., Bd. xi, S. 612.

[30] Rachford: Med. News, May 26, 1894.

Croftan,[31] moreover, found in all so-called uric acid disorders, "an absolute increase over the normal of the *sum* of uric acid and alloxuric bases" and considers the latter as the only true pathogenic agents. He also attributes their formation to deficient oxygenation, for "if oxygenation is sufficient," says this investigator, "we have the formation of uric acid; this is the normal process." This obviously brings us back again to debility of the adrenal system as the primary cause of all so-called "uricacidæmias."

These facts indicate, moreover, that xanthin and paraxanthin are not only renal irritants, but also intense neural excitants. These phenomena are readily accounted for since I have shown that the blood-plasma, the carrier of these poisons, circulates *in* the neural elements themselves, axis-cylinders, the fibrils of the cell-bodies, the dendrites, etc.

The *premonitory symptoms* of acute gout are similar to those of "lithæmia" and "irregular" gout and are due to the same subcatabolic poisons. Here, however, the pathogenic influence of xanthin, paraxanthin, etc., assumes the primary rôle. *It is to the renal disorder evoked by these poisons that the attack of acute gout is due* when the quantity excreted is sufficient to provoke marked hyperæmia or inflammation, whether the kidneys be previously diseased or not.* Hence the facts (1) that the premonitory signs cease before the onset of acute attack, (2) that they are not always followed by an access, or (3) that between the premonitory signs and the onset of acute gout there is usually a period of relief and well-being—all the result of a more or less complete renal elimination of the alloxuric poisons with what proportion of them may have been further catabolized into uric acid.* The attack of gout fails to develop if the kidneys are left permeable after this eliminatory process; conversely, it develops if the renal congestion produced is sufficiently active to inhibit markedly the excretion of uric acid and to cause it to be retained in the body in sufficiently large quantities.

Although renal disease is probably present in the vast majority of cases of gout, as we have seen, it cannot itself be the direct cause of the attack, since the latter would be continuous—in keeping with the renal lesion. As the average attack usually lasts but a few days and is followed by a period of health, it is evident that a temporary exacerbation of the local lesions or an ephemeral inflammatory process is necessary to account for it. Xanthin, hypoxanthin, etc., being irritants of the renal elements, become normal causes of this temporary morbid process, especially in view of the fact that even large doses of uric acid given orally or hypodermically, are harmless.

Although under these conditions, the excretion of uric acid or its salts during the attack must vary with the functional efficiency of the diseased kidneys, the nucleolytic activity of the blood, etc., and therefore, to a great extent, in different cases, and at different times in the course

* *Author's conclusion.*

[31] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.