of a given case—as observed clinically—the fact remains that various authors have noted a sudden diminution of the uric acid excretion immediately before the acute attack. His,[32] for example, found that while the average quantity of uric acid excreted by lithæmic subjects was similar to that excreted by healthy persons, "an acute attack of gout was practically invariably introduced by a very marked depression in the quantity of uric acid, or even its complete disappearance. This occurred on the day before the attack in 10 instances, two days before the attack in 2 instances, and three days before the attack in 3 instances." This is explained by the course of events outlined in the general text: the uric acid accumulated in the body (owing to increasing renal inflammation) during the one to three days preceding the attack, and the latter broke out as soon as the volume of uric acid reached a sufficient level.

Although carried by the blood-stream to all parts of the organism, uric acid accumulates in fluids such as the synovia of joints, lymph, etc., and tissues such as cartilage, ligaments, tendons, bursæ, etc., because it is not as actively exposed therein to the substances which in the blood serve to antagonize its morbid effects.* Gout being in reality a febrile disease, and the expression of an autoprotective function, the blood becomes loaded with defensive materials, namely, leucocytes capable of acting not only as phagocytes, but also as the purveyors of the trypsin and nuclein which, with the adrenoxidase dealt out by the red corpuscles, constitute the auto-antitoxin.* As uric acid can be further catabolized under these conditions to still simpler products, urea, allantoin, glycocoll, and other bodies more readily excreted by the congested kidneys than uric acid, the blood, especially while in transit through the liver, is kept relatively free of uric acid as long as the febrile process lasts. Not so, however, with the joints (and nerves) and other structures enumerated. In synovia, for example, the red corpuscles and leucocytes are absent under normal conditions, and uric acid failing to be destroyed therein as elsewhere, it accumulates in the joint.* During the attack the latter is the seat of an exudation containing many leucocytes, but as compared to the blood, very few red corpuscles. As the local supply of adrenoxidase, of which these cells are the carriers, is deficient, the heat energy available to raise the catabolic efficiency of the trypsin is far below that of the blood, and the curative process is slow in proportion. Hence the fact that the temperature of an affected joint in gout is sometimes as much as 6° F. (3.3° C.) lower than that of the body at large.*

* *Author's conclusion.*
[32] His: Deut. Archiv f. klin. Med., Bd. lxv, S. 166, 1899.

In the joint affected the lesion is that of a low grade of inflammation, involving, however, a certain degree of softening of the exposed cartilage, and penetration therein of the acicular crystals of the sodium salt of uric acid, *i.e.*, sodium biurate. The curative process therein is a counterpart of that carried on in the blood. It is efficient, therefore, in proportion as the activity of the adrenal system is marked, *i.e.*, in proportion as the relative volume of adrenoxidase, nuclein and trypsin in the fluids is great.* As leucocytosis is likewise commensurate, all else being equal, with the adrenal activity, there is (1) breaking down of the uric acid salt into simpler products, especially urea, by the auto-antitoxin, and (2) phagocytosis of the detritus—the cartilage being left somewhat granular.*

As stated by Lazarus Barlow,[33] "it has been repeatedly proved by quantitative analysis that the amount of uric acid in the blood is at its maximum immediately before an attack of gout, and diminishes immediately after the attack has subsided. This, taken in conjunction with the fact that the crystalline sodium biurate is actually found in joints that have been the seat of gouty inflammation, is sufficient evidence tnat gout depends upon the retention of uric acid." Analysis of these statements, which are based on a comprehensive view of the literature of the subject, will indicate that my interpretation of the process—that submitted above—is in accord with experimental evidence, besides harmonizing with the conclusions submitted in the foregoing pages.

"The power of the animal organism to catabolize uric acid like other nitrogenous compounds" is considered by Mendel, "one of the fruits of modern research which has profoundly changed our attitude toward the problems of purin metabolism." Wohler and Frerichs,[34] Wiener[35] and others have shown that uric acid could be destroyed in great part in the organism, and more or less completely converted into urea. Salkowski, Mendel, Brown, Minkowski have pointed to allantoin as an important product of uric acid, Wiener to glycocoll, etc. Chassevant and Richet,[36] Ascoli[37] and others found that the liver played a very prominent part in this process. Schittenhelm[38] recently found that *two* sets of ferments were concerned in this process, one of which *hydrolyses* and detaches the ammonia group, while the other *oxidizes* and breaks down the uric acid. The former is obviously the trypsic ferment and the latter adrenoxidase.*

That the joints should, conversely, be the seat of slow catabolism, is shown by the fact that even during active inflammation the local temperature is relatively low. Thus, Balfour[39] refers to "the absence of excessive heat in joints affected with gout" and to the fact that "some observers have found such joints lower in temperature than surrounding parts." Dyce Duckworth[40] observed a difference of five degrees.

* *Author's conclusion.*
[33] Lazarus-Barlow: "Manual of Gen. Pathol.," second edition, p. 597, 1904.
[34] Wohler and Frerichs: Annal. d. Chem. u. Pharm., Bd. lxv.
[35] Wiener: "Ergebnisse der Physiologie," Bd. i, Abt. i, 1902.
[36] Chassevant and Richet: C. r. de la Soc. de biol., vol. xlix, p. 743, 1897.
[37] Ascoli: Archiv f. d. ges. Physiol., Bd. lxxii, S. 340, 1898.
[38] Schittenhelm: Zeit. f. physiol. Chemie, Bd. xlv, S. 121 u. 161, 1905.
[39] Balfour: *Loc. cit.*
[40] Dyce Duckworth: "Treatise on Gout," London, 1889.

James Tyson[41] also says that "the local temperature, notwithstanding the sensation of heat, is five or six degrees below that of the axilla at the same time."

The urine often shows clearly the presence of renal obstruction: we have seen that it is scanty, highly colored, etc. While the uric acid, excreted in twenty-four hours before and during the attack, may be markedly reduced, as emphasized by Bartel, Dyce Duckworth and others,[42] having obtained but 0.2 to 0.5 gm. (3 to 8 grains) from 100 gms. ($3^1/_2$ ounces) of urine (which in health gives 1 to 1.5 gm.), along in some cases with all excrementitious products, the end of the attack is characterized by a free excretion of urea and uric acid which continues several days. Still, the clinical evidence on this score is quite contradictory. This is readily accounted for by the fact that the catabolizing properties of the blood and the degree of renal disorder may be said to vary with each case.

When the uric acid salts or biurates accumulated in joints (and elsewhere) fail to be adequately broken down to simpler products, they accumulate *in situ,* forming tophi. At first mortar-like and soft, these nodules gradually harden, and as succeeding accumulations occur, the joints become increasingly ankylosed and distorted. The development of tophi, *i.e.,* of *chronic gout,* is due to debility of the adrenal system, *i.e.,* to insufficiency in the body-fluids of the "digestive triad," *i.e.,* of auto-antitoxin, of the sensitizing thyroidase, and of the phagocytic leucocytes whose mission is to prevent such accumulations by ridding the regions attacked of all detritus.*

We have seen that chronic gout occurs in cases weakened by repeated attacks and in aged individuals—all subjects in whom debility of the adrenal system is self-evident. As stated by Levison, "the urine in chronic gout is pale and watery" and contains "casts of renal tubuli, hyaline or granulated," evidence of marked renal implication, while "the patients are weak and pale." Indeed, as taught by Bouchard[43] over twenty years ago, the phenomena often observed in chronic gout, œdema, cardiac lesions, cerebral and gastric disorders, etc., are in reality renal, and the patient dies of his renal disease.

Treatment.—Measures Indicated During an Acute Attack.—Between the use of "flannel and patience" recommended by Cullen and the modern local hot-air bath at 300° F. and above, applied to the affected joint, are many devices such as the hot douche, the local sweat pack, the local vapor bath, radiant heat, the hot dry pack, etc., the application of hot alcohol, hot anodyne liniments, etc., which, when judiciously employed, prove very efficacious. The mode of action of *heat*

* *Author's conclusion.*
[41] James Tyson: "Practice of Medicine," third edition, p. 785, 1905.
[42] Bartel, Duckworth and others: Cited by Pfeiffer: Lancet, Jan. 3, 1891.
[43] Bouchard: "Mal. par ralentissement de la nutrition," second edition, p. 282, 1885.

in this connection illustrates that of remedies which, given internally, have likewise been found useful. During the attack, the affected joint, we have seen, is invaded by leucocytes which supply it with this ferment and nuclein, while red corpuscles, the purveyors of adrenoxidase, are relatively few. Though trypsin and nuclein are plentiful, therefore, in the exudate the adrenoxidase is scanty, and the heat-energy liberated when it combines with nuclein is insufficient to raise the activity of the trypsin to a level that will insure prompt conversion of the accumulated uric acid into benign and eliminable products.* As the source of the heat-energy required in the process is immaterial, hot lotions, hot dry air, etc., are effective in proportion as they are able to raise the temperature of the interior of the joint to a level at which trypsin, *i.e.,* the local auto-antitoxin, becomes very active.* Hence the relatively great efficiency of hot dry air, which brings to bear upon the surface greater heat than any other procedure. *Massage,* when it can be borne, hastens local resolution by a similar process.*

We have seen that, as stated by Hammarsten, temperature exerts "a very important influence" on ferments. Roberts[44] showed, moreover, that the activity of trypsin increased with rising temperature until 60° C. was reached. Artificial heat was used here, the trypsin being *in vitro.* Active congestion of the joint, encouraged by using it, is beneficial in much the same way. Balfour[45] refers to several cases mentioned by Cullen, Sir William Temple, Gairdner and others, who "walked off" their attacks, and to Boerhaave's advice to take much and continuous exercise, and to rub the affected part, etc. Any procedure which increases the activity of the local circulation not only augments the proportion of "digestive triad" supplied to the part, but raises also the local temperature, and hastens the removal of detritus.* Hence the recognized value of massage.

Appropriate *purgatives* at the outset of an acute attack serve several purposes: they enhance the catabolic activity of the blood not only in the liver where the breaking down of toxic wastes is most active, but also in the body at large, and thereby tend to arrest the accumulation of uric acid in the joints.* Moreover, by increasing the exeretory activity of the intestinal canal they reduce the work imposed upon the kidneys and diminish the congestion of these organs.*

Most active in this connection are the *mercurial purgatives.* As they stimulate powerfully the adrenal center, the production

* *Author's conclusion.*
[44] Roberts: Proc. Royal Soc. London, vol. xxxii, p. 158, 1881.
[45] Balfour: *Loc. cit.*

of auto-antitoxin is increased and the specific action of these agents on the liver enhances actively the destruction of uric acid.* *Calomel* or *blue-mass* gives excellent results. *Colocynth* and *jalap* have likewise been used, but their effect upon catabolism is much less marked. A saline purgative given after either of these materially aids the beneficial effect by causing flushing of the intestine with a serous discharge.

The beneficial action of calomel has been emphasized by Grimm.[46] Having employed it expecting merely a purgative effect in a case, he obtained marked amelioration in the condition of the joints. Similar results were then observed in 18 out of 20 cases which form the basis of his report. Levison states that in England, where gout is especially common, practitioners often begin the treatment "by the administration of a free purgative: calomel and jalap or mistura sennæ composita."

The remedies which have held their own in gout, produce their main effect by acting much as do cholagogue purgatives. *Colchicum* is the most prominent of these agents. Like purgatives, it increases general catabolism in the blood, and particularly in the liver. Given in excessive doses, however, or too long, it stimulates powerfully, not only the adrenal center, but also the vasomotor and sympathetic centers, producing not only a marked increase of vascular pressure prejudicial to the kidneys, but also exposing the heart to inhibition by causing undue constriction of its coronary arteries.* The danger-signals are active purgation and weakness of the heart's action with, perhaps, some irregularity. It is to its action on the sympathetic center and the constriction of the peripheral arterioles that it owes its analgesic property, the supply of arterial blood to the sensory terminals of the skin being thus reduced.* In the average case 10 to 20 minims (0.61 to 1.22 gm.) of the wine may be given every three hours. Colchicine is preferred by many clinicians, the dose being $^1/_{50}$ grain (0.0013 gm.) every four hours, or better $^1/_{100}$ grain (0.00065 gm.) every two hours. The drug should be withdrawn when the pain is controlled (usually within 48 hours) or when purgation is marked.* The *Carlsbad waters* owe their marked beneficial effects in gout to their main constituent, a purgative salt, sodium sulphate, and to the ingestion of considerable water which their use entails; the

* *Author's conclusion.*
[46] Grimm: Deut. med. Woch., Bd. xix, S. 395, 423, 1893.

active ingredients of Scudamore's remedy are also purgative salines, magnesium sulphate and magnesia.

Colchicum is generally considered as a specific for gout. H. C. Wood[47] states that "so far as our knowledge reaches, colchicum or its alkaloid, when given in therapeutic doses, produces no definite symptoms save purgation." That it does more, however, is shown by evidence quoted by this author. As I previously stated, the curative process is due to the breaking down of uric acid into simpler products, urea, for instance: Christison found "in the colchicum-urine the *proportion* of urea nearly double;" in rheumatism, Maclagan[48] also found that "the *proportion* of urea was very greatly increased." This is not controverted either by the observations of Graves and Gardner, that the urates (*total*) "diminish under the use of the medicine," since the purgation deviates the excretory current from the kidneys, or by those of Noel Paton,[49] who found that "small doses of colchicum increased very distinctly the elimination of urea and uric acid, as well as the amount of urine; while large doses lessened the amount of urinary secretion and increased slightly the daily elimination of urea and uric acid" in dogs. Although the kidneys were, of course, not diseased, the catabolic action of the drug is emphasized by the effect of small doses, while the derivative action of purgative doses is shown by that of the larger doses. In the light of my views, therefore, the experimental testimony is not discordant, as generally believed.

The physiological action of *salicylic acid* and the *salicylates* in gout differs only from that of colchicum in that these drugs do not provoke purgation. By stimulating the adrenal they enhance the blood's catabolic activity, especially in the liver, and promote thereby the elimination of urea and uric acid.* As does colchicum, they relieve pain by stimulating the sympathetic center (a process that entails the same danger of arresting the heart when used recklessly), and thus causing constriction of the peripheral arterioles.* By thus reducing the blood supplied to the cutaneous capillaries, they lower the superficial temperature (its so-called antipyretic action).*

Some clinicians prefer the salicylate of sodium to colchicum, but the great majority regard it as inferior to the latter. Ten grains (0.6 gm.) every two hours give the best results. Many other preparations of salicylic acid are now available, but all act more or less actively in the same way.

The action of the salicylates on the liver is often overlooked. Wood, however, says in this connection: "The belief of many clinicians that the salicylates have a distinct action in stimulating the biliary secretion seems to have a solid experimental foundation" and refers to the researches of Moreigne,[50] Bain, Pfaff and Balch. As to their action

* *Author's conclusion.*
[47] H. C. Wood: "Therapeutics, etc.," twelfth edition, p. 525, 1905.
[48] Maclagan: Edinburgh Jour. of Med. Sci., vol. xiv, p. 3. 1852.
[49] Noel Paton: Brit. Med. Jour., July 31, 1886.
[50] Moreigne: Arch. de méd. expér. et d'anat. pathol., vol. xii, p. 300, 1900.

on metabolism, he states that the experiments have been "so numerous and concordant in their relations as to prove that in the normal man or animal, salicylic acid and its preparations increase to a very great extent the elimination of urea and uric acid."

Haig[51] observed that sodium salicylate failed when there was general debility, and in sequence to colchicum. In the former case, the adrenal center is itself sometimes too debilitated to react under the relatively weak stimulation of the salt, though it *would* act under a more powerful excitant, potassium iodide, for instance.* That it should not act after colchicum is obvious, since the latter drug is the more powerful adrenal stimulant.*

Curative properties are ascribed to *piperazine* mainly because it forms with uric acid *in vitro* a urate which dissolves in forty-seven times its weight of water. In practice, however, though it tends to increase the excretion of urea and diminish that of uric acid, it does not produce effects indicating that in the blood-stream it behaves as it does *in vitro,* and it has been found less efficient than either colchicum or the salicylates by the majority of clinicians, in acute gout. There is ground for the belief, however, that it tends to prevent the development of acute attacks by stimulating sufficiently the adrenal center to insure the breaking down of renal irritants, xanthin and hypoxanthin, into urea.* It is administered in the form of "piperazine water," a quart of which contains 15 grains (1 gm.) of piperazine. During acute gout this quantity is given in divided doses; as a prophylactic one-half of this, *i.e.,* 1 pint (500 gms.) daily is sufficient.

The large quantity of water thus taken is unquestionably an important feature of the remedy's action. Still, Biesenthal and Schmidt[52] obtained beneficial effects with the salt itself. Schweninger[53] found it especially efficacious when given with considerable water. In the form of "piperazin water" it has been found efficacious by Wilcox,[54] Page,[55] Eshner[56] and others, in various gouty conditions, as well as by a large number of foreign observers.

The ingestion of large quantities of *pure water* during an attack and in disorders due to the gouty diathesis facilitates greatly the elimination of uric acid by the kidneys, owing to the lower specific gravity of the blood-fluids produced. This action is enhanced, however, when alkaline *mineral waters* are used instead, especially those of which sodium carbonate and sodium

* *Author's conclusion.*
[51] Haig: Lancet, Aug. 12, 1899.
[52] Biesenthal and Schmidt: Provincial Med. Jour., Mar. 1, 1892.
[53] Schweninger: Jour. Amer. Med. Assoc., Sept. 24, 1892.
[54] Wilcox: Med. News, Nov. 27, 1897.
[55] Page: Med. News, Oct. 13, 1900.
[56] Eshner: Phila. Med. Jour., Apr. 23, 1898.

chloride are the main constituents. They not only increase the fluidity of the blood, but facilitate osmosis, the sodium ion activating simultaneously cellular metabolism, and, therefore, catabolism. When in acute gout the fever is at all marked, the free use of beverages of this kind is of paramount importance.

Over fifty years ago, Guelle showed that pure water ingested in large quantities increased the elimination of uric acid, and that after this process had continued a few days, the excretion fell and sometimes ceased, the blood having been, so to say, relieved of all free uric acid. Robin[57] recently confirmed this observation and noted that in women who, to reduce flesh, avoided fluids, the urine became dense, loaded with uric acid, and that renal lithiasis followed. The rôle of the blood-salts in osmosis has been reviewed at length elsewhere. Both Jacques Loeb and Overton[58] have shown that "the Nations of the blood as well as the sea-water are essential for the maintenance of life-phenomena." The importance of the alkaline salts in all febrile processes was emphasized in a preceding chapter. In stations such as Vichy and Carlsbad, where the waters are strongly alkaline, the temporary aggravation is sometimes witnessed; this is due to the liberation of pent-up uric acid, through increased osmosis, and is rightly considered by the local physicians as a favorable sign. Sir William Roberts's belief that sodium salts are harmful in gout is not sustained by practical evidence. As stated by Burney Yeo,[59] "notwithstanding the experimental evidence to the contrary, it has been amply demonstrated that the alkaline sodium salts have an effect upon the hepatic functions and do favorably influence gouty conditions."

PROPHYLACTIC TREATMENT.—Having ascribed the premonitory symptoms of acute gout, the various phenomena included under the "gouty diathesis," and chronic gout, to a common cause,* the measures indicated are necessarily similar in all these supposedly different conditions, a fact sustained by clinical experience.

The prophylactic measures indicated, in the light of the pathogenesis described in the foregoing pages, are (1) to reduce the intake of nucleins and thereby the purin bases of which they are the source, and (2) to enhance the functional efficiency of the adrenal system in order to insure the adequate conversion of toxic intermediate wastes into nontoxic and eliminable end-products.*

Reduction of the Intake of Nucleins.—The toxic intermediate waste-products being all nuclein derivatives, the pathogenic activity of food-stuffs is commensurate with the quantity of nuclein they contain. Especially rich in this connection are

* *Author's conclusion.*
[57] Robin: *Loc. cit.*
[58] Jacques Loeb and Overton: "Studies in General Physiology," Pt. ii, p. 556, 1905.
[59] Burney Yeo: Therap. Gazette, July 15, 1901.

glandular organs, such as liver, thymus (sweetbread) and kidney. This applies likewise to brain tissue, an enormous aggregate of nerve-cells, the cell-bodies of which all contain nuclei. Muscle tissue, *i.e.,* meat, is less rich in this particular, but hypoxanthin and xanthin are the main purin product of its nuclein. Beef extracts and the gelatinous extracts of tendons, bones, etc., are likewise rich in nucleo-albumins which yield the same purins —those, we have seen, that irritate the renal elements, and which take part in the pathogenesis of the various disorders of the "gouty diathesis."

The glandular tissues, sweetbread, liver, etc., should be strictly avoided. As to meats, the indications vary with the case; in excessive eaters, especially those subject to cutaneous disorders and in patients who suffer from migrainous attacks, flushes, etc., a temporary—a year or two at most—omission of heavy meats, *i.e.,* beef, mutton, pork and veal, from the diet, and the concurrent ingestion of at least a quart of pure water daily, is often very efficacious. In debilitated subjects, on the other hand, in which no evidence of renal lesion is present, lean beef may be allowed, but simultaneously with remedies that stimulate the adrenal center.*

Milk, fish, poultry and eggs, vegetables, fruit, especially strawberries, oranges and apples, butter, light bread and biscuits, with tea, coffee or cocoa in moderation, etc., are all permissible. Alcoholic beverages, malt liquors, sweet and heavy wines, are never beneficial and are not craved for when water is taken in large quantities. As alcohol becomes oxidized in the blood it antagonizes catabolism, and thus tends to aggravate the morbid process.* Meals should be taken at regular intervals.

In view of the experiments of Gaucher, confirmed by Kolisch, Tandler and Croftan, as to the pernicious influence of xanthin and hypoxanthin upon the kidneys, Halliburton's statement[60] that meat diet causes an increase of uric acid "mainly because it increases the exogenous uric acid from the purin bases, especially the hypoxanthin which it contains" is suggestive, since it is obvious that inadequate catabolism must increase the proportion of the latter and tend to promote not only renal lesions, but also general "gouty" disorders. Kionka and Frey[61] recently confirmed the observation of Kochmann, that excessive meat-feeding caused organic lesions in the liver and kidneys, and also those of Walker Hall, in rabbits, in which similar lesions

* *Author's conclusion.*
[60] Halliburton: "Physiol. Chem. of Muscle and Nerve," p. 45, 1904.
[61] Kionka and Frey: Zeit. f. exper. Pathol., Bd. ii, S. 1, 1905.

were produced by injections of hypoxanthin. Robin[62] found experimentally, that in man the addition of collagenous parts of meat, bones, ligaments, etc., to the diet, increased markedly the production of uric acid—which would mean that of hypoxanthin and xanthin in debilitated subjects. For the influence of alcohol the reader is referred to the article on this agent.

Measures to Increase the Functional Activity of the Adrenal System.—Those of our remedies which approach nearest the normal physiological stimulant of the adrenal thyroidin, in its effects, namely, *iodine* and its salts, especially the potassium and sodium iodide, are of recognized value in this connection, when employed in gradually increased doses, beginning with 5 grains (0.3 gm.) three times daily in a tumblerful of water. *Thyroid extract* is also efficacious, but not in the large doses usually recommended, which increase too suddenly general metabolism and increase the waste-products in proportion; 3 grains (0.2 gm.) after meals may be given without increasing the dose.* *Oxygen* inhalations begun the third day after beginning the use of the thyroid extract will hasten the curative process, since at that time the blood will be found by the coagulation test to contain a larger proportion of fibrin ferment, *i.e.,* adrenoxidase.* (See also p. 782, vol. i.)

Among other agents that have been found efficacious are *strychnine* and *nux vomica,* which not only stimulate the adrenal center, but also the vasomotor center, thus causing constriction of the mesenteric trunks and projection of the blood towards the peripheral capillaries, including those of the liver* where poisons are most actively destroyed. Strychnine is only of real use, however, in debilitated cases, attended with pallor.* This applies likewise to iron, to promote the formation of hemoglobin.

The value of the iodides in gout is well known. Bain[63] found potassium iodide of "peculiar value" in chronic gout, and that it retarded the development of vascular and renal changes. Haig employs the sodium iodide with success, using in conjunction, sometimes, ammonium chloride. I have found thyroid extract, when used as recommended above, of considerable value in gouty cases in which migraine was a prominent symptom. Inhalations of oxygen gas were employed by Croftan[64] with "striking" results, "both as regards amelioration of the subjective symptoms" as well as laboratory findings. That this measure should prove of still greater value when the blood's adrenal secretion is increased by means of thyroid extract, seems obvious. Strychnine has been recommended by Robin[65] and others.

* *Author's conclusion.*
[62] Robin: *Loc. cit.*
[63] Bain: Brit. Med. Jour., June 9, 1900.
[64] Croftan: N. Y. Med. Jour., Aug. 11, 1900.
[65] Robin: Bull. gén. de thérap., vol. cxlvii, p. 603, 1904.

MIGRAINE.

SYNONYMS.—*Sick Headache; Megrim; Hemicrania; Bilious Headache.*

Definition.—Migraine is due to marked hyperæmia of the nerves and nervi nervorum of the painful area, the result, in turn, of abnormal constriction of all arterioles, excepting those of that area which fail to contract owing to functional weakness (sometimes due to organic disease) of their walls. The general constriction of the arterioles is due to excitation of the sympathetic center by toxic wastes, probably of the purin group, which accumulate in the blood owing to hypoactivity of the adrenal system, the insufficiency of auto-antitoxin reducing correspondingly the catabolic properties of the blood.**

Symptoms and Pathology.—Migraine corresponds with epilepsy in its pathogenesis and symptomatology, and the latter may, therefore, be divided into three stages: (1) a prodromal stage or aura, (2) a stage in which the sympathetic system is morbidly active, and (3) a stage in which the vasomotor overactivity is superadded.*

The *prodromal* stage or *aura* differs from that of the epileptic aura, in that it is relatively prolonged, lasting minutes, hours, or days even, in some cases. It may include one or more of the following phenomena: a sensation of pressure at the seat of oncoming pain, dark or bright spots, flashes and other luminous sensations, impaired vision, tinnitus, olfactory and other sensory auræ, vertigo, confusion of ideas, hallucinations, visions, hebetude, somnolence and despondency, anæsthetic areas in the scalp and face, aphonia, etc. In rare instances the premonitory signs occur during sleep, in the form of exciting dreams, violent nightmares, etc. Anorexia, nausea and creeping chills are common precursors of the migrainous attack, however, which usually begins in the morning.

In the *sympathetic* variety, the ordinary migraine, the patient is pale, the features are contracted and the surface is relatively cool, the temporal arteries being small and tense. The pain, at first dull, then more or less acute, is usually unilateral and often located in the supra-orbital, frontal and temporal

* *Author's conclusion.*
** *Author's definition.*

regions; sometimes, however, it extends to the parietal and even the occipital regions. In some cases, the disorder is quite localized, the site of pain being hypersensitive, while the surrounding tissues are relatively cool and insensitive. Unilateral salivation, lachrymation and diaphoresis are occasionally observed. In rare instances, the pain leaves one region to appear in another, which may be quite remote, the stomach, for instance, then suddenly returns to its former location.

Vomiting may occur early in the course of the seizure, but usually it heralds recovery. At the end of a few hours, sometimes days, the patient falls asleep and is soon about. Such attacks occur with more or less regularity, perhaps once a month, every other week, etc., year after year. In men they often cease after middle life, and in women after the menopause.

This form of migraine is primarily due to irritation of the sympathetic center.*

This form, Dubois-Raymond's angiospastic hemicrania, is now generally attributed to a disorder of the sympathetic system. Mollendorff and Latham[66] both attributed migraine to morbid activity of this system, but "in consequence of a defective control or inhibition by an exhausted or enfeebled cerebro-spinal system." The kinship with epilepsy is now generally recognized. Rachford,[67] for instance, says, in a comprehensive study of this relationship: "All writers on this subject are agreed that migraine and epilepsy are kindred diseases, and that this kinship is so close that these diseases are not infrequently twin inheritances from the same neurotic ancestors," and refers to Tisset, Parry, Liveing and Gray as having emphasized this kinship, by cases in which epilepsy appears, and the epilepsy returning when the migraine disappears." Spiller[68] likewise lays stress on this kinship. In a case reported by H. C. Wood[69] the paroxysms began as a migraine, including the prodromes; this lasted two or three hours, then lapsed into a typical epileptic fit, the patient frothing at the mouth, biting his tongue, etc.

The pain, in this form of migraine, is due to marked congestion in the area involved, the result, in turn, of a passive, strictly localized, dilation of the arterioles of that area.* While all the other arterioles of the body contract under the impulses received through their sympathetic terminals, the arterioles of the region affected fail to do so, owing to lesions of their muscular layer.* The nerve region being rendered intensely hyperæmic—since the blocking of all other arteries tends greatly

* *Author's conclusion.*
[66] Mollendorff and Latham: Cited by Liveing: "On Megrim, Sick-headache, etc.," p. 319, 1873.
[67] Rachford: Amer. Jour. Med. Sci., Apr., 1898.
[68] Spiller: *Ibid.*, Jan., 1900.
[69] H. C. Wood: Med. News, Dec. 29, 1894.

to increase the local blood-pressure—severe pain, due mainly to pressure and hyperæmia of the local nervi nervorum, is caused.*

The general sympathetic constriction of the systemic arterioles is shown by the marked relaxation of the abdominal viscera, *i.e.*, the stomach, intestines, liver, etc., to which French clinicians, Glénard, Trastour, Dujardin-Beaumetz and others, have called attention. Their observations were fully confirmed by the more recent researches of Mangelsdorf,[70] in 409 cases, all of which, with one exception, had marked gastric dilation. Examination of a large number of cases suffering from nervous disorders failed to show this symptom, with the sole exception of epileptic subjects. Constriction of the gastric arterioles readily accounts for this phenomenon; the blood supplied to the muscular walls being inadequate, they relax.* This applies as well to any organ, since the irritability of the sympathetic is of central origin, and, therefore, general—in opposition to Dubois-Raymond's view, that it is limited to the cervical sympathetic. The many cases in which tingling and other forms of paræsthesia occur in various parts of the body also point to a central origin.

As to the localized vasodilation which gives rise to pressure upon the nervi nervorum, Mollendorff, Latham, Guttmann, Wilks and Ellenburg have all held that the local lesion was attended by vasodilation and hyperæmia, though unable to account for these phenomena apart from the general statement that they were of "sympathetic-tonic" origin. Henschen, Nordström and Rosenbach, and Bum[71] found lesions in the muscles of the painful areas of the face and scalp. The arteries of these areas being sometimes found to have undergone arteriosclerosis, as is well known, the pathological cause of their tendency to remain patent (while those of normal regions contract) is self-evident.

The second, or *vasomotor* form, corresponds with major epilepsy, in that irritation of the vasomotor center is superadded to that of the sympathetic center.* It is, therefore, but an aggravated form of that just described. The general blood-pressure being raised, the diseased or lax arterioles allow a still greater quantity of blood to reach the sensory terminals, and the arteries of the painful area are dilated and pulsate strongly, the area itself being deeply congested. The pupil in this form—or stage—of migraine is contracted, the blood having penetrated its arterioles notwithstanding the sympathetic constrictor impulses to them.* Hence the greater variety of symptoms witnessed in some cases, spasm of facial muscles, paralysis of the ocular muscles and of the extremities, transient aphasia, etc.

The connection between the sympathetic and vasomotor types is clearly shown by the statement of Gowers,[72] that in some cases, "the pallor gives place to flushing as the pain in the head develops." While admitting, with other neurologists, a vasomotor disturbance, unlike them he regards the latter as of central origin. That engorgement of

* *Author's conclusion.*
[70] Mangelsdorf: Berl. klin. Woch., Bd. xl, S. 1004, 1903.
[71] Bum: Wiener med. Presse, Bd. xxxvi, S. 761, 1895.
[72] Gowers: "Diseases of the Nerv. System," vol. ii, p. 844, 1893.

the local vessels is present is shown by the occurrence of hæmorrhage in some cases—in the orbit, for instance, as in a case reported by Brasch and Levinsohn.[73] "At the end of an attack in which the final dilatation has been marked," writes Gowers, "puffiness of the scalp has been observed in rare cases, and even ecchymoses at the seat of the most intense pain."

At the present time the sympathetic and vasomotor forms are interwoven, owing to the prevailing confusion as to the functions of each system as a unit. A clear differentiation of the two forms was, therefore, impossible, and the pathology of the disease has, therefore, remained obscure. Thus Latham states that there is "first of all, *contraction* of the vessels of the brain, and so diminished supply of blood produced by excited action of the sympathetic." So far, I am fully in accord with him. He adds, however, that "the *exhaustion* of the sympathetic following on this excitement causes the *dilatation* of the vessels and the headache." Here, I cannot sustain him, for "exhaustion of the sympathetic" would entail pain wherever the sympathetic fibers govern the peripheral circulation, *i.e.*, over the entire surface. There is no exhaustion, as I interpret the process: certain arterioles are weaker functionally or organically (as is the heart in many subjects) than others; and are unable as well as the latter to resist the centrifugal pressure of the blood, and yield. Hyperæmia of the cutaneous sensory terminals following, pain is experienced. The meninges and brain may likewise become the seat of an hyperæmic area; hence the convulsive seizures sometimes observed in cases of migraine.

Etiology and Pathogenesis.—The principal cause of migraine, *i.e.*, of the excessive vasoconstrictor phenomena to which the attacks are due, is probably paraxanthin, an active poison, and other members of the xanthin group. These intermediate products of metabolism accumulate in the blood between the migrainous attacks, and when the blood attains a certain degree of toxicity, provoke them by irritating the sympathetic and general vasomotor centers.* They accumulate because they are not adequately converted in the blood into benign and eliminable end-products, owing to deficient activity of the anterior pituitary, and, therefore, of a deficiency of auto-antitoxin in the blood.* In most cases this condition is inherited, gouty disorders of the nervous system being readily traceable in proximate ancestors. The majority of cases develop during or after adolescence, when the adrenal system has not kept pace with the general development. In such cases, this system is able to carry on its functions under ordinary conditions; when, however, any unusual stress is imposed upon it by an excess of physiological poisons, it is not equal to the task and they accumulate.* This accumulation may be hastened by indiscretions in

* *Author's conclusion.*
[73] Brasch and Levinsohn: Berl. klin. Woch., Bd. xxxv, S. 1146, 1898.