in the red corpuscles; it serves to hold the albuminous portion of the hæmoglobin, *i.e.*, the adrenoxidase, within these cells, pending its distribution.* While the adrenal center and the bone-marrow are being stimulated, therefore, as stated above, the iron itself is absorbed by the red corpuscles to form hæmatin, and this pigment, owing to its affinity for adrenoxidase, forms hæmoglobin—or, rather, oxyhæmoglobin.*

The remarkable way in which iron increases the formation of hæmoglobin, in chlorosis for instance, is as well known as is the fact that it is the most important constituent of hæmatin. As to its functional connection with adrenoxidase, the reader is referred to the thirteenth chapter. We have seen that iron is taken up mainly from the duodenum by leucocytes; additional evidence to this effect was recently contributed by Matzner.[203] It is then, as shown by many investigators, including Wöltering[204] and Macallum,[205] deposited in the liver, where, according to Wöltering, Kunkel[206] and others, it undergoes changes that fit it for the formation of hæmoglobin. The researches of Quincke,[207] W. S. Hall,[208] Schmey[209] and others have shown that besides the portion converted into hæmoglobin, any excess of iron was stored in the liver itself, the spleen and the muscles, particularly the myocardium. I have submitted in the first volume evidence suggesting that part of the iron in the liver was carried by eosinophile leucocytes to the capillaries of the alveoli, where it was absorbed by red corpuscles along with the albuminous portion of hæmoglobin, the adrenoxidase.

The presence of iron in chromatin, the living substance of cells, and in the nucleo-proteid out of which it is built, points to a third important action when this metal is administered to subjects in which it is actually deficient:* being endowed with marked catalytic properties, iron probably serves as a catalytic. The red corpuscle being a living cell, its hæmatin, owing to its rich iron content, is its nucleus. The normal elaboration of hæmoglobin is carried on through the iron-laden chromatin of nuclei derived from meats, fruit, vegetables, etc., which thus becomes the mother-substance or "hæmatogen" of hæmoglobin. But once in the corpuscle, the life or working efficiency of its hæmatin (which remains in the cell) must be maintained. Its iron fulfills the identical rôle that the adrenal principle does in the tissue-cell, viz., the albuminous portion of the hæmoglobin (the adrenoxidase), to which it is linked, serving as source

* *Author's conclusion.*
[203] Matzner: Die Heilkunde, 1903.
[204] Wöltering: Zeit. f. phys. Chemie, Bd. xxi, S. 186, 1896.
[205] Macallum: Jour. of Physiol., vol. xvi, p. 268, 1894.
[206] Kunkel: Archiv f. d. ges. Physiol., Bd. lxi, S. 595, 1895.
[207] Quincke: Sajous's "Annual of the Univ. Med. Sci.," vol. v, a-95, 1896.
[208] Hall: Archiv f. Anat. u. Physiol., Physiol. Abth., S. 49, 1896.
[209] Schmey: Hoppe-Seyler's Zeit. f. physiol. Chemie, Bd. xxxix, S. 215, 1903.

of oxygen, the catalytic process continues uninterruptedly until the corpuscle itself is worn out and destroyed.*

Hammarsten refers to the now familiar fact that "the nucleo-proteids contain iron," and that the ash of muscle (meat) contains from 0.04 to 0.1 per 1000 parts.[210] Iron was found in chromatin by Macallum,[211] in the chromatin granules, fibrils and nodal points of the chromatin network in the nuclei of animal and vegetable cells examined, and sometimes in the cytoplasm. Molisch[212] found that in the absence of iron, plants fail to form chlorophyll. The presence of assimilated iron was discerned by Macallum even in the lowest forms of life, the protozoa. Bunge had been led to conclude that the chromatin of plants was the mother-substance of hæmoglobin; Macallum reached the same conclusion as regards both animal and vegetable chromatin.

The catalytic property of iron is now generally recognized. A. Robin and Bardet[213] conclude in this connection that "all the researches of recent years tend to demonstrate that soluble oxides and the metals themselves, when in the colloidal state, can fulfill the part of ferment." As the albuminate formed in the stomach is a colloid and the adrenoxidase converts the organic iron ingested into an oxidase, we have the conditions required for this purpose.* Referring to the function of this ferment, Robin and Bardet remark: "One should say, in truth, that they are catalytic ferments," which "borrow from the left to deal out to the right."

Poisoning.—Poisoning by iron ingested by the mouth is rendered practically impossible by the fact that it is absorbed very slowly, the rest passing out by the intestinal canal. Attempts have been made to ascertain its toxic effects by injecting iron salts, such as the tartrate of iron and sodium, into animals. But introduced in this artificial manner, iron fails to undergo the preliminary gastro-intestinal treatment which prepares it for physiological assimilation.* The results, therefore, are apt to be misleading and are, at best, purely of academic interest.

Therapeutics.—Iron is chiefly used in *anæmia*, and particularly in *chlorosis*. As will be shown in the article on Anæmia, however, it is indicated in a limited number of cases, depression of the functional efficiency of the vasomotor and adrenal centers accounting for the majority of instances in which pallor, muscular weakness, etc., are witnessed.* In the cases of true anæmia, those due to food containing an insufficient quantity of iron, its effects are, of course, striking, as they are in chlorosis. This is readily accounted for in view of the cardinal functions this metal fulfils in the economy.

* *Author's conclusion.*
[210] Hammarsten: *Loc. cit.*, p. 402, 1904.
[211] Macallum: *Loc. cit.*, and Rep. of Brit. Assoc. Adv. of Sci., vol. 1896.
[212] Molisch: Sitz. Wien. Akad., Bd. ciii, Abt. i, S. 554, 1894.
[213] Robin and Bardet: Bull. gén. de thérap., Feb. 25, 1905.

PHOSPHORUS.

Physiological Action.—The rôle of phosphorus in the organism is of cardinal importance in view mainly of its identity as a component: (1) of the nuclein of all cells, including the leucocytes;* (2) of the nucleo-proteid granulations which these cells secrete into the tissue cells to take part in their vital interchanges, and into the blood, to sustain (with adrenoxidase) its normal temperature;* (3) of the thyro-parathyroid ferment, thyroidase;* (4) of the myelin of nerves, which, with the adrenoxidase circulating in the axis-cylinders and their networks in the myelin, generates the nerve-impulse;* (5) of the cell-bodies of all neurons and their dendrites as chromatin, sustaining therein (with their oxychromatin, adrenoxidase) their vitality and functional activity, as it does in all other cells;* (6) of bones, chiefly in the form of calcium phosphate.

The human organism acquires its phosphorus in organic combination from animal and vegetable foods, and it is in such a combination that phosphorus is absorbed. When, therefore, it is administered in an assimilable form in disorders due entirely or partly to deficiency of this element in either or all of the organic bodies enumerated above, it can, in suitable cases, restore function.

The important functions I ascribe to phosphorus were reviewed in the fifteenth chapter, to which the reader is referred. The far-reaching rôle of this element in the organism which the foregoing statements indicate, is well shown by experiments of Forster[214] in dogs, which led this author to conclude that deprivation of phosphorus proved fatal more rapidly than actual starvation. The animals were fed on meat from which all the phosphorus in organic combination was as much as possible removed artificially. The animals soon reached a condition of extreme exhaustion. Conversely, Pouchet and Chevalier,[215] referring to the effects of organic compounds of phosphorus, state that "they increase nutrition, as shown by increase of weight; ameliorate nervous activity and muscular tonus; increase the percentage of hæmoglobin—all phenomena which indicate marked synthetic assimilation under the influence of these compounds."

The therapeutic effects of phosphorus are best obtained by administering this element in organic combination, the glycerophosphates for instance. When phosphorus or any of its oxidizable preparations is used, it becomes oxidized in the stom-

* *Author's conclusion.*
[214] Forster: Zeit. f. Biol., Bd. ix, S. 297, 1873.
[215] Pouchet and Chevalier: Bull. gén. de thérap., Dec. 30, 1905.

ach by the adrenoxidase of the gastric juice, or in the intestine by that of the intestinal juice.* It is then absorbed as hypophorous or phosphoric acid, an inert substance which the organism eliminates as a useless waste along with the phosphoric acid derived from tissue metabolism. Hence the frequency with which phosphorus proves of no therapeutic value.

Cushny[216] states that "the fate of phosphorus in the body is still obscure," but that "it is possible that some of it is oxidized to phosphoric acid." Ranvier[217] found that when phosphorus was introduced under the skin, the only result was arrest of local nutrition. Being endowed with intense affinity for oxygen, it obviously depletes the neighboring tissues of theirs and becomes itself oxidized. Cau[218] also found that phosphorus was oxidized by the tissues. The presence of adrenoxidase in the tissue fluids fully accounts for this, since it forms part, as we have seen, of the gastric secretions. The oxidized portion of what phosphorus is ingested loses its toxicity, for, as stated by Cushny, "as soon as it is oxidized, phosphorus loses its specific action, all the acids being comparatively harmless." This has been emphasized by the researches of Bókay,[219] Stassano and Billon,[220] Frenkel[221] and others. The last-named author found that, "contrary to the affirmations of the partisans of phosphoric acid, the latter is incapable of assimilation by the economy, and is excreted in its totality."

Untoward Effects and Acute Poisoning.—The presence of adrenoxidase in the blood* explains many facts which so far have remained obscure.*

If the dose of phosphorus is sufficiently small, it may all be oxidized and prove harmless. When, however, the dose is large, the secretions are not alone deprived of their oxygen,* but the cellular elements of the gastric mucous membrane likewise. Severe gastric pain, eructations of gas emitting a strong odor of garlic occur, and the patient experiences a sensation of heat along the œsophagus, with great thirst, headache, nausea, vomiting, the vomitus being often luminous in the dark —all due to a severe gastro-adenitis thus excited. Erosions may involve the local vascular supply and entail the presence of blood in the vomited material. What portion of the phosphorus remains unoxidized on passing down to the intestine excites therein corresponding lesions, even the colon being involved in the morbid process. The violent burning pain in the

* *Author's conclusion.*
[216] Cushny: *Loc. cit.*, fourth edition, p. 601, 1906.
[217] Ranvier: Cited by Manquat: *Loc. cit.*, vol. i, p. 969.
[218] Cau: Thèse de Paris, 1901.
[219] Bókay: Zeit. f. physiol. Chem., Bd. i, S. 157, 1877-78.
[220] Stassano and Billon: C. r. de la Soc. de biol., T. lv., p. 482, 1903.
[221] Frenkel: Le progrès méd., Mar. 3, 1906.

epigastrium gradually extends throughout the entire abdomen; diarrhœa develops rapidly into violent purging, the dejecta likewise being phosphorescent in the dark, and sometimes bloody. At times the local inflammatory process is so severe that reflex excitation of the intestinal glandular elements and muscles can no longer occur and constipation results.

The well-known gastric lesions are duplicated in the intestinal canal. Plavec[222] found experimentally in dogs that phosphorus caused hæmorrhagic injection of the duodenal mucous membrane, and in some instances ulceration. In an acute case reported by Newey,[223] the stomach, which contained eight ounces (250 gms.) of blood, showed areas of softening and ulceration. The entire intestine presented corresponding signs, the transverse colon being intensely inflamed. The vascular engorgement observed even in acute cases is not due to the local action of the poison alone, however, as is shown below.

Death may occur suddenly during this, the acute stage, but it is due to a cause differing entirely from that which entails a fatal issue when the case is prolonged, namely, reflex inhibition of the heart,* by excessive (sympathetic) constriction of its arterioles.* This organ becomes suddenly very weak, the pulse likewise; the pupils are widely dilated, and coma and death soon follow.

Wood[224] states that "in the very acute cases of phosphorus-poisoning a primary condition of pronounced cardiac weakness, passing into paralysis, may be present." Witherstine[225] refers to a case in which death occurred in half an hour. Chtchebrak[226] found that the first action of the drug was to increase the rapidity of the circulation and to raise the blood-pressure, this being immediately succeeded by a decline of vascular tension. As inhibition of the heart is due to excessive vasoconstriction of its arterioles,* the preliminary rise of blood-pressure indicates how phosphorus can provoke cardiac paralysis.

In the majority of cases, the symptoms, after a period of acute suffering, lasting from a few hours to two days, abate, and recovery apparently occurs. After one or more days of relative comfort, however, the acute symptoms reappear. But now the pain extends to the liver, which organ may be found to be enlarged, and the vomiting often contains "coffee-ground" material, *i.e.*, altered blood. The stools, if diarrhœa prevails, are occasionally bloody and are apt to be clay-colored, the latter fact indicating the absence of bile. Neither the vomited

* *Author's conclusion.*
[222] Plavec: Arch. f. exp. Path. u. Pharm., Bd. xlviii, S. 150, 1902.
[223] Newey: Lancet, Sept. 22, 1900.
[224] Wood: *Loc. cit.*, thirteenth edition, p. 461, 1906.
[225] Witherstine: Sajous's "Annual and Analyt. Cyclo.," vol. v, p. 471, 1900.
[226] Chtchebrak: "Les Bactéries," Paris, 1891.

material nor the stools are phosphorescent at this stage—evidence to the effect that the greater part, at least, of the phosphorus (the unoxidized remnants) has been gradually absorbed into the circulation, and that the dejecta now contain only phosphorus oxides.

As previously stated, a portion of the phosphorus is oxidized in the alimentary canal by the oxidizing substance of its secretions. "It has of late years been demonstrated," says Wood,[227] "that phosphorus passes into the blood as *phosphorus*, and not in the form of phosphoric acid or other compound." Wegner,[228] Husemann and Marmer, Dybkowsky[229] and others have found phosphorus not only in the blood and liver, but also in practically all tissues. On the other hand, Poulet[230] has ascertained that it was eliminated as hypophosphoric acid, while Santesson and Malmgren[231] observed after administering large doses of phosphorus sesqui-sulphide to rabbits, a remarkable excess in the output not only of nitrogen, sulphates and ammonia, but also of phosphoric acid.

The recurrence of acute symptoms marks the beginning of the so-called "subacute" stage, a time when the blood's functional activity has become impaired mainly by active hæmolysis.* This is due to the fact that the phosphorus-laden nucleo-proteid of the plasma is supplemented by the phosphorus absorbed from the alimentary canal.* The simultaneous presence of an excessive proportion of phosphorus and adrenoxidase in the blood-plasma, by liberating heat-energy to an unusual degree, correspondingly enhances the proteolytic activity of the blood's trypsin, and hæmolysis, *i.e.*, destruction of the red corpuscles, occurs.* As an inordinate proportion of adrenoxidase is utilized in the process and the coagulating properties of the blood are due to this substance (which is, we have seen, the "fibrin ferment"), the blood itself loses its coagulating properties.* It becomes unduly fluid, and, passing readily through the capillary walls, ecchymoses occur in various parts of the body, besides, in many instance, hæmorrhages from the nose, uterus, in the retina, and occasionally gangrene. The normal result of such a condition of the blood soon shows itself, *i.e.*, great weakness, collapse, and death by cardiac failure—often preceded by convulsions caused by the accumulation of

* *Author's conclusion.*
[227] Wood: *Loc. cit.*, eleventh edition, p. 438, 1900.
[228] Wegner: Virchow's Archiv, Bd. lv, S. 11, 1872.
[229] Dybkowsky: Hoppe-Seyler's Med.-Chem. Untersuchungen, H. i, S. 54, 1866.
[230] Poulet: Gaz. méd. de Paris, Aug. 17, 1872.
[231] Santesson and Malmgren: Skand. Arch. f. physiol., Bd. xv, S. 259, 1904.

toxic wastes which the deficiency of adrenoxidase in the blood entails.*

Corin and Ansiaux[232] ascertained that "fluidity of the blood is found only in cases of phosphorus-poisoning which have followed a *subacute* course." When introduced into the blood-stream, phosphorus is independent therein of the synthesis of nucleins, for Röhmann[233] found that inorganic phosphorus compounds were hardly used at all. It is, therefore, as *surplus* to the nucleo-proteid's phosphorus that it occurs in the blood—the aggregate thus becoming pathogenic by increasing, with the adrenoxidase, general metabolism. That this actually occurs is shown by the fact that there is, as stated by Cushny,[234] "a very considerable increase in the nitrogen" during this stage, "even although the patient continues to *fast*." That red corpuscles are destroyed during this process has been emphasized by the investigations of Vogel[235] in birds; the hæmolysis began the second day, and by the sixth the comparative blood-count showed that one-half of the red corpuscles had been destroyed. Similar experiments in mammals (dogs) by d'Amore and Falcone[236] gave similar results. Wood[237] refers to Concato as having shown that the red corpuscles were "diminished in size and altered in form"—proof that they were undergoing destructive metamorphosis.

The fluidity of the blood is evidently a feature of the subacute stage. Cevidalli[238] found that in order to render the blood uncoagulable in dogs, phosphorus had to be injected from five to ten days. Again, it is undoubtedly to the destruction of adrenoxidase (the fibrin ferment) that the fluidity of the blood is due. Cevidalli also observed a "gradual diminution and disappearance of the coagulating ferment." The lethal phenomena are obviously, under these conditions, due to the same cause: Cushny,[239] referring to Araki,[240] remarks: "In the statement that lack of oxygen plays a part in phosphorus-poisoning, he only confirms the impression of many earlier writers."

A striking symptom of the subacute stage is jaundice, first of the conjunctivæ, then of the whole body, which may appear from thirty-six hours to several days after ingestion of the poison. This is the result of several factors. The phosphorus from the alimentary canal having first to pass through the liver, it provokes therein a process identical to that in the blood; here, however, the red corpuscles are not alone attacked, but the hepatic structures *per se* likewise, and necrotic foci are formed in various parts of the organ.* Hence the fact that it becomes enlarged and painful. At first the activity of the liver-cells is greatly enhanced, as shown by a marked increase

* *Author's conclusion.*

[232] Corin and Ansiaux: Vierteljahresschrift f. gerichtliche Med. u. Sanitäts., S. 80, 212, 1894.
[233] Röhmann: Berl. klin. Woch., Bd. xxxv, S. 789, 1898.
[234] Cushny: *Loc. cit.*, fourth edition, p. 599, 1906.
[235] Vogel: Arch. intern. de pharm. et de thérap., T. x, fasc. iii et iv, 1902.
[236] d'Amore and Falcone: Arch. de pharmacod. de Gand, vol. i, p. 247, 1894.
[237] Wood: *Loc. cit.*, thirteenth edition, p. 436, 1906.
[238] Cevidalli: Riforma Med.; Phila. Med. Jour., Feb. 7, 1904.
[239] Cushny: *Loc. cit.*, third edition, p. 603, 1899.
[240] Araki: Zeit. f. physiol. Chem., Bd. xvii, S. 311, 1892-93; Bd. xix, S. 433, 1894.

in the pigment excreted—"pigment," meaning here bilirubin and hæmatoidin, both of which, we have seen, are reduced adrenoxidase.* Finally, the bile thickens, owing to the presence therein of its usual constituents, and also of cellular detritus, broken-down corpuscles, etc.—all of which contribute to block the biliary passages. Jaundice appears at this time.

By "jaundice" here is meant a condition due to the resorption into the general circulation of reduced adrenoxidase that should have passed out with the bile.* On reaching the skin, this substance, by a process similar to that which prevails in the pathogenesis of bronzing, gives it its yellow hue—an early stage of melanosis.* The reduced adrenoxidase is at the time, and even before, found in the urine as "bilirubin" or "hæmatoidin."

That destruction of the hepatic tissues is due to the action of some autolytic ferment has been suggested by Jacoby.[241] He also noted the disappearance of fibrinogen from the hepatic blood; this substance, we have seen, is composed of nucleo-proteid fibrinogen proper and adrenoxidase (fibrin ferment). The destructive process in the liver is a familiar pathological fact. Podwyssotsky[242] found necrotic foci in this organ. West[243] found the hepatic cellular elements converted into a fine granular detritus amidst which the nuclei could hardly be detected. Cushny[244] states that "the jaundice may also be accounted for in part by the destruction of the red cells of the blood and consequent increase of pigment formation in the liver." The intra-corpuscular constituent of hæmoglobin (which only leaves them under abnormal conditions, one of which is when the corpuscles are broken up) is, we have seen, hæmatin. Wood[245] states that "hæmatin crystals are occasionally found in the viscera." Demarbaix and Wilmart,[246] moreover, found hæmatoidin (adrenoxidase) in the urine. The sequence of events given above was traced in dogs with great assiduity by Stadelmann.[247]

The engorgement of the biliary passages, besides deflecting into the hepatic veins what reduced adrenoxidase should have passed out with the bile, thus causing its return to the blood-stream,* simultaneously provokes engorgement of the entire vascular system. The vessels, whose walls tend already to dilate owing to the lowered metabolism in their muscular walls incident upon the hæmolysis and deficiency of adrenoxidase in the blood *per se*, are thus submitted to centrifugal pres-

* *Author's conclusion.*

[241] Jacoby: Zeit. f. physiol. Chem., Bd. xxx, S. 174, 1900.
[242] Podwyssotzky: St. Petersburg med. Woch., Bd. xiii, S. 211, 1888.
[243] West: Lancet, Feb. 4, 1893.
[244] Cushny: *Loc. cit.*, fourth edition, p. 598, 1906.
[245] Wood: *Loc. cit.*, thirteenth edition, p. 464, 1906.
[246] Demarbaix and Wilmart: Presse méd., vol. xxi, p. 25, 1869.
[247] Stadelmann: Archiv f. exp. Path. u. Pharm., Bd. xxiv, S. 270, 1888.

sure and still further dilated.* The cerebral vascular system, including its cellular elements, becoming hyperæmic,* headache, restless and dreamy sleep or wakefulness are complained of. If the cerebral congestion becomes very great,* wild delirium may occur. A similar condition of the spinal system* may evoke disorders of sensation, particularly of the temperature sense, hyperalgesia, pains suggesting neuritis, muscular twitchings, localized spasms or even general convulsions, the latter being often the precursors of death.

In cases that recover, the phosphorus available in the intestine has finally been either oxidized, eliminated or absorbed; the destruction of red corpuscles and hepatic cellular elements then ceases. The bile gradually losing its viscidity, the accumulated detritus is voided into the intestine and eliminated; and the skin "pigment" being absorbed, relatively normal conditions are restored, though the patches of destroyed tissue in the stomach and liver may become the seat of interstitial connective-tissue proliferation. In the liver, this may assume the type of a true cirrhosis with atrophy of the organ. Digestive and nervous disorders often persist some time after recovery.

A striking feature of the morbid process is the presence of fatty degeneration in all organs, including the smallest arterioles of the spinal cord. The so-called "fat" here is a mixture of blood-constituents, fibrin, nucleo-proteid, etc., formed when the supply of adrenoxidase is inadequate to maintain the temperature and fluidity of the blood.* It is a post-mortem phenomenon corresponding in a measure with that of myosin formation.*

That the blood-pressure is lowered has been observed by a number of investigators. Schiff[248] years ago noted that the arteries were so widely dilated after death from phosphorus-poisoning, that the veins were comparatively empty. Pal[249] ascribed this vasodilation, not to the weakened cardiac power, but to dilation of the vessels themselves. Cornil and Brault[250] ascribe the lesions found in the interstitial process in the vascular walls and the organs in general to a *sui generis* fatty process, *i.e.*, one preceded by no inflammation, and beginning six or seven hours after the ingestion of the poison and terminating four to seven days thereafter. Vollbracht,[251] in accord with these observations, found the vascular walls degenerated and associated with gangrene of both extremities.

* *Author's conclusion.*
[248] Schiff: *Ibid.*, Bd. ii, S. 345, 1874.
[249] Pal: Wien. klin. Woch., Bd. ix, S. 999, 1896.
[250] Cornil and Brault: Manquat: *Loc. cit.*, vol. i, p. 972, 1903.
[251] Vollbracht: Wien. klin. Woch., Bd. xiv, S. 1288, 1901.

The "fatty degeneration" of phosphorus-poisoning is due, as elsewhere, to a deficiency of adrenoxidase.* After referring to the older view, that lessened oxidation of proteid fats explained fatty degeneration, as inconsistent with known facts, Cushny[252] remarks: "Lessened oxidation and fatty degeneration occur together under so many conditions, however, that there must almost certainly be a causal relation between them, though it is impossible to state at present its exact nature."

Chronic Phosphorus Poisoning. — This form of poisoning, observed usually among persons employed in the manufacture of white sulphur matches, differs from the acute form in that the quantity inhaled at a given time is inadequate to provoke acute phenomena. The continued absorption from the respiratory surfaces, however, finally gives rise to practically all the symptoms already enumerated, the most common of which are weakness, abdominal pains, anorexia, a garlicky breath, gastric disorders, diarrhœa or obstinate congestion, a subicteric color of the skin, wasting, etc. These cases differ from those of the acute type, in that they suffer from necrosis of the lower jaw. This condition has been found to be the result of penetration of phosphorus-fumes to this bone through the intermediary of carious teeth. This process is readily explained when the fact that bony tissues are dependent, like all others, upon adrenoxidase for their oxygen, is taken into account: the nutrient plasma of the bone being deprived of its oxygen by the phosphorus, which has a greater affinity for it than the bone itself, the latter, no longer nourished, dies.*

Wegner[253] found that rabbits kept in phosphorus-fumes suffered in no way from necrosis if their teeth were sound, but that injuries in which the jaw-bone could be reached by the fumes were followed by periostitis and necrosis. Magitot[254] observed that phosphorus-workers supplied with perfect teeth were free from necrosis even after years' employment at this occupation, while all those who had bad teeth suffered from necrosis.

The *treatment of phosphorus poisoning* is described in a special section at the end of this volume.

Therapeutics.—The physiological function I have ascribed to phosphorus in the tissue-cells (including nerve-cells) and blood, viz., to liberate heat-energy by combining with oxygen of the adrenoxidase,* places this element among our chief resources as a therapeutic agent, since it constitutes one of the

* *Author's conclusion.*
[252] Cushny: *Loc. cit.*, third edition, p. 605, 1899.
[253] Wegner: Virchow's Archiv, Bd. lv, S. 11, 1872.
[254] Magitot: C. r. de l'Acad. de méd., Mar. 12, 1895.

pillars of the vital process itself.* By the use of strychnine, digitalis, coca, etc., we greatly stimulate functional activity, but the judicious adjunction to them of substances which actually take part in function, such as phosphorus, iron, appropriate foods, etc., we supply besides, the building material.* It is as such that phosphorus is especially beneficial in *neurasthenia* due to overwork, anxiety, mental strain and sexual excesses. Here, it actually replaces missing materials.* In *anæmia*, the addition of phosphorus to iron will render the latter effective where before it was useless, because the improvement of the oxygenizing power of the blood requires a corresponding increase of available nuclein.* In *impaired nutrition* following exhausting diseases, such as influenza, typhoid, typhus, intermittent fevers, etc., the same indication prevails. This applies likewise to debility following *prolonged lactation, overwork, shock, sorrow,* etc. In the disorders which are thought to be normal results of old age, such as *loss of memory, mental torpor, insomnia,* etc., an inadequate supply of phosphorus, iron and iodine, is the pathogenic factor, and these agents will often serve to prolong a useful life. In the depraved condition to which *morphinomania* and *chronic alcoholism* finally drive the patient, the judicious use of phosphorus after cessation of the habit is conquered, not only hastens recovery, but tends to prevent its recurrence by enhancing the nutrition and conductivity of all nerves.* Finally, the value of phosphorus in *rickets* and *osteomalacia* is generally recognized.

* *Author's conclusion.*

CHAPTER XX.

THE INTERNAL SECRETIONS IN THEIR RELATION TO PHARMACODYNAMICS (*Continued*).

THE SYMPATHETIC CENTER AS THE SLEEP CENTER.

Bradbury, in his Croonian Lecture,[1] stated eight years ago, that "notwithstanding the brilliant and laborious researches of physiologists and neurologists during recent years, the phenomenon of sleep is still enveloped in mystery"—a conclusion which is still applicable. The reason for this is plain in view of the fact pointed out by myself in the first volume, that this function is intimately connected with the circulation of oxidizing substance (adrenoxidase) *in* the neurons and their dendrites, that sleep is due to a diminution of this substance in these elements, and that the adrenal system is intimately connected with this process. To overlook this intrinsic nervous circulation and the ductless glands in this connection is to perpetuate the "mystery" to which Bradbury refers. And this applies not only to the mechanism of sleep, but also to a widespread source of suffering, insomnia, and, moreover, to the action of hypnotics and anæsthetics.

A diminution of adrenoxidase in the nervous elements referred to entails a corresponding reduction of metabolic activity and other phenomena connected therewith. Howell[2] wrote recently: "The central and most important fact of sleep is the partial or complete loss of consciousness, and this phenomenon may be referred directly to a lessened metabolic activity in the brain tissue, presumably in the cortex cerebri." Again, "the physiological oxidations are also decreased, as shown by the diminished output of carbon dioxide." A fall of blood-pressure is also present, as shown by Tarchanoff[3] in dogs and by Brush and Fayerweather[4] in man.

[1] Bradbury: Lancet, June 24, 1899.
[2] Howell: "T. B. of Physiol.," p. 238, 1905.
[3] Tarchanoff: Arch. ital. de biol., vol. xxi, p. 318, 1894.
[4] Brush and Fayerweather: Amer. Jour. of Physiol., vol. v, p. 199, 1901.