CHAPTER XXXI.

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

THE ADRENAL SYSTEM IN DISEASES OF THE BLOOD.

The pathogenesis of the "anæmias" is considerably elucidated by the views and evidence I submit in the present volume. In true anæmia, the fact that the adrenal system governs the proportion of adrenoxidase—oxyhæmoglobin—that the blood contains, at once imposes itself as an important feature of the problem, especially in view of the purpose I have ascribed to the iron-laden hæmatin, viz., to anchor this oxidizing substance in the red corpuscles pending its distribution to the tissues. The pathogenesis of the disease, as I conceive it—absence of iron to hold the oxyhæmoglobin (adrenoxidase) and insufficiency of the latter through depressed activity of the adrenal system—becomes self-evident. In pernicious anæmia, the exaggerated hæmolysis finds as ready an explanation in an excess of auto-antitoxin in the blood through overactivity of the adrenal system, excited by autotoxins derived from food and tissue-wastes. In chlorosis we have a more complicated order of phenomena: marked hypoactivity of the adrenal system, and, as a result, general vasodilation and ischæmia of the peripheral vessels. The general vascular relaxation entails another important pathogenic feature, however: inadequate circulation of the blood in the hepatic capillaries, and therefore imperfect assimilation of iron, a function in which the liver plays a cardinal rôle. Finally, in hæmophilia, we have an example of congenital hypoactivity of the adrenal system. This entails a constant deficiency of adrenoxidase in the blood, and since adrenoxidase is the fibrin ferment, the coagulative properties of the blood are very deficient; it preserves its fluidity even when a vessel is ruptured therefore, and flows from the vessel as if it were water.

ANÆMIA.

Definition.—Anæmia, a disorder characterized by pallor, in which the red corpuscles may or may not be destroyed, may be brought on by several morbid conditions, the most prominent of which are: a deficiency in the corpuscular hæmatin, of the iron which anchors the adrenoxidase (oxyhæmoglobin) in the red corpuscles pending its distribution to the tissues; hypoactivity of the adrenal system and the resulting general vasodilation, a condition which entails an accumulation of blood in the splanchnic area and ischæmia of the cutaneous capillaries.*

Symptomatology, Pathology and Pathogenesis.—Some pallor of the skin and mucous membranes, with perhaps slight dyspnœa, and a tendency to become fatigued without undue exertion, constitute the entire symptomatology of mild cases. In more advanced or grave cases, the pallor may become very marked; the mucous membranes, especially those of the fauces and gums, being almost blanched. There is mental and physical depression and a marked tendency to indolence. "Palpitations," faintness, irritability, neuralgia, anorexia, indigestion, dyspnœa on exertion, headache, disorders of menstruation, and constipation are common phenomena. There is general hypothermia of the periphery, the hands and feet being usually cold. The pulse is often rapid, large and soft, though no fever be present. The specific gravity of the urine is low, and the urea excreted may be considerably below normal. Œdema, especially of the ankles, is occasionally observed. Physical examination in severe cases usually elicits the fact that the heart is dilated, and a venous hum in the veins of the neck, coupled with a systolic bellows murmur over the carotid arteries, is frequently heard. In some instances, a systolic murmur may be detected over the aorta and pulmonary artery.

These phenomena may be said to represent the aggregate symptomatology—as to main signs—of the various forms of benign anæmia. In some instances but few of these signs appear; in others the entire symptom-complex is very marked.

Examination of the blood may reveal no diminution of the red corpuscles, or of the hæmoglobin. But this is a *spurious* or *pseudo-anæmia*, the result of relaxation of the vascular system

* *Author's definition.*

and accumulation of the blood in the great central vessels at the expense of that in the peripheral capillaries. This condition, due to depression of the vasomotor center, such as that produced by chloral, the bromides (*q.v.*), etc., is generally observed in nervous disorders, in new-comers in tropical countries, and arteriosclerosis and other conditions.

Ehrlich and Lazarus[1] define anæmia as "a quantitative and qualitative diminution of the amount of blood." This definition does not include, however, a morbid condition which explains many cases of benign anæmia we meet in practice, *i.e.*, those due to an accumulation of blood in the greater central blood-channels, a condition which, by depleting the peripheral capillaries, provokes pallor. Under the caption "Local Anæmia," Osler,[2] for instance, states that "local anæmia of the brain, causing swooning, ensues when the mesenteric channels, *capable of holding all the blood of the body*, are wide open." Vasomotor relaxation alone accounts for this and the sudden pallor that attends swooning proves that chronic depletion of the cutaneous vessels may be a cause of chronic pallor, which may be, and often is, taken for true anæmia. Indeed, several other characteristic symptoms of true anæmia may appear; thus dyspnœa may result from the fact that the capillaries of the air-cells likewise fail to receive sufficient blood to satisfy the needs of the body, as emphasized by J. H. White.[3] The irritability so often observed in anæmics finds an explanation in the fact that autotoxins accumulate in neural elements, including those of the brain, when the oxidation processes therein are slackened. The increase of cardiac dullness which denotes dilation, a symptom upon which F. Müller[4] lays stress, may likewise be caused by diminution of the blood supplied to the myocardium. Cohnstein and Zuntz[5] long ago attributed to vasomotor narrowing of the peripheral vessels the marked fluctuations in the number of red cells so often observed. This undoubtedly accounts for the observation of Pokrowsky[6] that the first dose of iron (which, we have seen, stimulates the vasomotor center) sometimes causes a rise of temperature—which would mean, in the light of the foregoing data, that the peripheral capillaries become richer in arterial blood.

Anæmia due to *insufficient food* likewise belongs to the category of pseudo-anæmias.* The red corpuscles not only fail to become reduced in number during periods of experimental starvation, but they are sometimes increased. The percentage of leucocytes, however, may be considerably reduced, owing to the absence of the periodical leucocytosis connected with digestion and inadequate nutrition of the leucocytogenic organs.* Since the salts of the blood, especially sodium chloride, are obtained from food, they are also deficient; the albumins

* *Author's conclusion.*

[1] Ehrlich and Lazarus: Nothnagel's "Encyclo. of Pract. Med.," Amer. ed., vol. on Dis. of Blood, p. 15, 1905.

[2] Osler: "Pract. of Med.," sixth edition, p. 718, 1905.

[3] J. H. White: Birmingham Med. Rev., Oct., 1900.

[4] Müller: Berl. klin. Woch., Bd. xxxii, S. 824, 1895.

[5] Cohnstein and Zuntz: Pflüger's Archiv, Bd. xlii, S. 303, 1888.

[6] Pokrowsky: Virchow's Archiv, Bd. xxii, S. 476, 1861.

are likewise diminished for the same reason. The hypothermia, coldness of the extremities, etc., observed in those cases indicate that, as in the group reviewed above, there is not only deficient general oxygenation—owing to the depressed condition of the adrenal center—but also depression of the general vasomotor center and recession of blood from the periphery to the great central mesenteric channels.*

Senator and Müller[7] observed in the fasting subjects, Cetti and Breithaupt, that in the former the number of red corpuscles was increased 1,000,000 after ten days' fast, while the leucocytes decreased from 12,000 to 4200. Referring to this and other experiments, Lazarus[8] says in this connection, "from exact experiments on man and animals, therefore, the conclusion can be drawn that sudden absolute withdrawal of nourishment is not capable of producing an anæmia." In the course of his remarks on the influence of insufficient food, he also states: "Sahli first, after him Laache, Oppenheimer and others, demonstrated that individuals with very pale skin and mucous membranes frequently showed a normal percentage of hæmoglobin and a normal number of corpuscles."

In the toxic anæmias, *i.e.*, those due to *various poisons* and to *bacterial toxins*, the vasomotor center is likewise depressed.* To this category belong the anæmias observed (1) in workers in lead and arsenic, (2) in chronic alcoholism and the excessive use of tobacco, (3) syphilis, malaria, malignant tumors, diphtheria, tuberculosis and helminthiasis.

In this group of anæmias, however, another morbid factor asserts itself, namely, deficient functional activity of the adrenal center, which entails a corresponding deficiency of adrenoxidase in the blood.* Adrenoxidase being fibrin ferment,* the coagulation period of the blood is lengthened. The diminution of adrenoxidase causing the quantity formed to be utilized by the blood itself and the tissues with unusual rapidity,* the red corpuscles, its carriers,* become more or less reduced in size (poikilocytosis) because they are inordinately depleted. As adrenoxidase is likewise the albuminous constituent of the hæmoglobin molecule,* the hæmoglobin is reduced (oligochromæmia), but less so usually than the red corpuscles themselves; since the adrenoxidase is continually being reformed through the adrenals,* while the red cells are diminished pathologically. The reduction of

* *Author's conclusion.*

[7] Senator and Müller: *Ibid.*, Bd. cxxxi, Supp., 1893.

[8] Lazarus: Nothnagel's "Encyclo. of Pract. Med.," vol. on Dis. of Blood, p. 191, 1905.

the red corpuscles (oligocythæmia) is a normal result of the deficiency of adrenoxidase—the bone-marrow being inadequately nourished,* the genesis of the cells is correspondingly inhibited. The same morbid influence naturally impairs leucocytogenesis;* if, therefore, the blood is examined between the postprandial periods of leucocytosis,* the relative percentage of leucocytes is found reduced. When this is marked, the postprandial leucocytosis is also unusually low and less food, including blood-salts, being taken up from the alimentary canal,* the alkalescence of the blood is deficient. This is shown by the increase of the blood-platelets,* a concomitant phenomenon.

The familiar paralytic phenomena of chronic lead-poisoning clearly point to the impairment of nutrition caused by lead, a function governed, we have seen, by the vascular and adrenal systems. As to arsenic, ample evidence has been submitted showing that it is the physiological antagonist of thyroidase which upholds the functional efficiency of the adrenal center. As to its influence on the vasomotor center, H. C. Wood[9] states that "arsenic greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure." Chronic mercurial poisoning provokes symptoms similar to those of lead, but as we will see, the anæmia here is due to hæmolysis.

As to the rôle of the vasomotor and adrenal systems in the anæmias due to various toxins, Grawitz[10] has shown that extracts of malignant growths do not, when injected into the blood, affect the red corpuscles or the hæmoglobin directly, thus proving that the anæmia is due to some indirect influence. The identity of the organ upon which this influence is produced is well shown by the observation of Loeb and Smith,[11] that the cephalic portion of ankylostoma contains a substance which *inhibits* coagulation. As adrenoxidase is the fibrin-ferment, the depressing action of the toxic substance on the adrenal center is self-evident. In the light of this fact and others previously submitted, the sequence of events recited above assumes a normal aspect.

The *anæmias due to hæmorrhage* following injuries, or from the lungs, stomach, intestines, uterus, kidneys, and ruptured aneurism, lesions of intestines due to parasites, violent epistaxis, or occurring in the course of purpura, scurvy, etc., are marked in proportion as the blood lost during a given time is great. The anæmia is rapidly developed, the face being blanched if the loss is great. This is promptly followed by great muscular weakness, weak and rapid pulse, cold sweats, coolness, especially of the extremities, dyspnœa, vertigo, fainting, weakness of the voice, tinnitus, hallucinations of smell, flashes of light

* *Author's conclusion.*
[9] H. C. Wood: "Therapeutics," etc., eleventh edition, p. 447, 1900.
[10] Grawitz: Virchow's Archiv, Bd. lxxvi, S. 353, 1879.
[11] Loeb and Smith: Proceedings Pathol. Soc. of Phila., vol. xxv, p. 173, 1904.

and finally syncope, during which there may be delirium and convulsions, and finally, death. If, however, the hæmorrhage cease spontaneously, or be arrested before one-half of the blood in the body has been lost, recovery may ensue, the patient remaining extremely weak for some time. In less severe cases, two or three weeks suffice to complete the recovery, especially in women.

After moderate hæmorrhages the liquid portion of the blood is replaced at the expense of the lymph in the tissues. As this liquid is serum, the cellular elements are alone reduced, the red cells numbering as low as 2,000,000 in these cases and below 1,000,000 after severe hæmorrhages, though the leucocytes, which are produced with great relative rapidity,* may be somewhat increased. Water being simultaneously absorbed from the alimentary canal in the more severe cases, the increase of both fluids in the blood is more rapid than that of the cells and hæmoglobin; as the case progresses, therefore, examination of the blood may suggest an unfavorable course, *i.e.*, that the cells and hæmoglobin are steadily reduced. This phenomenon is but a temporary one, however; after a few days the tide turns and uninterrupted recovery follows. This is mainly because the adrenals, of all organs, seem alone to continue their important functions uninterruptedly.* Proof of this is afforded by the facts that the blood becomes much more coagulable immediately after bleeding and that the blood-platelets are also greatly increased. Both the blood-platelets and the fibrin ferment being adrenoxidase, the manner in which the coagulability is increased is obvious.* The relative paucity of red corpuscles causes some, at least, of these cells to absorb an unusual proportion of adrenoxidase and they appear swollen.* In most cases, however, their size is somewhat reduced; they are paler than usual, and many of them are nucleated.

The leucocytosis that attends the digestive process, inflammatory processes, etc., indicates that a great relative genesis of these cells can occur physiologically as implied above. The increase of coagulability is referred to by Ehrlich and Lazarus[12] as an "important alteration which takes place immediately after the hæmorrhage, and is sometimes active in checking it. According to E. Freund's investigations," add these authors, "the time of coagulation may be hastened from nine to three minutes by hæmorrhage." Under hæmophilia we will see that this is

* *Author's conclusion.*
[12] Ehrlich and Lazarus: *Loc. cit.*, p. 163, 1905.

precisely what occurs when thyroid extract is given, and that the increase of coagulability is due to an increase of fibrin-ferment, *i.e.*, of oxidase, in the blood. The fact that the fibrin ferment (adrenoxidase) and the blood-platelets are identical substances, is further sustained by the additional statement of Ehrlich and Lazarus that, as observed by Hayem, "the blood-platelets are markedly increased in post-hæmorrhagic anæmia"—concurrently, therefore, with the increased coagulating properties of the blood.

Another important cause of anæmia, especially among the poor, is the use of *food deficient in iron*, as the only nutriment, *i.e.*, milk, bread, rice, potatoes, etc. The hæmoglobin percentage not only fluctuates according to the quantity of iron in the food, because this metal is the fundamental constituent of hæmatin (the coloring-matter of hæmoglobin), but also because it serves as binding agent between the hæmatin and the adrenoxidase (the albuminous portion of the hæmoglobin molecule) as the latter is being formed in the lungs.* Besides this cardinal function, iron is an ubiquitous component of the chromatin of nuclei, the living portion of the cell.* Hence it is also found in nucleo-proteid, the food-product from which the structural components of both hæmoglobin and chromatin are derived. Food deficient in iron produces anæmia, therefore, by reducing the proportion of hæmoglobin built up in the body; moreover, it inhibits general nutrition by impairing the molecular structure of the living substance of the tissue-cell.* This form is mainly observed among subjects who are deprived of meat and fruit, which contain enough iron to satisfy the needs of the organism.

Verdeil, in 1849, showed that the blood-ashes of dogs fed on bread showed considerable less iron than when they were fed on rich meat diet. Von Höslin found that a diminution of iron in food and not of the albumin altered the composition of the blood, and particularly its hæmoglobin, an observation confirmed by Bunge, Kunkel and others.[13] Bunge[14] and Häusermann[15] also showed that very few articles of food (egg-albumin, rice, pearl-barley and wheat flour) contained less iron than milk, *i.e.*, 2.3 milligrams to 100 grams, a fact recently confirmed by Schmey.[16] In the case of an adult who lived exclusively on milk, observed by Häusermann, the number of corpuscles was normal, but the percentage of hæmoglobin was reduced to 60 per cent.

That the chromatin (living substance*) of nuclei contains iron was shown by Bunge and Macallum[17] in animals and plants, including

* *Author's conclusion.*

[13] Bunge, Kunkel and others: Cited by Ehrlich and Lazarus: *Loc. cit.*, p. 192, 1905.

[14] Bunge: Zeit. f. physiol. Chemie, Bd. xvi, S. 174, 1891.

[15] Häusermann: *Ibid.*, Bd. xxiii, S. 586, 1897.

[16] Schmey: Hoppe-Seyler's Zeit., Bd. xxxix, S. 215, 1903.

[17] Macallum: Jour. of Physiol., vol. xvi, p. 268, 1894, and Reports of Brit. Assoc. for Adv. of Sci., 1896.

those, of course, which are used as foods. But this fact in itself proves that our own chromatin contains iron, and that food deficient in this element must impair not only the hæmoglobin-forming process, but also the vitality of our tissues—including that of all the nerve-centers—as shown by experimental and clinical evidence.

Treatment.—*Iron* is used promiscuously in anæmia; but the foregoing groups indicate that in the majority of instances, its administration will prove futile unless the cause of the blood-disorder be eliminated.

The only exception is the form of anæmia due to *food deficient in iron*, in which this metal, coupled with a diet richer in this metal than the patient's usual food, will prove beneficial without other remedies. Blaud's pill, one three times daily for a week, then increased by one pill daily until three pills are taken after each meal, and the addition of beef, eggs (the yelk of which is rich in iron), spinach, asparagus and fruit, especially apples, insure recovery, especially if the patient is able to spend a few weeks at the sea-shore or in the mountains. Unfortunately, a change of diet of this kind is inaccessible to the majority of cases, since this form of anæmia occurs mainly among the poor. Here, however, spinach, which is twice as rich as beef in iron, green cabbage leaves prepared in various ways, and which contain as much iron as lean beef, may be added to the customary diet. White beans, carrots and wheat-bran are inexpensive, but contain more iron than potatoes or any of the porridge cereals. Ferratin, or the dried sulphate of iron, may be used advantageously in the rare cases in which Blaud's pill is not well borne.

The tincture of the chloride of iron so often used is not a good remedy. It tends to provoke constipation. The majority of cases in which iron proves valueless are instances of erroneous diagnosis, in which the anæmia is due to active destruction of the red cells, *i.e.*, hæmolysis. Such cases may rapidly grow worse under the influence of iron. Barnes recommends a neutral odorless and tasteless solution he terms iron vitellin. Murrell,[18] in a clinical study of various forms of iron, including Blaud's pill, found that the dried sulphate gave the best results among the inorganic preparations, while iron vitellin, of all the organic preparations, not only proved the most active, but also 50 per cent. more so as to red corpuscles and 25 per cent. as to hæmoglobin, than the best inorganic iron.

In the *toxic anæmias*, the first indication, of course, is to eliminate the causative poisons, extrinsic or intrinsic, *i.e.*, those which are depressing the vasomotor and adreno-thyroid centers.*

* *Author's conclusion.*

[18] Murrell: Medical Press, July 6, 1904.

In workers in lead, *potassium iodide,* given in increasing doses after meals, and in large quantities of water, is of recognized value; these salts stimulate powerfully the adreno-thyroid center, and secondarily the vasomotor center.* In arsenic anæmia, *thyroid gland* is indicated,* since arsenic and thyroidase are physiological antagonists, the latter being the normal stimulant of the test-organ.* In the anæmia of alcoholism or nicotinism, cessation of the use of alcohol and tobacco is sufficient, since alcohol robs the blood of its oxygen directly, while nicotine is a vasomotor depressant.* In syphilis, the *iodides* or *mercury* come first in order after thyroid extract,* while in the anæmia due to malaria, *quinine,* as an active stimulant of the vasomotor and adrenal systems, is of especial value.

The relationship between arsenic and thyroid extract is based on the observation of Bêdart and Mabille,[19] confirmed by Ewald,[20] that the untoward phenomena caused by iodothyrin could be reduced and even prevented by the simultaneous use of arsenic.

In the post-hæmorrhagic form, no remedies are required. A copious diet and fresh air soon cause the blood to resume its normal condition. The process may be hastened, if necessary, by means of small doses of *thyroid gland,* 1 grain (0.06 gm.) after each meal.

PERNICIOUS ANÆMIA.

SYNONYMS.—*Progressive Pernicious Anæmia; Idiopathic Anæmia.*

Definition.—Pernicious anæmia, a disease of the blood characterized by extreme pallor and a marked reduction of the red corpuscles, is due to the presence in the blood of toxic substances which, by overstimulating the test-organ, keep the blood sufficiently overladen with auto-antitoxin to produce progressive hæmolysis.**

Symptoms and Pathology.—The most prominent symptom is extreme pallor, both face and body gradually assuming a lemon-yellow tint. The yellowish color usually deepens as the case progresses, but it may appear suddenly. In contrast with this hue is the blanched appearance of the membranes, the mouth, lips and gums.

* *Author's conclusion.*
** *Author's definition.*
[19] Bédart and Mabille: C. r. de la Soc. de biol., 10 série, vol. v, p. 556, 1898.
[20] Ewald: Die Therapie der Gegenwart, Sept., 1899.

The blood is correspondingly pale and watery. Examination reveals a very marked reduction of the red blood corpuscles. While normally the proportion is about 5,000,000 to the cubic millimeter, it may be reduced in this disease to below 500,000, and even to a lower ratio. Quincke reported a case in which there were only 143,000 immediately before death. While the hæmoglobin is also reduced, the ratio of this pigment to the blood corpuscles is higher than usual. This is an effort at compensation, and proves again that the red corpuscles are but storage cells for oxyhæmoglobin.* Many of the corpuscles become greatly enlarged, being then termed *megalocytes.* Some are irregular in shape, *i.e., poikilocytes,* while others again may be smaller than usual: *microcytes;* but neither of these two modifications of shape is pathognomonic. Nucleated red corpuscles are almost always found, however, the normal-sized *normoblasts,* the nucleus of which is markedly stained, and the large *megaloblasts* with pale nuclei.

The onset of pernicious anæmia is gradual and insidious. Weariness and weakness increase until the patient reaches a state of extreme debility, with marked tendency to vertigo and fainting. Numbness beginning at the extremities, weakness or absence of tendon reflexes, and paralysis are sometimes witnessed. Dyspnœa on exertion and sighing are also prominent features. And yet, no emaciation occurs.

These phenomena are generally ascribed to a gradual destruction of the red corpuscles. This view is sustained and elucidated by the functions of the adrenal system. A connection between this disease and the adrenals was suggested by Addison in 1855.

The adrenoxidase, of which the red corpuscles are the carriers, being one of the triad that insures the functional efficiency of all tissues,* reduction of the number of red corpuscles correspondingly reduces the volume of this substance. As the muscles constitute the bulk of the body tissues, progressive weakness is the most prominent sign. This explains also the paræsthesia, loss of tendon reflex, and paralysis. The tendency to fainting is due to a similar condition of the brain cells. The dyspnœa and sighing are characteristic signs of inadequate tissue oxygenation. The absence of emaciation is ascribable to the fact that the leucocytes, which supply the nutrient granules to the tissues, are not destroyed concurrently with the red corpuscles.*

The cardio-vascular symptoms are very marked. The pulse is rapid and large, but soft, and sometimes jerky. The arteries and veins may pulsate and throb visibly. A loud venous hum

* *Author's conclusion.*

can usually be detected, with the stethoscope, in the vessels of the neck. Cardiac murmurs may also be heard. The blood coagulates slowly. Retinal hæmorrhage is frequently observed; epistaxis, menorrhagia, purpuric eruptions, and cerebral hæmorrhage may occur. Œdema of the ankles, face, and lungs, and dropsical effusions may appear at any stage.

These are all manifestations of two conjoined factors: general vascular dilation and the diminution, in the blood, of fibrin ferment, *i.e.*, adrenoxidase.* The vascular dilation is due to relaxation of the muscular coat of all vessels incident upon lowered oxygenation of the vessel walls. As a result, and in accord with Marey's law, the pulse rate is increased. The relaxation of the vascular walls facilitates penetration of the blood-plasma wherever hypostatic congestion occurs; hence the œdema. The adrenoxidase being the fibrin ferment which converts fibrinogen into fibrin, the coagulating power of the blood is impaired and the hæmophilic state is initiated.* This, added to the watery condition of the blood, provokes the hæmorrhagic phenomena.*

Gastric and intestinal disorders are the rule. There is indisposition to eat and disgust for food, rather than true anorexia. Indigestion, nausea, vomiting, and diarrhœa are frequently observed. The gastric juice is generally deficient in hydrochloric acid.

The activity of all the gastric functions, muscular and secretory, is primarily lowered owing to the inadequate supply of adrenoxidase, which destruction of the red cells entails. The peristaltic action of the walls of the stomach being imperfect, the food undergoes correspondingly deficient preparatory digestion, a morbid process aggravated by the fact that pepsinogen, nucleo-proteid and adrenoxidase, the three active factors of gastric juice, are not secreted in sufficient quantities.* The deficiency of hydrochloric acid shows that such is the case. The concurrent relaxation of the cardiac and pyloric muscular fibers allows the imperfectly digested food to penetrate the intestines, where it meets correspondingly impaired muscular and secretory functions. The succus entericus is deficient in auto-antitoxin, hence the presence of gastro-intestinal disorders.*

The liver, kidneys and spleen show an increase of iron pigment. In the liver it is usually found in great quantities in the lobules and the bile capillaries. The urine, on the other hand, may be pale, but it often contains urobilin and is dark.

Both the iron and the urobilin are products of broken-down red corpuscles. The iron which passes to the intestines with the bile is usually recovered by the intestinal leucocytes* and utilized in the reconstruction of hæmoglobin. The decrease of red corpuscles limiting the use of all the iron, the surplus accumulates in the various organs mentioned. Considerable adrenoxidase may also be wasted; this substance and urobilin being identical bodies, it darkens the urine when oxidized, precisely as it does in the skin when bronzing occurs.* Bronzing is also observed sometimes in pernicious anæmia.

* *Author's conclusion.*

Etiology and Pathogenesis.—Repeated parturition is a predisposing factor in many cases, the disease being seldom encountered in primiparæ. Prolonged and immoderate lactation also appear as precursors in a small proportion of cases. Both in men and women, malaria, syphilis, purulent foci, especially pyorrhœa alveolaris; septicæmia, gastric ulcer, etc., are included among the causative intoxications. The imperfectly digested food-stuffs that remain in the gastro-intestinal canal, as explained under the previous heading, or intestinal disorders provoked by intestinal parasites, also act as foci for a practically continuous auto-intoxication.

The disease is due to the presence in the blood of any poisonous substance generated directly or indirectly through any one of these morbid conditions, and to the irritating influence of this poison upon the test-organ.* The adreno-thyroid center being overstimulated, a sufficient excess of auto-antitoxin is present in the blood* to destroy the red corpuscles more or less actively, *i.e.*, to cause hæmolysis.

The fact that the blood contains a substance which destroys the red corpuscles in this disease, as shown by Bordet and also Ehrlich, who termed it "hæmolysin," is now generally recognized. The nature of the substance, however, has remained obscure. As shown above, the process is readily accounted for through excessive functional activity of the adrenal system, the auto-antitoxin including also, as I have shown, the iodine-laden thyroidase which contributes markedly to the destructive process.

The excessive functional activity of the anterior pituitary, *i.e.*, of the test-organ, in this disease, is well shown by the fact that in pregnancy—a frequent cause of the disease—the organ is always overactive, being kept so, we have seen, by the excess of toxic wastes which the fœtus contributes to the maternal blood. In 1898 Comte[21] examined histologically the pituitary of a number of women who had died during pregnancy, and found the anterior pituitary hypertrophied in every case. This was confirmed by Launois and Mulon.[22] Douglas Stanley[23] found marked lesions in the adrenals in a case of pernicious anæmia. The excessive activity of the adrenals, by causing an overproduction of adrenoxidase, increases correspondingly the oxidizing power of the blood. In the liver, where the temperature is higher than elsewhere, the proteolytic activity of the blood is raised beyond the resisting power of the red corpuscles, and those cells are destroyed (hæmolysis)* in this organ with greater rapidity than in the general blood-stream. Colman,[24] after a study of 22 cases, concluded, in fact, that the disease was essentially due to a destruction of these cells in the liver. The disease was attributed to hæmolysis by Quincke, thirty years ago, his opinion being

* *Author's conclusion.*

[21] Comte: Thèse de Lausanne, 1898.
[22] Launois and Mulon: Ann. de gynéc. et d'obstét., 2 série, vol. i, p. 2, 1894.
[23] Douglas Stanley: Brit. Med. Jour., Feb. 16, 1895.
[24] Colman: Edinburgh Med. Jour., Mar. and Apr., 1901.

based on the marked accumulation of iron in the liver. This view has been accepted by most observers, and is now the prevailing one, as already stated.

Treatment.—In true pernicious anæmia, iron is obviously useless, since it merely adds to that already accumulated in large quantities in the liver and other organs.

Arsenic—which acts by depressing the excessive activity of the test-organ, *i.e.*, the adrenal system, reducing thereby the proportion of the auto-antitoxin to which the hæmolysis is due—has proven of real value, but only when given in comparatively large doses. Beginning with 5 minims of Fowler's solution, the dose should be increased at the rate of 1 minim (0.06 gm.) each day, until 30 minims (2 gms.) are administered three times a day. It should be persisted in for months, with intermissions of a few days, but only if necessary; and in all cases its use should go hand in hand with repeated examinations of the blood. The recovery, as previously stated, is often ephemeral. The case should be closely watched at least two years after disappearance of the morbid symptoms, and the use of the remedy resumed as soon as any indication of recurrence, as shown by blood count at intervals, appears. Sodium cacodylate is suitable for hypodermic use, $^1/_2$ grain (0.033 gm.) being injected three times daily.

The beneficial action of arsenic is readily accounted for when its depressing influence on the adrenal system is taken into account, as above.* Bédart and Mabille[25] found that arsenic counteracted all the morbid effects of thyroid medication, a fact confirmed by Ewald[26] and others. In pernicious anæmia, therefore, it diminishes the production of auto-antitoxin and thus arrests the hæmolytic process.*

Antiseptics have been advocated to counteract the auto-intoxication engendered by the putrefactive contents of the gastro-intestinal canal. *Salol,* 10 to 15 grains (0.6 to 1 gm.), in capsules, three times a day, or *betanaphthol,* 2 grains (0.13 gm.), in pills, twice or thrice daily, have each given satisfactory results occasionally, particularly in cases in which arsenic could not be used, or had to be discontinued. *Lavage of the stomach* and enemata of *normal saline solution* have also been used, mainly to remove accumulations of undigested food-stuffs. They do more, however; the saline solution being partly absorbed, the osmotic properties of the blood, which are impaired by the continuous overactivity of the adrenal system, are improved.* Enemata plus subcutaneous injections of saline solution and arsenic are very efficient.

* *Author's conclusion.*
[25] Bédart and Mabille: *Loc. cit.*
[26] Ewald: *Loc. cit.*

Finely powdered *bismuth subnitrate,* in 10-grain (0.6 gm.) doses, twenty minutes before meals, is a far better antiseptic than either of the above.* It is slowly absorbed, and counteracts gastro-intestinal irritation. If an impure salt happens to be taken, the contaminating agent is arsenic—which cannot but enhance its beneficial effects.

Salol on reaching the alkaline intestinal juice splits into salicylic acid and carbolic acid. The latter anæsthetizes the gastro-intestinal mucous membrane, but, with the salicylic acid, disinfects putrefactive contents. Beta-naphthol also dulls the sensibility of the canal, retards digestion, acting similarly *in vitro;* and is likewise a disinfectant. Hence both remedies may aggravate the gastro-intestinal disorder, but their antiseptic properties prove beneficial when the intestinal contents happen to be very toxic.*

As to the use of saline solution, Alex. McPhedran[27] relates the case of a man, aged 55 years, in whom the blood-count showed 480,000 per cubic millimeter; hæmoglobin, 20 per cent. There was delirium, vomiting and diarrhœa. Treatment by subcutaneous injections of normal saline solution on every alternate day, and the intervening of saline enemata, with arsenic internally. The patient, at the time of the report, was practically well.

Various other sources of intoxication must be antagonized. The presence of pyorrhœa alveolaris, considered by Hunter as a prominent source of auto-intoxication, imposes the use of antiseptic mouth washes and dentifrices. Useful for this purpose, after cleansing the teeth, is the following preparation:—

Fl. ext. of hamamelis ..... ℥ij (8 gm.).
Alcohol,
Rose water, of each ..... ℥ss (15 gm.).

Apply to the gums with a cotton wad after carefully cleansing the teeth following each meal.

Some clinicians emphasize the need of rest in an armchair or in bed, relapses having been known to follow fatigue, *i.e.,* muscular exertion. A light nutritious diet is also recommended.

A *milk diet* is a valuable measure in this connection. Practically no waste-products being formed by this food, the adrenal system, subdued directly by the arsenic and indirectly by the bismuth and the oral hygiene, soon loses its overactivity,

* *Author's conclusion.*
[27] Alex. McPhedran: Canadian Pract., Nov., 1897.

and ceases to produce the excess of adrenoxidase to which the destruction of red corpuscles is due.

G. L. Gulland[28] lays special stress on diet in the treatment of pernicious anæmia. This should be arranged with care to suit each case, but the broad principles are that, as long as the blood-count is low, it should consist entirely of milk and farinaceous food; no meat of any kind should be permitted. Of course, this change of diet partly meets the second indication, the diminution of bacterial processes in the intestine. It is not uncommon to find that patients when they are first seen have large quantities of indican and similar substances in the urine, and that after a week or two on a farinaceous diet these practically disappear.

Muscular exertion entails the production of wastes which must be converted in the blood into eliminable end-products. This means overactivity of the adrenal system and, therefore, increased destruction of red corpuscles.* The same untoward effect is provoked when meats are allowed. Their conversion into assimilable granules is imperfectly performed and toxic wastes also unduly excite the adrenal system, thus aggravating the morbid process.*

CHLOROSIS.

Synonyms.—*Green Sickness; Chloranæmia; Chloræmia; Morbus Virgineus.*

Definition.—Chlorosis, a form of anæmia characterized by a yellowish or greenish tinge of the skin, and occurring usually in young girls, is due to the presence of three concurrent morbid factors: (1) depressed functional activity of the adrenal system; (2) inadequate assimilation of the iron from foodstuffs; and (3) marked diminution of the iron-laden hæmatin which holds the adrenoxidase in the red corpuscles pending its distribution to the tissues.**

Symptomatology and Pathology.—The most striking symptom of this disease is a yellowish-green hue of the skin, lips, conjunctiva and all mucous membranes, coinciding with an absence of emaciation. In a small proportion of cases, however, the blood-changes observed in chlorosis appear irrespective of these objective phenomena, the face being normal as to color and the cheeks rosy. The patient may, in fact, show some tendency to adiposis. Even in these instances, however, as in the typical cases, there is marked weakness, lassitude and indisposition to exertion. The appetite is either greatly reduced, or capricious, the patient longing for pickles, vinegar, etc., and ingesting such

* *Author's conclusion.*
** *Author's definition.*
[28] G. L. Gulland: Brit. Med. Jour., Jan. 12, 1907.

articles as chalk, slate pencils, soil, etc. Enteroptosis, gastroptosis, hyperchlorhydria, gastrodynia (due in some cases to gastric ulcer), and movable kidneys are commonly observed. Constipation is almost the rule. Dyspnœa, palpitations, sometimes accompanied with some irregularity in the heart's action, though the pulse be large and soft, are frequently noted, along with purely functional cardiac murmurs, usually located at the base, and sometimes at the apex, when the heart is markedly dilated. The murmurs may often be traced up along the vessels of the neck. Along the course of the jugular vein, especially on the right side, a peculiar venous hum, the "bruit du diable," is also discernible in over one-half of the cases. Neuralgia, vertigo, fainting, moroseness, and hysterical phenomena are not uncommon, especially in young girls, who constitute the great majority of cases. The eyes are unusually brilliant, as in some febrile disorders, and the sclerotic appears bluish. In fact, fever is not infrequently observed in these cases. The menstrual flow is usually scanty and sometimes suppressed, but in a large proportion of cases, there is metrorrhagia or dysmenorrhœa. The urine is of low specific gravity and deficient in urea, and is generally very pale. Œdema of the face and ankles occurs in advanced cases. In a small proportion of cases there is a tendency to thrombosis, especially of the veins of the legs, which exposes the patient to a dangerous complication: pulmonary thrombosis. The cerebral sinuses may also be affected.

Birch-Hirschfeld[29] and Kockel,[30] according to Lazarus,[31] "believe that chlorotic blood has a greater tendency to coagulate, and they associate this with the increased number of blood-platelets." Indeed, we have seen that adrenoxidase is the fibrin ferment, and that the platelets are but droplets of the former. Stengel[32] refers to Leichtenstern's[33] study of 1658 cases of chlorosis in which thrombosis positively occurred only 11 times, and "probably in a mild form in a few other instances." Thrombosis is evidently a rare complication.

In typical cases of chlorosis, the red corpuscles are not diminished to any material degree, the salient feature being a reduction of the hæmoglobin. So decided is this in most cases, that the blood and the corpuscles themselves appear quite pale.

[29] Birch-Hirschfeld: Congr. f. innere Med., Bd. xi, S. 28, 1892.
[30] Kockel: Deut. Archiv f. klin. Med., Bd. lii, S. 557, 1894.
[31] Lazarus: Nothnagel's "Encyclo. of Pract. Med.," vol. on Dis. of the Blood, p. 402, 1905.
[32] Stengel: *Ibid.*
[33] Leichtenstern: Münch. med. Woch., Bd. xlvi, S. 1603, 1899.

The percentage of corpuscles per cubic millimeter may exceed 80 per cent. of the normal, while that of the hæmoglobin may be 40 or lower. Properly speaking, however, what is absent is not hæmoglobin-proper, but that portion of it which remains in the red corpuscles, *i.e.*, hæmatin,* the true blood-pigment. Its albuminous portion, adrenoxidase, is not only present in a free state in the plasma,* but in rare instances it occurs in excess in the latter, as shown by the blood's increased coagulability—adrenoxidase being the fibrin ferment.* The paucity of hæmatin in the corpuscles renders them incapable of holding the albuminous portion of hæmoglobin,* they appear not only paler than normal, as stated, but smaller. Conversely, some may, here and there, appear enlarged, their undivided content in hæmatin being in that case sufficient to anchor an unusual quantity of adrenoxidase, owing to the abnormal quantity available in the plasma.* Small nucleated red corpuscles (normoblasts), which are derived from the bone-marrow, are also found in the blood, especially when an active regenerative process is going on. This proves futile, however, if hæmatin, the link between the red corpuscles and the albuminous hæmoglobin, be deficient.* The white corpuscles appear normal in all respects.

The marked diminution of hæmoglobin as compared to that of red corpuscles was first observed by Duncan nearly forty years ago, and the diagnostic importance has been sustained by the researches of Hayem, Sörensen, Stockman,[34] Gräber[35] and others. In 63 consecutive cases examined by Thayer in Osler's clinic,[36] the average of red corpuscles was 4,096,544, or over 80 per cent., while the average percentage of hæmoglobin was 42.3 per cent. The variations in size of the red corpuscles have remained unexplained; this is readily accounted for by the fact that the albuminous portion of the hæmoglobin has never been taken into account. As to the nucleated cells, Lazarus refers to the investigations of Neumann, Bizzozero and Ehrlich as having shown beyond a doubt, that they are "the evidence of active regenerative processes in the blood-forming organs (bone-marrow)."

Etiology and Pathogenesis.—Although the chromatin of meat, vegetables, fruit, etc., is the mother-substance of hæmatin, the proportion of metallic iron absorbed daily from these foodstuffs is at best very limited, namely, from 6 to 10 milligrams ($^1/_{10}$ to $^1/_6$ gr.) Moreover, this intake cannot be considered as an asset, since it varies but little, if at all, from the output by the

* *Author's conclusion.*
[34] Stockman: Brit. Med. Jour., Dec. 14, 1895.
[35] Gräber: Cited by Lazarus: *Loc. cit.*
[36] Osler: *Loc. cit.*, p. 722, 1905.

urine and fæces. This indicates that the body absorbs from the alimentary proteids only just enough iron to replace the quantity normally utilized in the blood and tissues, and that in case of need, it draws upon its reserves in the liver, spleen, bone-marrow, etc.*

We have seen in the article on iron that Bunge and Macallum had shown that the chromatin of the various proteids, animal and vegetable, was the mother-substance of hæmoglobin. As to the ingestion of iron, Stockman[37] found that "the quantity of metallic iron in ordinary dietaries seldom exceeded 10 milligrams ($^1/_6$ gr.) per day, and" that it "might be as low as 6 milligrams ($^1/_{10}$ gr.) in people of ordinary appetite and digestion." In a subsequent article, Stockman and Greig[38] demonstrated that "the iron metabolism is extremely small so far as intake and output is concerned." In one observation they "almost exactly coincided;" in others the output even exceeded the intake.

That conversely, iron may be lost or eliminated by way of the intestine, is sustained by considerable evidence. As far back as 1852 Bidder and Schmidt[39] ascertained that from six to eight times more iron was eliminated with the fæecs, even during fasting, than with the urine. Gottlieb,[40] after feeding puppies on iron-free food, injected iron subcutaneously and found nearly 97 per cent. in the fæces. That this is by no means all excreted by way of the liver and with the bile, is proven by the experiments of Nathan,[41] which showed that the greater part of the iron excreted was carried to the large intestine by leucocytes. Hochhaus and Quincke[42] hold that the accumulation of iron in the submucous tissue of the large intestine is connected with its excretion, and that this is probably effected by the extrusion of iron-laden leucocytes. The opportunities for an output even in excess of the intake are evident.

In the great majority of cases of chlorosis, the disease is due to three morbid factors acting concurrently: (1) a deficiency of iron in the patient's regular diet, (2) depressed functional activity of the adrenal center,* and (3) its results,* imperfect digestion and assimilation.

As to the first cause, chlorosis is most common among ill-fed working girls or "sweat-shop" hands, whose diet seldom includes meat, fruit, and other foods rich in iron. Among the well-fed classes, chlorotics are likewise seen, but here the tastes are catered to, and the diet consists mainly of desserts, especially sweets, cakes, candy, ice-cream, milk, etc., all of which are extremely poor in, or devoid of, iron.

* *Author's conclusion.*
[37] Stockman: Jour. of Physiol., vol. xviii, p. 484, 1895.
[38] Stockman and Greig: *Ibid.*, vol. xxi, p. 55, 1897.
[39] Bidder and Schmidt: "Die Verdauungssäfte u. d. Stoffwechsel," S. 411, 1852.
[40] Gottlieb: Zeit. f. physiol. Chemie, Bd. xv, H. 5, 1891.
[41] Nathan: Deut. med. Woch., Feb. 15 and 22, 1900.
[42] Hochhaus and Quincke: Arch. f. exp. Path. u. Pharm., Bd. xxxvii, S. 159, 1896.

Still, a multitude of girls, under identical conditions, do not suffer from chlorosis; a predisposing cause must prevail, therefore, in addition to these conditions. This is represented by the second cause mentioned. The age at which chlorosis most usually occurs, between 15 and 20 years, coincides with the period of greatest development, and when the adrenal system, therefore, is under the greatest stress.* If, as is often the case with the genitalia, the pelvis and the breasts in these cases, the organs forming the adrenal system are inadequately developed, they fail to meet the needs of the organism, and the vital process in all tissues is deficient.* Hence the muscular relaxation—the cause, in turn, of the weakness and lassitude, of the gastroptosis and enteroptosis, of the cardiac and vascular dilation, of the large and soft pulse, of constipation, of all menstrual disorders, etc., briefly, of all disorders in organs supplied with muscular elements. Hence, also, the many other morbid phenomena which general vascular relaxation entails, viz., accumulation of blood in great mesenteric channels, and recession of blood from the brain, lungs and skin, which, in turn, give rise to the familiar vertigo and tendency to fainting, dyspnœa, coldness of the surface and extremities, and pallor.* Finally, the hæmatopoietic organs themselves are the seat of inadequate metabolism, as shown by the average reduction of about 20 per cent. of red corpuscles, a proportion which is sometimes greatly exceeded.

The third cause is a normal consequence of the second. The dilation of the stomach and intestines, the constipation, and the many symptoms appertaining thereto, clearly point to imperfect digestion, a condition which in itself diminishes the likelihood that the small proportion of iron absorbed daily from the alimentary canal under normal conditions will be reduced. The intake being diminished, the reserves in the liver, spleen, etc., are drawn upon and the time finally comes when they are exhausted. This marks the onset of the disease, *i.e.*, the time when the red corpuscles, failing in their supply of hæmatin, gradually lose their hold upon what proportion of albuminous hæmoglobin, or adrenoxidase, the adrenal system is able to produce.*

* *Author's conclusion.*

A diet deficient in iron thus becomes more of an aggravating factor than a primary cause of chlorosis; but we must not forget that in many instances the deprivation of wholesome food has existed from infancy, and that this in itself has tended to inhibit the development of the adrenal system, to prepare the soil, in other words, for chlorosis.*

All this applies as well to other causes of chlorosis. The great majority of cases occur in delicate, blond (*i.e.*, hair devoid of iron), illy-developed girls, and sometimes boys; while its causes are all of a debilitating kind, squalor, overwork, prolonged lactation, exhausting drains, profuse menstruation, masturbation, grief, nostalgia, etc., all of which tend to depress the functional efficiency of the adrenal center, directly or indirectly. This is the underlying cause of chlorosis, but only when the intake of iron from the blood fails to compensate for the output.*

The presence of adrenoxidase in unusual quantities in the plasma previously referred to, does not mean that an excess of this body is produced; it only signifies that what proportion is unabsorbed by the red corpuscles as the albuminous moiety of hæmoglobin circulates in a free state in the blood-stream. The activity of the adrenal center may, therefore, be far below normal and adrenoxidase still occur in the plasma.

Treatment.—To administer iron to such cases without increasing the functional activity of the adrenal system is not judicious, since it tends to increase constipation, while being wasted through the alimentary canal. The first feature which requires attention is the state of the blood. We have seen that it has a marked tendency to coagulate, and that this has been ascribed to blood-platelets. As this points to a deficiency of blood-salts,* the use of *normal saline solution* is indicated. The best method in these cases is to give it in the form of a large, hot (110° F.—43.3° C.) enema every other night, and, if the case be severe, to administer it in small quantities either endovenously or hypodermically, three days in succession, then every other day. The only other indication at this time is the *diet* recommended for anæmia, which includes foods rich in iron and alkaline salts.

At the end of a week, the blood will have regained, at least to a certain extent, its normal osmotic properties, and, the vege-

* *Author's conclusion.*

tables aiding, its normal alkalescence. The *thyroid gland,* in small doses, 2 grains (0.13 gm.) during meals, should then be begun, to enhance, through the adrenal system, metabolism in all its tissues, including the muscles of the heart and vessels.* The tone of the latter being improved, the distribution is equalized, and the adrenoxidase-laden plasma, instead of circulating in the larger, deeper vessels, where it is of but little use to the vital process of the organism at large, will now increasingly flow through the capillaries of all organs. As this applies also to the muscles of the stomach and intestine, the gastroptosis and the constipation will also be corrected. The resumption by the vessels of their normal caliber will have another all-important effect in this connection: it will correct the main factor in the loss of iron ingested, viz., *abnormal intrahepatic vasodilation and failure of the iron-laden leucocytes to circulate through the capillaries of the hepatic cells.* The iron, which, under these conditions, was imperfectly prepared for absorption, will then simply be excreted with the fæces—along with other food-products for the formation of hæmatin. After two weeks of thyroid gland, this stage will have been reached, and *iron,* preferably Blaud's pills, will now prove beneficial, since the stomach, liver and intestines will have been rendered able to prepare it for its assimilation by the red corpuscles, which, under the influence of the thyroid gland, will also have appeared in greater number in the blood.* *Adrenal gland* in 2-grain (0.07 gm.) doses hastens recovery by supplying the oxidizing constituent of the hæmoglobin.

Others have observed the beneficial effects of thyroid gland. Battey Shaw[43] writes: "Capitan and Camus describe the favorable results of thyroid treatment in cases of severe chlorosis. Treatment by iron was found to be more successful when combined with thyroid treatment."

Other agents which have proven beneficial are the iodides. But even the *iodides* tend to increase the gastric disturbance in these cases. The syrup of the *iodide of iron* is sometimes borne without trouble, in 10- or 15-drop doses in a half tumblerful of water. *Strychnine,* in full doses, with inhalations of *oxygen,* is very efficient in mild cases. All are adrenal stimulants. The seashore hastens recovery in such cases.

* *Author's conclusion.*
[43] Battey Shaw: "Organotherapy," p. 99, 1905.

HÆMOPHILIA.

SYNONYMS.—*Bleeder's Disease; Sporadic Hæmophilia.*

Definition.—A tendency to serious and sometimes uncontrollable hæmorrhage, due to a deficiency of fibrin ferment (adrenoxidase) in the blood and a corresponding diminution of the coagulability of the latter.*

Symptoms and Pathology. — The abnormal tendency to bleed is usually discovered through occurrences to which, as a rule, little importance is attached: nose-bleed, the extraction of a tooth, the application of a leech, a slight cut, vaccination, religious circumcision, etc. It may occur as the unsuspected source of metrorrhagia, or as the so-called "renal" hæmophilia, the urine being bloody. The skin is frequently the seat of hæmophilia; vesicles are formed either during apparent health or during eruptive diseases, scarlatina, varicella, etc., or more or less extensive extravasations appear under the skin, owing to capillary oozing, either as the result of a pinch, a blow, etc., or without provocation. The hæmorrhages may be internal; hæmophilia may thus act as the underlying cause of cerebral hæmorrhage. Reddish striæ of minute dilated vessels are sometimes witnessed in these cases.

The pathological anatomy of the disease affords but little information. The walls of the blood-vessels are said to be "thin" or "fatty," but Nancrede[44] says that this supposed thinness has only been witnessed once histologically. As to their being fatty, we have seen that "fatty degeneration" so-called is due to post-mortem changes. Abderhalden[45] recently ascribed hæmophilia to localized changes in the development and structure of the venules and arterioles of the regions involved, but, as shown below, vascular changes are of secondary importance in that they only tend to predispose these regions to act as outlets for the blood. In a case noted by Chauffard,[46] for instance, the recurrent hæmorrhages were always from the same areas.

Affections of the joints are very important in this connection, as many hæmophilics have lost their lives through surgical intervention. A joint in such subjects may suddenly and without appreciable injury become filled with blood, swell, become painful, etc., and slowly recover. This may recur repeatedly, but ultimately be attended by alterations of the synovial membrane and cartilages and finally deformity. It is in these cases

* *Author's definition.*
[44] Nancrede: Dennis's "System of Surgery," 1895-96.
[45] Abderhalden: Ziegler's Beiträge, Bd. xxxv, S. 213, 1903.
[46] Chauffard: Le bull. méd., vol. x, p. 356, 1896.

of hæmophilic arthritis that a fatal error in diagnosis may be made. These cases usually show a pallor of the membranes; but the characteristic features are a history of hæmophilia, ecchymotic patches, and dilated capillaries. Recurrent epistaxis should always awaken suspicion. In tuberculous arthritis—the diagnosis usually made—the doughy patches of ecchymosis are absent, scars are likely to be present; inequality of the femoral condyles or of the head of the tibia may at times be discerned.

Froelich,[47] who lays stress on these diagnostic points, states that aspiration of the joint, tenotomy and forcible extension should not be attempted in such cases. As shown below, however, even major operations may be done after appropriate treatment. Without such, however, surgical procedures of any kind, even cauterizations, as shown by Nové-Josserand,[48] are likely to lead to a fatal issue.

Etiology and Pathogenesis.—Heredity is a marked feature of hæmophilia, having been traced back in one family through nearly three centuries. It is often transmited by women not themselves affected (Nasse's so-called law). Another peculiarity is the marked fertility of bleeders' families. Again, a woman belonging to a family of bleeders may not herself be a bleeder, and may bear offspring who are, especially if her children are males.

The genealogy of a family of bleeders traced back nearly 300 years was recorded by Hoessli.[49] A marked example of transmission through non-hæmophilic women reaching back 200 years and affecting only males was published by C. Hicks.[50] All suffered from arthritic disorders. Steiner[51] observed a case in a negro, the first on record in this race, and traced it back to the great-great-grandmother. The family was extremely fertile, but both males and females were bleeders, though invariably transmitted through the females. Pincus[52] states positively that hæmophilics should not marry, but this view is subject to modification, in view of the facts submitted below.

Deficiency of the fibrin ferment—the adrenoxidase—in the blood is the underlying cause of hæmophilia. Fibrin ferment being a necessary constituent to the formation of fibrin, this substance is not formed in adequate quantities and the blood cannot coagulate.*

Hæmophilic subjects appear normal because coagulation requires an excess of fibrin ferment (adrenoxidase) over and above

* *Author's conclusion.*
[47] Froelich: Revue d'orthopédie, vol. xv, p. 289, 1904.
[48] Nové-Josserand: Revue de chir., vol. xx, p. 768, 1899.
[49] Hoessli: Zeit. f. klin. Med., Bd. xv, S. 277, 1888.
[50] C. Hicks: Trans. Med. Assoc., Georgia, 1903.
[51] Steiner: Johns Hopkins Hosp. Bull., Feb., 1900.
[52] Pincus: Central. f. Gynæk., Bd. xxvi, S. 573, 1902.

the needs of tissue respiration, and this excess is not available in them. As adrenoxidase is the oxygen-laden adrenal secretion, the primary cause, therefore, is a deficiency of adrenal secretion.*

I have shown that fibrin contains adrenoxidase and that it is identical with fibrin-ferment. That the adrenals are the source of this substance, and that a deficiency of their secretion is the primary cause of hæmophilia, is illustrated by the fact that stimulation of the adrenal center by its normal stimulant, *i.e.*, thyroid extract, counteracts the hæmophilia. This is emphasized by several cases given in outline under Treatment. In the first series, thyroid extract was employed empirically; in the second, Dr. W. J. Taylor's cases, I had recommended its use with the view of increasing the fibrin-ferment. Dr. Taylor carefully noted the blood's coagulability and found that it increased from day to day under the influence of the thyroid extract. Direct proof is afforded by the fact that adrenalin likewise arrests the bleeding in these cases; here it does simply what, as I have shown, it does in the lungs.

Treatment.—We have in *thyroid gland* not only a prophylactic, but also a curative agent, since it stimulates powerfully the pituitary body and raises its functional activity when its use is prolonged. Three grains (0.2 gm.) three times daily, *i.e.*, after each meal, suffice for this purpose. This causes gradual increase in the coagulating power of the blood, thus rendering even serious operations safe when the coagulating time has been reduced to the minimum normal, *i.e.*, three minutes.

The cases in which thyroid extract has been used successfully are already quite numerous. Délace[53] promptly stopped a menorrhagia which had lasted fourteen days in a hæmophilic; alveolar and subcutaneous hæmorrhages were also present. Instances in which unmistakable cases were successfully treated have been reported by Combemale,[54] C. R. Jones,[55] Scheffler,[56] E. Fuller[57] and others. The remedy was administered empirically in these cases, as previously stated. Not so with three cases reported by William J. Taylor,[58] however. Having in mind my view that it was by increasing the coagulating power of the blood that thyroid extract prevented hæmorrhage, he tested the blood's coagulating time: in a profuse bleeder requiring an operation it was reduced from 11½ minutes to 2 minutes and 6 seconds, and *nephropexy* was successfully performed, the wound being "remarkably dry." Thyroid gland was also given by him in a case of osteomyelitis attended with constant bleeding, and caused the latter to cease in one week. In a third case, it rendered possible the extraction of a tooth in a hæmophilic, no hæmorrhage occurring, though the gums were badly lacerated.

* *Author's conclusion.*
[53] Délace: Jour. de méd. de Paris, vol. x. p. 46, 1898.
[54] Combemale: La méd. moderne. vol. ix, p. 278, 1898.
[55] C. R. Jones: Brit. Med. Jour., Nov. 10, 1900.
[56] Scheffler: Arch. de méd. et de pharm. milit., vol. xxxvii, p. 246, 1901.
[57] E. Fuller: Medical News, Feb. 28, 1903.
[58] W. J. Taylor: Monthly Cyclo. of Pract. Med., July, 1905.

Calcium chloride has likewise given good results, owing to the well-known influence on coagulation, but its effect is only temporary. It is given in 10-grain (0.6 gm.) doses, three times daily. If given to prevent bleeding during a minor operation (it allows of no other than trifling ones, extraction of teeth, opening of small abscesses, etc.), the coagulation time should be taken, and if this does not reach below five minutes, thyroid extract should be given in addition. *Digitalin* in full therapeutic doses is also useful.

Sympson,[59] Wallace,[60] Parry[61] and others have obtained good results with calcium chloride in hæmophilia. Ballantyne[62] used it successfully as an antenatal remedy, *i.e.*, to prevent hæmophilia in the third child of a woman whose two first children were bleeders. I used tincture of digitalis and obtained a prompt recovery in the case of a boy whom recurrent hæmorrhages had almost exsanguinated.

The most valuable local hæmostatic is *adrenal chloride* (1 to 1000 solution), gauze saturated with it being applied directly to the wound. A thick layer of the powdered extract also arrests the bleeding promptly. The ordinary styptics, *perchloride of iron, ergot,* etc., have been used, but seldom with success in serious cases. *Fresh entire blood* may be transfused, a small quantity being sometimes sufficient to arrest a profuse flow.

Adrenalin has been used successfully in the above manner by W. Milligan,[63] E. Francis,[64] and the extract by W. T. Thomas[65] and others. The use of entire blood was recommended by Hayem,[66] who thought that his "hæmotoblasts" caused the formation of a clot. I have shown[67] that these hæmatoblasts or blood-platelets are droplets of adrenoxidase, *i.e.*, of fibrin-ferment.

---

[59] Sympson: Lancet, May 13, 1899.
[60] Wallace: Brit. Med. Jour., May 10, 1902.
[61] Parry: Lancet, Feb. 21, 1903.
[62] Ballantyne: Jour. Amer. Med. Assoc., Aug. 24, 1901.
[63] W. Milligan: Brit. Med. Jour., Feb. 1, 1902.
[64] E. Francis: *Ibid.*, May 28, 1904.
[65] W. T. Thomas: *Ibid.*, Nov. 23, 1901.
[66] Hayem: Le bull. méd., vol. ii, p. 1235, 1267, 1888.
[67] *Cf.* this vol., p. 829.

CHAPTER XXXII.

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

THE ADRENAL SYSTEM IN INFECTIONS OF THE LYMPHATIC SYSTEM.

We have already seen that in tuberculosis, infection occurs to a great extent through the lymphatic system. In the diseases reviewed in the present chapter, syphilis and bubonic plague, infection not only occurs by way of this system, but the lymphatic glands act as foci for the development of pathogenic organisms. Hence the occurrence of buboes and kindred complications. An important feature emphasized is the need of energetic measures, as represented by the value of mercury, the iodides, etc., in the treatment of such disorders. Toxæmias are readily antagonized by ordinary adrenal stimulants because it is in the blood that the bactericidal and antitoxic agents which these remedies evoke first appear. In the lymphatic system, however, the protective process is relatively deficient, owing to the absence of red corpuscles, and therefore of adrenoxidase, in the lymph, a fact which involves a deficiency of auto-antitoxin in this fluid. Hence the freedom with which bacteria multiply therein; hence also the presence in the lymphatic glands of a multitude of phagocytes, small and large, whose purpose is to rid them of pathogenic elements of all kinds. The aim, therefore, should be to increase the proteolytic power and the aggressiveness of the phagocytes by agents which cause their digestive vacuoles to be well supplied with auto-antitoxin (their digestive triad) and to sensitize actively the bacteria. These requirements are met by mercury, the iodides and thyroid extract, as suggested below.

SYPHILIS.

SYNONYMS.—*Lues; Pox; Lues Venerea.*

Definition.—A specific disease due to inoculation, probably by the *spirochæta pallida,* characterized by three stages: (1) the *primary* stage, in which the seat of inoculation is con-