groups which present the characters of a progressive and pernicious anæmia and are etiologically different. Thus, a fatal anæmia may be due to the presence of parasites, or may follow hæmorrhage, or be associated with chronic atrophy of the stomach; but when we have excluded all these causes there remains a group which, in the words of Addison, is characterized by a "general anæmia occurring without any discoverable cause whatever, cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease."

Idiopathic anæmia is widely distributed. It is of frequent occurrence in the Swiss Cantons, and is not uncommon in this country. It affects middle-aged persons, but instances in children have been described. Griffith mentions about ten cases occurring under twelve years of age. The youngest patient I have seen was a girl of twenty. Males are more frequently affected than females. Of my 27 cases, 10 were females and 17 were males. Of 110 cases collected by Coupland, 56 were in men and 54 in women.

With the following conditions may be associated a profound anæmia not to be distinguished clinically from Addison's idiopathic form:

(*a*) *Pregnancy and Parturition.*—The symptoms may develop during pregnancy, as in 19 of 29 cases of this group in Eichhorst's table. More commonly, in my experience, the condition has been post partum; thus, of my 27 cases, 5 followed delivery.

(*b*) *Atrophy of the Stomach.*—This condition, early recognized by Flint and Fenwick, may certainly cause a progressive pernicious anæmia. By modern methods it may now be possible to exclude this extreme gastric atrophy.

(*c*) *Parasites.*—The most severe form may be due to the presence of parasites, and the accounts of cases depending upon the anchylostoma and the bothriocephalus describe a progressive and often pernicious anæmia.

After the exclusion of these forms there remains a large proportion, numbering eighteen cases in my series, which correspond to Addison's description. The etiology of these cases is still dark. The researches of Quincke and his student Peters showed that there was an enormous increase in the iron in the liver, and he suggested that the affection was probably due to increased hæmolysis. This has been strongly supported by the extensive observations of Hunter, who has also shown that the urine excreted is darker in color and contains pathological urobilin. The lemon tint of the skin or the actual jaundice is attributed, on this view, to the changes in the liver cells produced by the excessive amount of pigment, but in the light grades it is unquestionably hæmatogenous. To explain the hæmolysis, it has been thought that in the condition of faulty gastro-intestinal digestion, which is so commonly associated with these cases, poisonous materials are developed, which when absorbed cause destruction of the corpuscles. Certainly the evidence for hæmolysis is very

strong, but we are still far away from a full knowledge of the conditions under which it is produced.

On the other hand, F. P. Henry, Stephen Mackenzie, and other authorities incline to the belief that the essence of the disease is in defective hæmogenesis, in consequence of which the red blood-corpuscles are abnormally vulnerable. A point noted by Copeman, that the hæmoglobin crystallizes from the blood-corpuscles with great readiness, can scarcely be regarded as favoring the view of imperfect hæmogenesis, since this is a feature specially characteristic of the blood of the young.

Morbid Anatomy.—The body is rarely emaciated. A lemon tint of the skin is present in a majority of the cases. The muscles often are intensely red in color, like horse-flesh, while the fat is light yellow. Hæmorrhages are common on the skin and serous surfaces. The heart is usually large, flabby, and empty. In one instance I obtained only two drachms of blood from the right heart, and between three and four from the left. The muscle substance of the heart is intensely fatty, and of a pale, light-yellow color. In no affection do we see more extreme fatty degeneration. The lungs show no special changes. The stomach in many instances is normal, but in some cases of fatal anæmia the mucosa has been extensively atrophied. In the case described by Henry and myself the mucous membrane had a smooth, cuticular appearance, and there was complete atrophy of the secreting tubules. The liver may be enlarged and fatty. In most of my autopsies it was normal in size, but usually fatty. The iron is in excess, and in striking contrast to cases of secondary anæmia. It is deposited in the outer and middle zones of the lobules, and in two specimens which I examined seemed to have such a distribution that the bile capillaries were distinctly outlined. This is certainly, as Hunter states, a special and characteristic lesion, possibly peculiar to pernicious anæmia. A. J. Scott examined for me the livers in forty-five consecutive autopsies without finding (except in pernicious anæmia) this special distribution of pigment.

The spleen shows no important changes. In one of Palmer Howard's cases the organ weighed only an ounce and five drachms. The iron pigment is usually in excess. The lymph glands may be of a deep red color. The amount of iron pigment is increased in the kidneys, chiefly in the convoluted tubules. The bone marrow, as pointed out by H. C. Wood, may resemble that of a child. This observation has been repeatedly confirmed, but the condition does not appear to be constant. Changes in the ganglion cells of the sympathetic have been reported on several occasions. Lichtheim has found sclerosis in the posterior columns of the cord, which he thinks secondary to the anæmia, and a similar change has been met with in two recent cases by Morris Lewis and Burr.

Symptoms.—The patient may have been in previous good health, but in many cases there is a history of gastro-intestinal disturbance, mental shock, or worry. The description given by Addison presents the chief

features of the disease in a masterly manner. "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted, the pulse perhaps large, but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness in attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless, the flabbiness of the solids increases, the appetite fails, extreme languor and faintness supervene, breathlessness and palpitations are produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles; the debility becomes extreme—the patient can no longer rise from bed; the mind occasionally wanders; he falls into a prostrate and half-torpid state, and at length expires; nevertheless, to the very last, and after a sickness of several months' duration, the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect."

The Blood.—The corpuscles may sink to one fifth or less of the normal number. They may sink to 500,000 per cubic millimetre, and in a case of Quincke's the number was reduced to 143,000 per cubic millimetre. The hæmoglobin is relatively increased, so that the individual globular richness is plus, a condition exactly the opposite to that which occurs in chlorosis, in which the corpuscular richness in coloring matter is minus. The relative increase in the hæmoglobin is probably associated with the average increase in the size of the red blood-corpuscles. The accompanying chart illustrates these points. Microscopically the red blood-corpuscles present a great variation in size, and there can be seen large giant forms, megalocytes, which are often ovoid in form, measuring eight, eleven, or even fifteen micromillimetres in diameter, a circumstance which Henry regards as indicating a reversion to a lower type. Laache thinks these pathognomonic, and they certainly form a constant feature. There are also small round cells, microcytes, from two to six micromillimetres in diameter, and of a deep red color. The corpuscles show a remarkable irregularity in form, elongated and rodlike or pyriform; one end of a corpuscle may retain its shape while the other is narrow and extended. To this condition of irregularity Quincke gave the name poikilocytosis. The leucocytes are generally diminished in number, and the relative percentage of the mononuclear elements is somewhat higher than in normal blood.

Nucleated red blood-corpuscles are constantly present, as pointed out by Ehrlich. Besides the ordinary form, which is of the same size as the common corpuscle and which has a small, deeply stained nucleus (normoblasts), there are very large forms with large, palely staining nuclei (gigantoblasts), which resemble somewhat the larger megalocytes. Ehrlich re-

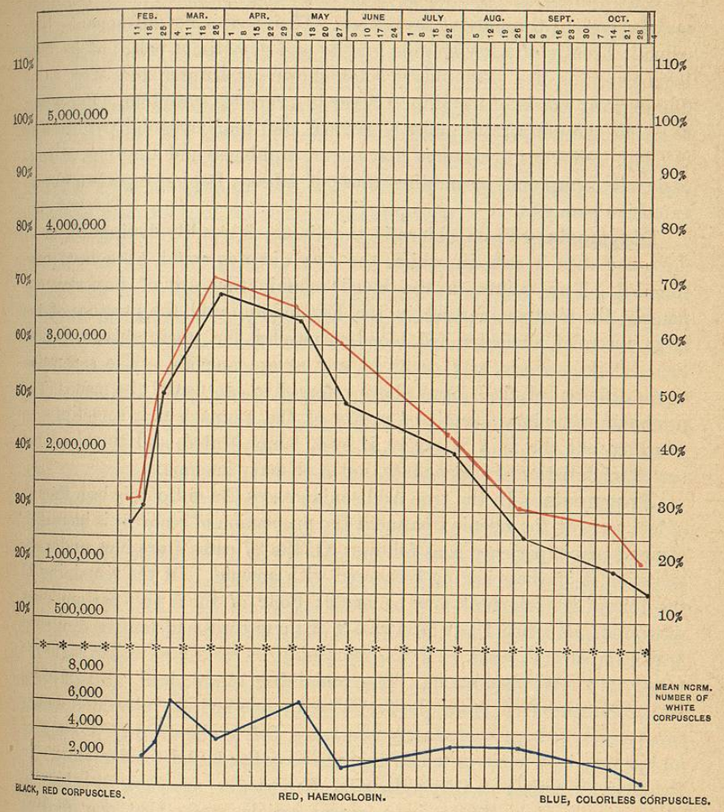

CHART XVIII.—Pernicious anæmia.

gards the presence of these as almost distinctive of progressive pernicious anæmia; they are only found here and in the later stages of leukæmia. The blood-plates are either absent or very scanty.

The cardio-vascular symptoms are important and are noted in the description given above. Hæmic murmurs are constantly present. The larger arteries pulsate visibly and the throbbing in them may be distressing to the patient. The pulse is full and frequently suggests the water-hammer beat of aortic insufficiency. The capillary pulse is frequently to be seen. The superficial veins are often prominent, and in two cases I have seen well-marked pulsation in them. Hæmorrhages may occur, either

in the skin or from the mucous surfaces. Retinal hæmorrhages are common. There are rarely symptoms in the respiratory organs.

Gastro-intestinal symptoms, such as dyspepsia, nausea, and vomiting, may be present throughout the disease. Diarrhœa is not infrequent. The urine is usually of a low specific gravity and sometimes pale, but in other instances it is of a deep sherry color, shown by Hunter and Mott to be due to great excess of urobilin. Fever is a variable symptom. For weeks at a time the temperature may be normal, and then irregular pyrexia may develop. Nervous symptoms may occur, numbness and tingling, and occasionally symptoms resembling those of tabes. Lepine reports a case of extensive paralysis.

Diagnosis.—From chlorosis the disease is readily distinguished. I have not seen a case in which the two diseases could have been confounded. Two points in the blood examination are of importance—namely, the relative increase in the hæmoglobin and the presence of the large forms of nucleated red blood-corpuscles, the gigantoblasts of Ehrlich. Poikilocytosis may occur in any severe anæmia. The separation of the different clinical forms above referred to can usually be made. The profound secondary anæmia of cancer of the stomach may sometimes be puzzling, but the skin is rarely, if ever, lemon-tinted, and the blood has the characteristics of a secondary, not a primary anæmia.

Prognosis.—In the true Addisonian cases the outlook is bad, though of late years on the arsenic treatment the proportion of recovery is increased. My personal experience is as follows: Of the 27 cases 4 are now under observation, 2 of these having recovered with arsenic. Of the remaining 23 the following statement may be made: Four of the 5 post-partum cases recovered, and when I left Montreal 3 of these cases had remained in good health for several years. Of the remaining 18 cases 2 were lost sight of; 1 had improved very much. The remaining 16 are dead. Six of these fatal cases recovered from the first attack; one had an interval of nearly three years, and another nearly two years, before the return. I know of no instance in a male in which the recovery has lasted for five years. In Pye-Smith's article in Guy's Hospital Reports, he mentions twenty cases of recovery. Hale White, in a recent article, states that one of these cases, treated by arsenic in 1880, remained alive and well January, 1891. One of my patients made an apparently complete recovery and resumed active business and political duties. So characteristic are recurrences in this affection that Stephen Mackenzie, in his recent lectures, considered them under a separate heading of relapsing pernicious anæmia.

Treatment of Anæmia.—*Secondary Anæmia.*—The traumatic cases do best, and with plenty of good food and fresh air the blood is readily restored. The extraordinary rapidity with which the normal percentage of red blood-corpuscles is reached without any medication whatever is an important lesson. The cause of the hæmorrhage should be sought and the necessary indications met. The large group depending

on the drain on the albuminous materials of the blood, as in Bright's disease, suppuration, and fever, is difficult to treat successfully, and so long as the cause keeps up it is impossible to restore the normal blood condition. The anæmia of inanition requires plenty of nourishing food. When dependent on organic changes in the gastro-intestinal mucosa not much can be expected from either food or medicine. In the toxic cases due to mercury and lead, the poison must be eliminated and a nutritious diet given with full doses of iron. In a great majority of these cases there is deficient blood formation, and the indications are briefly three—plenty of food, an open-air life, and iron. As a rule it makes but little difference what form of the drug is administered.

The treatment of *chlorosis* affords one of the most brilliant instances—of which we have but three or four—of the specific action of a remedy. Apart from the action of quinine in malarial fever, and of mercury and iodide of potassium in syphilis, there is no other remedy the beneficial effects of which we can trace with the accuracy of a scientific experiment. It is a minor matter *how* the iron cures chlorosis. In a week we give to a case as much iron as is contained in the entire blood, as even in the worst case of chlorosis there is rarely more than a deficit of two grammes of this metal. Iron is present in the fæces of chlorotic patients before they are placed upon any treatment, so that the disease does not result from any deficiency of available iron in the food. Bunge believes that it is the sulphur which interferes with the digestion and assimilation of this natural iron. The sulphides are produced in the process of fermentation and decomposition in the fæces, and interfere with the assimilation of the normal iron contained in the food. By the administration of an inorganic preparation of iron with which these sulphides combine the natural organic combinations in the food are spared. In studying a number of charts of chlorosis it is seen that there is an increase in the red blood-corpuscles under the influence of the iron, and in some instances the globular richness rises above normal. The increase in the hæmoglobin is slower and the maximum percentage may not be reached for a long time. I have for years in the treatment of chlorosis used with the greatest success Blaud's pills, made and given according to the formula in Niemeyer's text-book, in which each pill contains 2 grs. of the sulphate of iron. During the first week one pill is given three times a day. In the second week, two pills; in the third week, three pills, three times a day. This dose should be continued for four or five weeks, at least, before reduction. An important feature in the treatment of chlorosis is to persist in the use of the iron for at least three months, and if necessary subsequently to resume it in smaller doses, as recurrences are so common. The diet should consist of good, easily digested food. Special care should be directed to the bowels, and if constipation is present a saline purge should be given each morning. Such stress does Sir Andrew Clark lay on the importance of constipation in chlorosis that he states that if limited to the choice of one drug in the treatment of the

disease he would choose a purgative. Dilute hydrochloric acid, manganese, phosphorus, and oxygen have been recommended.

Treatment of Pernicious Anæmia.—Since the introduction by Byrom Bramwell of arsenic in this affection a large number of cases have been temporarily, a few permanently, cured by it. It should be given as Fowler's solution in increasing doses. It is usually well borne, and patients, as a rule, take up to twenty minims three times a day without any disturbance. I usually begin with three minims and increase to five at the end of the first week, to ten at the end of the second week, to fifteen at the end of the third week, and, if necessary, increase to twenty or twenty-five. In a case in which the recovery persisted for nearly three years, the dose was gradually increased to thirty minims. These patients seem to bear the arsenic extremely well. It is sometimes better borne as arsenious acid in pill form. Vomiting and diarrhœa are rare; occasionally puffiness of the face is produced, and in some cases pigmentation of the skin.

Rest in bed and a light but nutritious diet (giving the food in small amounts and at fixed intervals) are the first indications. I always prefer to begin the treatment of a case of pernicious anæmia, whatever the grade may be, with rest in bed as one of the essential elements. Massage will also be found very beneficial. I have abandoned the use of rectal injections of dried blood. Iron seems to have no action in this form, but in a case in which the arsenic disagrees it may be tried.

II. LEUKÆMIA.

Definition.—An affection characterized by persistent increase in the white blood-corpuscles, associated with enlargement, either alone or together, of the spleen, lymphatic glands, or bone marrow.

The disease was described almost simultaneously by Virchow and by Bennett, who gave to it the name leucocythæmia.

Etiology.—We know nothing of the conditions under which the disease develops. It is not uncommon on this continent. Of 17 cases of which I have notes, 11 occurred in Montreal, 2 in Philadelphia, and 4 within the past two years at the Johns Hopkins Hospital. It does not seem more frequent in the southern parts of the country.

The disease is most common in the middle period of life. The youngest of my cases was a child of eight months, and cases are on record of the disease as early as the eighth or tenth week. It may occur as late as the seventieth year. Males are more prone to the affection than females. Of my cases 11 were in males and 6 in females. Birch-Hirschfeld states that of 200 cases collected from the literature, 135 were males and 65 females.

A tendency to hæmorrhage has been noted in many cases, and some of the patients have suffered repeatedly from nose-bleeding. In women

the disease is most common at the climacteric. There are instances in which it has developed during pregnancy. The case described by J. Chalmers Cameron, of Montreal, is in this respect remarkable, as the patient passed through three pregnancies, bearing on each occasion non-leukæmic children. The case is interesting, too, as showing the hereditary character of the affection, as the grandmother and mother, as well as a brother, suffered from symptoms strongly suggestive of leukæmia. One of the patient's children had leukæmia before the mother showed any signs, and a second died of the disease. At the last report this patient had gradually recovered from the third confinement and the red blood-corpuscles had risen to 4,000,000 per cubic millimetre, and the ratio of white to red 1 to 200. Sänger has reported a case in which a healthy mother bore a leukæmic child.

Malaria is believed by some to be an etiological factor. Of 150 cases analyzed by Gowers, there was a history of malaria in 30; in my series there was a history in at least 7. Syphilis appears in some cases to have been closely associated with the disease. The disease has followed injury or a blow.

The lower animals are subject to the affection, and cases have been described in horses, dogs, oxen, cats, swine, and mice.

Morbid Anatomy.—The wasting may be extreme, and dropsy is sometimes present. There is in many cases a remarkable condition of polyæmia; the heart and veins are distended with large blood-clots. In Case XI of my series the weight of blood in the heart chambers alone was 620 grammes. There may be remarkable distention of the portal, cerebral, pulmonary, and subcutaneous veins. The blood is usually clotted, and the enormous increase in the leucocytes gives a pus-like appearance to the coagula, so that it has happened more than once, as in Virchow's memorable case, that on opening the right auricle the observer at first thought he had cut into an abscess. The coagula have a peculiar greenish color, somewhat like the fat of a turtle. The alkalinity of the blood is diminished. The fibrin is increased. The character of the corpuscles will be described under the symptoms. Charcot's octohedral crystals separate from the blood after death. The specific gravity of the blood is somewhat lowered. There may be pericardial ecchymoses.

The spleen in the great majority of cases is enlarged. Strong adhesions may unite it to the abdominal wall, the diaphragm, or the stomach. The capsule may be thickened. The vessels at the hilus are enlarged; the weight may range from two to eighteen pounds. The organ is in a condition of chronic hyperplasia. It cuts with resistance, has a uniformly reddish-brown color, and the Malpighian bodies are invisible. Grayish-white, circumscribed, lymphoid tumors may occur throughout the organ, contrasting strongly with the reddish-brown matrix. In the early stage the swollen spleen pulp is softer, and it is stated that rupture has occurred from the intense hyperæmia. Enlargement of the lymphatic glands may