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

occur, either in conjunction with splenic enlargement or alone. In only one of my cases was the enlargement notable. In the cases of lymphatic leukæmia the cervical, axillary, mesenteric, and inguinal groups may be much enlarged, but the glands are usually soft, isolated, and movable. They may vary considerably in size during the course of the disease. The tonsils and the lymph follicles of the tongue, pharynx, and mouth may be enlarged.

In the majority of cases the bone marrow is involved with the spleen, the lieno-medullary form of the Germans. The marrow may be involved alone, forming a pure myelogenous leukæmia. Instead of a fatty marrow, the medulla of the long bones may resemble the consistent matter which forms the core of an abscess, or it may be dark brown in color. In Ponfick's case there were hæmorrhagic infarctions. There may be much expansion of the shell of bone and localized swellings which are tender and may even yield to firm pressure. Histologically, there are found in the medulla large numbers of nucleated red corpuscles in all stages of development, numerous cells with eosinophilic granules, and also many cells corresponding to the *myelocytes* found in the blood. Large mononuclear cells in the process of division by karyokinesis may be abundant. Polynuclear leucocytes are also present, as well as a certain number of small mononuclear elements.

The thymus is rarely involved, though it has been enlarged in some of the cases of acute lymphatic leukæmia.

In a few instances there have been leukæmic enlargements in the solitary and agminated glands of Peyer. In a case of Willcocks there were growths on the surface of the stomach and gastro-splenic omentum.

The liver may be enlarged, and in a case described by Welch it weighed over thirteen pounds. The enlargement is usually due to a diffuse leukæmic infiltration. The columns of liver cells are widely separated by leucocytes, which are partly within and partly outside the lobular capillaries. There may be definite leukæmic growths.

There are rarely changes of importance in the lungs. The kidneys are often enlarged and pale, the capillaries may be distended with leucocytes, and leukæmic tumors may occur. The skin may be involved, as in a case described by Kaposi.

Leukæmic tumors in the organs are not common. They were present in only one of the twelve autopsies in my series. In 159 cases collected by Gowers there were only thirteen instances of leukæmic nodules in the liver and ten in the kidneys. These new growths probably develop from leucocytes which leave the capillaries. Bizzozero has shown that the cells which compose them are in active fission.

Symptoms.—The onset is insidious, and, as a rule, the patient seeks advice for progressive enlargement of the abdomen and shortness of breath, or for the enlarged glands or the pallor, palpitation, and other symptoms of anæmia. Bleeding at the nose is common. Gastro-intestinal

symptoms may precede the onset. Occasionally the first symptoms are of a very serious nature. In one of the cases of my series the boy played lacrosse two days before the onset of the final hæmatemesis, and in another case, a girl who had, it was supposed, only a slight chlorosis, died of fatal hæmorrhage from the stomach before any suspicion had been aroused as to the true condition.

Blood.—In all forms of the disease the diagnosis must be made by the examination of the blood, as it alone offers distinctive features. In the normal blood Ehrlich recognizes the following varieties of colorless elements: (*a*) Lymphocytes—small cells about the size of a red blood-corpuscle, and probably derived from the lymphatic glands, which have a single large, round, deeply staining nucleus, surrounded by a narrow rim of non-granular protoplasm. (*b*) Large mononuclear leucocytes—cells several times as large as the red blood-corpuscle, with an oval or elliptical nucleus and a relatively larger amount of ungranulated protoplasm. (*c*) Transitional forms—cells which resemble the last variety, but have indentations and irregularities in the nucleus. (*d*) Polynuclear leucocytes—these are about the same size or a little smaller than the last variety. The nucleus is a long, deeply staining body which is bent and twisted on itself into irregular shapes. The protoplasm of these cells is filled with granules, which are stained, not by acid or basic coloring matters alone, but only by a combined fluid. The granules are therefore termed neutrophilic, and the name "neutrophiles" is given to these cells. (*e*) Cells about the same size as the last, but containing large, highly refractile, fat-like granules, which have an affinity for acid coloring matters. On account of their affinity for eosin, Ehrlich terms them *eosinophiles*. In normal blood these cells occur in a definite proportion to each other; the lymphocytes fifteen to thirty per cent, the polynuclear sixty-five to eighty per cent, the mononuclear and transitional forms about six per cent, and the eosinophiles two to four per cent.

The most striking change in the more common form, the lieno-myelogenic, is the increase in the colorless corpuscles. The average number of white per cubic millimetre is estimated at about 6,000; thus the proportion of white to red is 1 to 500—1,000. In leukæmia the proportion may be 1 to 10, or 1 to 5, or the ratio may reach 1 to 1. There are instances on record in which the number of leucocytes has exceeded that of the red corpuscles.

The character of the cells in splenic myelogenous leukæmia is as follows: The lymphocytes are little, if at all, increased; relatively they are greatly diminished. The eosinophiles are present in normal or increased relative proportion, so that there is a great total increase, and their presence is a striking feature in the stained blood-slide. The polynuclear neutrophiles may be in normal proportion; more frequently they are relatively diminished, and in the latter stages they may form but a small proportion of the colorless elements. The most characteristic feature

of the blood in this form of leukæmia is the presence of cells which do not occur in normal blood. They appear to be derived from the marrow, and are called by Ehrlich *myelocytes*. They are as large or even larger than the large mononuclear leucocytes, and are similar to them in appearance, but differ from them in the fact that the protoplasm is filled with the fine neutrophilic granules. Müller has recently found many large mononuclear elements with karyokinetic figures in leukæmic blood and in the marrow.

Nucleated red blood-corpuscles are present, usually in considerable numbers. There is, as a rule, only a moderate reduction in the number of red blood-corpuscles, rarely under two million per cubic millimetre. The hæmoglobin is usually reduced in a somewhat greater proportion. The accompanying blood chart is from a case of leukæmia with an enormously enlarged spleen.

The histological characters of the blood in acute lymphatic leukæmia differ materially. The increase in the colorless elements is never so great as in the preceding form; a proportion of one to ten would be extreme. This increase takes place solely in the lymphocytes, all other forms of leucocytes being present in greatly diminished relative proportion. In Uthemann's case ninety-three per cent of all the leucocytes were lymphocytes. Eosinophiles and nucleated red corpuscles are rare. Myelocytes are not present. As occasionally combined forms of leukæmia may occur, so undoubtedly variations from these two types of blood may be met with, and in a case of acute leukæmia observed at the Johns Hopkins Hospital, in which glands, marrow, and spleen were affected, there was present, besides a large proportion of lymphocytes and myelocytes, a considerable number of large mononuclear leucocytes. Among other points about leukæmic blood may be mentioned the feebleness of the amœboid movement, as noted by Cafafy, which may be accounted for by the large number of mononuclear elements present, the polynuclear alone possessing this power. The blood-plates exist in variable numbers; they may be remarkably abundant. The fibrin network between the corpuscles is usually thick and dense. In blood-slides which are kept for a short time, Charcot's octohedral crystals separate, and in the blood of leukæmia the hæmoglobin shows a remarkable tendency to crystallize.

The pulse is usually rapid, soft, compressible, but often full in volume. There are rarely any cardiac symptoms. The apex beat may be lifted an interspace by the enlarged spleen. Toward the close, as a consequence of the feeble circulation, œdema may occur in the feet or there may be general anasarca. Hæmorrhage is a common symptom and may be either late or early. Epistaxis is the most frequent form. Hæmoptysis and hæmaturia are rare. Bleeding from the gums may be present. Hæmatemesis proved fatal in two of my cases, and in a third a large cerebral hæmorrhage rapidly killed. The leukæmic retinitis is a part of the hæmorrhagic manifestations.

There are very few pulmonary symptoms. The shortness of breath is due, as a rule, to the anæmia. Toward the end there may be œdema of

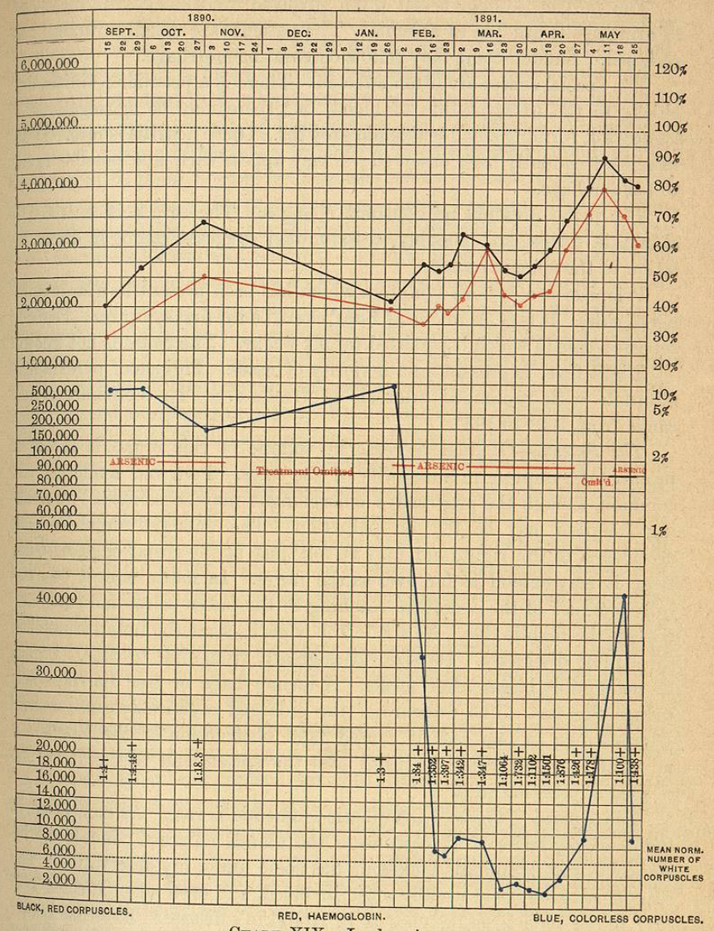

CHART XIX.—Leukæmia.

the lungs or pneumonia may carry off the patient. The gastro-intestinal symptoms are rarely absent. Nausea and vomiting are early features in some cases. Diarrhœa may be very troublesome, even fatal. Intestinal hæmorrhage is not common. There may be a dysenteric process in the colon. Jaundice rarely occurs, though in one case of my series there were recurrent attacks. Ascites may be a prominent symptom, probably due

to the presence of the splenic tumor. A leukæmic peritonitis also may be present, due to new growths in the membranes.

The nervous system is not often involved. Headache, dizziness, and fainting spells are due to anæmia. The patients are usually tranquil and resigned. Sudden coma may follow cerebral hæmorrhage.

The special senses are often affected. There is a peculiar retinitis, due chiefly to the extravasation of blood, but there may be aggregations of leucocytes, forming small leukæmic growths. Optic neuritis is rare. Deafness has frequently been observed; it may appear early and possibly is due to hæmorrhage.

The urine presents no constant changes. The uric acid excreted is always in excess, and possibly, as Salkowski suggests, stands in direct relation to the splenic tumor.

Priapism is a curious symptom which has been present in a large number of cases. It may, as in one of Edes' cases, be the first symptom. Peabody reports a case in which it persisted for six weeks. The cause is not known.

Slight fever is present in a majority of cases. Periods of pyrexia may alternate with prolonged intervals of freedom. The temperature may range from 102° to 103°.

The Spleen.—Gradual increase in volume of this organ is the most prominent symptom in a majority of the cases. Pain and tenderness are common, though the progressive enlargement may be painless. A creaking fremitus may be felt on palpation. The enlarged organ extends downward to the right, and may be felt just at the costal edge, or when large it may extend as far over as the navel. In many cases it occupies fully one half of the abdomen, reaching to the pubes below and extending beyond the middle line. As a rule, the edge, in some the notch or notches, can be felt distinctly. Its size varies greatly from time to time. It may be perceptibly larger after meals. A hæmorrhage or free diarrhœa may reduce the size. The pressure of the enlarged organ may cause distress after eating; in one case it caused fatal obstruction of the bowels. A murmur may sometimes be heard over the spleen, and Gerhardt has described a pulsation in it.

The Lymph Glands.—Lymphatic leukæmia is rare. As mentioned, in but 1 of my series of 17 cases were the glands enlarged; indeed, no instance of pure lymphatic leukæmia has come under my observation. The superficial groups are usually most involved, and even when affected it is rare to see such large bunches as in Hodgkin's disease. External lymph tumors are rare.

The pure myelogenous cases without associated enlargement of the spleen are rare. The most extreme hyperplasia of the bone marrow may exist without any tenderness. Occasionally the sternum, ribs, and flat bones show great irregularity and deformity, owing to definite tumor-like expansions.

Diagnosis.—The recognition of leukæmia can be determined only by microscopical examination of the blood. The clinical features may be identical with those of ordinary splenic anæmia, or with Hodgkin's disease An interesting question arises whether real increase in the leucocytes is the only criterion of the existence of the disease. Thus, for instance, in the case whose chart is given, on page 701, the patient came under observation in September, 1890, with 2,000,000 red blood-corpuscles per cubic millimetre, thirty per cent of hæmoglobin, and 500,000 white blood-corpuscles per cubic millimetre—a proportion of one to four. As shown by the chart, throughout September, October, November, and December, this ratio was maintained. Early in January, under treatment with arsenic, the white corpuscles began to decrease and gradually, as shown in the chart, the normal ratio was reached. At this time could it be said that the case was one of leukæmia without increase in the number of leucocytes? The blood examination by Ehrlich's method, as made by Thayer, showed that the characteristic myelocytes, elements which are not present in normal blood, were still present in numbers sufficient, at any rate, to suggest, if the patient had come under observation for the first time, that leukæmia might occur. By Ehrlich's method of blood examination a condition of leucocytosis can readily be distinguished from that of leukæmia, for in all ordinary leucocytoses the increase takes place solely in the polynuclear neutrophilic leucocytes, forming quite a different picture from the characteristic conditions described above.

Prognosis.—Recovery occasionally occurs. A great majority of the cases prove fatal within two or three years. Unfavorable signs are a tendency to hæmorrhage, persistent diarrhœa, early dropsy, and high fever. Remarkable variations are displayed in the course, and a transient improvement may take place for weeks or even months. The pure lymphatic form seems to be of particular malignancy, some cases proving fatal in from six to eight weeks.

Treatment.—Fresh air, good diet, and abstention from mental worry and care, are the important general indications. The *indicatio morbi* cannot be met. There are certain remedies which have an influence upon the disease. Of these, arsenic, given in large doses, is the best. I have repeatedly seen improvement under its use. On the other hand, there are curious remissions in the disease which render therapeutical deductions very fallacious. I have seen such marked improvement without special treatment that the patient, from a bed-ridden, wretched condition, recovered strength enough to enable him to attend to light duties.

Quinine may be given in cases with a malarial history. Iron may be of value in some cases, as may also inhalations of oxygen.

Excision of the leukæmic spleen has been performed twenty-four times, with one recovery—the case of Franzolini. Fussell gives the statistics of 105 cases of splenectomy with 48 deaths. Of the cases of simple hypertrophy, 28 in number, 9 recovered. Of 16 cases of floating spleen, 15 recovered.