fected. Extensive changes in the kidney are much more serious than those of the liver or spleen, as they lead to death within a few weeks or months.

PROGNOSIS.—This is in general unfavorable. It is probable that amyloid, when once formed, is not removed from the site of deposit. In all cases in which the condition is so marked that the diagnosis is certain, death usually occurs within short periods. Temporary improvement may take place; and in some cases, especially after operation for chronic purulent conditions of bone, the disease apparently comes to a standstill, marked general improvement takes place, the liver swelling decreases, and the albuminuria disappears. It is, of course, impossible to say to what extent these symptoms were due to the amyloid disease. A similar improvement has been noticed as the result of a prolonged inunction cure in a case of amyloid associated with syphilis. Corneal tumors may slowly disappear under the influence of local irritation and inflammation.

TREATMENT.—For the well-established condition it is hardly probable that treatment will avail, though iodine, ammonium chloride, potassium iodide, dilute nitric acid, etc., have been recommended. The improvement of the local or general primary condition is, of course, the most important therapeutic line to be followed; and in connection with this the general improvement of nutrition. Of far greater importance are prophylactic measures, even to the extent of such radical procedures as amputation in cases of chronic varicose ulcerations, chronic suppuration of bones, etc., in which persistent operative and therapeutic measures have been without result. *Aldred Scott Warthin.*

ANABOLISM. See *Metabolism.*

ANACARDIACEÆ, or **TEREBINTHINACEÆ.**—(The Cashew family.) A remarkable and important family of some fifty-nine genera, chiefly tropical or subtropical, exceedingly varied in the nature of its products. The mango, the cashew, and the spondias or hog-plum, are important fruits; those of Pistacia furnish a well-known flavoring agent, while its bark yields the commercial resin mastic; the milk juice of several Japanese species of Rhus furnishes Japanese lacquer, and the leaves and fruits of other species of this genus yield tanning agents. The oil which abounds in several species of Rhus (more properly called *Toxicodendron*), and in some other genera, acts as a powerful cutaneous poison. (See *Poisonous Plants.*) *H. H. Rusby.*

ANÆMIA, PERNICIOUS.—(Synonyms: *Progressive perniziöse Anämie,* Biermer; *Idiopathic anæmia,* Addison; *Essentielle Anämie,* Lebert; *Essentielle maligne* or *Essentielle fébrile Anämie,* Immermann; *Perniziöse Anämie,* Quincke; *Anémie progressive,* Lepine.)

DEFINITION.—Pernicious anæmia is a grave form of anæmia which is characterized by a reduction in the total amount of the blood and by a change in its physical, anatomical, and chemical characters. The blood is thin and pale and not coagulable. The red corpuscles are lessened in number and changed in size and shape. It is a peculiar circumstance that the adipose tissue is generally maintained, while at the same time secondary fatty degeneration of the heart is almost always found to be present. The disease is distinguished, clinically, by the symptoms of grave anæmia, often by an irregular fever, retinal hemorrhages, and hemorrhages underneath the skin and from mucous membranes. Its course is usually progressive, its termination fatal, its duration from seven weeks to from two to three years. Complications are rare; death is due to exhaustion, to syncope, to œdema of the lungs, or to cerebral complications.

This symptom complex may be dependent on some evident anatomical change or it may have no demonstrable organic basis. Thus we distinguish secondary or symptomatic progressive pernicious anæmia and a primary, essential, or cryptogenic form. Some authors limit the term pernicious anæmia to the latter group, but it seems better, in view of the identity of the two conditions anatomically and clinically, to apply the term to that peculiar form of anæmia which possesses the characteristics enumerated above, whatever its cause may be. In the secondary form of pernicious anæmia the symptoms of the blood changes dominate the clinical picture so that the symptoms referable to the causal lesion are comparatively insignificant, and the anæmia becomes practically a disease *per se.* This characteristic marks the distinction between pernicious anæmia and simple chronic anæmia in which the symptoms of the primary disease hold the first place, although the anæmia may be severe.

HISTORY PREVIOUS TO 1872.—The publication by Biermer, in 1872, of a series of cases of this disease, and his assertion that he was the first to recognize it, aroused the latent energies of the English, so that since then they have justly and successfully shown that to one of their countrymen is due the credit of having identified it long before that time. Addison certainly had observed and taught the clinical course of the disease, and had made inquiries into its pathology. He clearly established that what he called idiopathic anæmia was an independent affection, and so impressed it upon his colaborers and students that ever since then it "has not been lost sight of at Guy's." The wards of that hospital have furnished most of the cases for English memoirs, and its reports contain many observations and discussions on this disease. Prior to Addison, Coombe, Marshall Hall, and Barclay reported isolated cases of fatal anæmia. Since then, and before Biermer's publication, Wilks, Bristowe, Leared, and Habershon made contributions to our knowledge of the disease. The labors of Taylor, of Pye-Smith, of Mackenzie, and of others have clearly proven the fact of English priority. Professor Eichhorst, in his elaborate monograph, admits these claims, while Pepper, in the United States, was one of the earliest to point out the credit due Addison. In the mean time, the French, through Lepine, presented their claims of priority in the early recognition of the disease. Lepine justly admits the valuable work of Addison and his followers, but says that Andral was the earliest observer, and that Piorry, Cazenave, and Perroud had recognized the affection, the latter detailing four cases, with autopsies. A dissenting voice arose among the Germans. Lebert claimed that he had, in separate papers, described this disease, but the evidence from them shows that he had confused chlorosis with pernicious anæmia. Lately, it has been found that American physicians can enter claims of priority for one of their countrymen. Channing described cases of fatal anæmia in connection with, and independent of pregnancy as early as 1832. Not only was he himself perfectly familiar with it, but so also were many of his associates.

HISTORY SINCE 1872.—The time of the publication of Biermer's essay on "Progressive Pernicious Anæmia" makes an epoch in the history of this strange disease. He not only embodied in his essay as faithful a portrayal of the disease, as Addison and others had done, but he added to it more accurate accounts of the blood changes and the occurrence of retinal hemorrhages. Moreover, he so impressed the medical world with the important results of his observations that since then the knowledge of the disease, instead of being confined mostly to England, has become universal, and multitudes of observations have been in a short time added to the previous comparatively scanty data. In 1874 Immermann, in 1875 Zenker, and in 1876 Quincke, made valuable contributions to the study of the disease, while in 1877 important and elaborate monographs, by Müller and Eichhorst respectively, appeared. Since then German literature has been rich in observations of isolated cases. Among Englishmen, Pye-Smith, in 1875, published two cases in the *Deutsches Archiv,* and since then, among others of his countrymen, Bramwell, Mackenzie, Finney, Coupland, and William Hunter have written interesting and important articles. In America, Pepper, Howard,

Osler, Stengel, Thayer, Cabot, and others have made valuable observations. From a study of its history we find that a true conception of pernicious anæmia has been arrived at only through the combined labors of many observers. Thus Addison clearly defined the limitations of the primary type of the disease; Wilks first observed some of the blood changes; Biermer described the retinal hemorrhage. Then Immermann showed the relations and importance of the febrile process; Quincke contributed to the microscopical appearances of the blood, and showed its extreme deficiency in hæmoglobin, and the occurrence of siderosis. About the same time Eichhorst published the blood changes which he considered pathognomonic, and Pepper first demonstrated the possible relationship of this disease to an affection of the bone marrow. His work was corroborated by Scheby-Buch, Cohnheim, and Osler. The latter author has also made valuable investigations on the appearances of the blood. Professor Howard was the first to consider the relations of this form of anæmia to other forms, and to show that any form of anæmia may become pernicious. Granting the credit due these eminent observers for the work they have done, it is not detracting from it to say that about the year 1830 a coterie of physicians in and about Boston were well aware of the occurrence of fatal anæmia without assignable cause, and that they had discussed its nature and clinical course in their societies, and had published their observations to the world.

Etiology.—This is obscure. It is extremely difficult to reckon the influence of the age, the sex, the habits, and the condition of life as predisposing factors; and at the same time our want of knowledge of the pathology of the disease makes it as difficult to determine the exciting cause. In fact, all that can be said is that under certain circumstances and influences the disease develops more frequently than under others, without our being able to give a reason. According to some (Coupland, Eichhorst) it is divided about equally between the sexes. Bristowe says it is more frequent in the males. Müller, Immermann, and Biermer give predominance to the female sex. It is found to occur as early as at the age of five, or as late as at sixty-eight.

The following table, taken from Pye-Smith's very able article, shows well the relations of age and sex, according to various authors. "Many of the cases are common to all four lists."

	H. Müller.		Coupland.		Eichhorst.		Pye-Smith.
	Male.	Female.	Male.	Female.	Idiop.	Second.	
Under 15.....	0	0	1	0	0	1	6
15 to 20.....	2	4	2	4	2	1	4
21 to 30.....	2	9	8	18	4	17	29
31 to 40.....	1	19	9	16	8	22	25
41 to 50.....	2	2	19	9	4	16	21
51 to 60.....	2	1	14	7	4	9	13
61 to 70.....	..	..	3	1	1	1	4

It is thus seen that early adult life is the period of greatest liability. The position in life and the occupation seem to have some predisposing influence. In Germany the poorer classes, half-starved ordinary laborers, are more frequently attacked. There are notable exceptions to this in England and in this country. Cases have been reported of the wealthy and the well nourished being affected. Intemperate habits are frequently recorded in the reports. The residents of the country are as often affected as those living in the city, if not oftener. The occurrence of the disease with unusual frequency in parts of Switzerland led Immermann to suggest an endemic influence. Though the disease is not so frequent in other countries, it is sufficiently so to disprove such statements.

Aside from these factors, that probably act merely as predisposing causes, there are a number of conditions that have been shown to stand in the closest causal relationship to the anæmia; chronic suppuration, venereal excess, and diarrhœa appear to be the exciting causes in certain cases. Repeated bleedings, such as occur in hemorrhoids, may lead to this condition. Atrophy and sclerosis of the mucous membrane of the stomach and intestines seem often to be a cause. Infections, particularly syphilis and typhoid fever, are held to account for some cases. Biermer in his earliest communication recognized the causal relation of pregnancy and parturition to the disease. Two intestinal parasites, the Ankylostomum duodenale and the Bothriocephalus latus, cause a form of pernicious anæmia, probably by the elaboration of a poison. Many observers have insisted upon the occurrence of shock, grief, or anxiety as exciting causes. This is notably the opinion of Lepine, Wilks, and Coupland. Curtin, not knowing of the views of these men, long ago formulated such an idea, and has recorded cases which appear to have arisen from such cause.

Morbid Anatomy.—The appearance of the body after death is characteristic. The entire surface indicates an absence of blood—extreme pallor of the face, the extremities, the trunk, and the external mucous membranes, so that, if not for the dirty-yellow or straw-colored appearance of the face and hands, a sudden profuse hemorrhage might be considered the cause of death. On the extremities, the back of the hands, and the dorsum of the feet, the ankles and wrists, minute extravasations of blood are often seen. They vary from the size of a pin's head to that of a split pea, and are purple or yellow red in color. Œdema of the feet and ankles, of the hands and of the face is sometimes seen. The œdema may be limited to the eyelids or may be general. It may vary from this slight amount to a universal anasarca. Wasting of the body is often not marked; in fact, this absence of emaciation was thought in the early history of the disease to be the rule, but a few well-authenticated cases are recorded in which it was present. The presence of fat—for it is the adipose and not so much the muscular tissue that remains—is more noticeable in the abdominal walls than in any other region of the body. It is said that rigor mortis does not develop early after death.

On section, the most striking feature is the bloodlessness of all the tissues. A large proportion of cases exhibit the presence of subcutaneous œdema in the parts indicated above, while œdema of the lungs and meninges is common. Passive effusions into the serous cavities occur less frequently; they are generally small in amount, and hence are not appreciated during life. Considerable ascites, hydrothorax of one side, and hydropericardium are changes which have been seen only rarely. The exuded serum is of a deeper yellow color than usual. The preservation of adipose tissue is remarkable, not only in amount, but also in appearance. The subcutaneous and subserous accumulations remain, and the appendices epiploicæ are well preserved. The color of the fat is bright, or sulphur yellow, this being due probably as Lepine suggests, to ferrous sulphide. The muscles are generally firm and red, though the bulk is reduced. Fatty degeneration of the diaphragm and of the abdominal muscles has been observed.

In addition to the absence of emaciation and the extreme bloodlessness of the body, one of the characteristics of pernicious anæmia is the occurrence of small hemorrhages. These are seen in the skin as minute extravasations; they are found underneath the serous membranes—the pericardium, the peritoneum, and rarely the pleura—as minute points and specks; under the endothelium of the blood-vessels they have also been seen. They frequently occur in the brain substance as capillary hemorrhages. Similar hemorrhages are found in the mucous membrane of the œsophagus, the stomach, and the intestines, in the lungs and upper air passages, and in the bladder. The most frequent seat of these extravasations, however, is the retina. These hemorrhages are due to rupture of capillaries on account of the diseased state of their walls, or to diapedesis.

The last general change that is often seen on section of the body is the occurrence of a dark-gray staining of the organs. This has been proven to be due to an excess

of iron in the tissues. Rosenstein found 0.5187 per cent. of iron in the liver, 0.2275 per cent. in the spleen, 0.0422 per cent. in the kidneys. Quincke found 0.6 per cent. metallic iron in the liver and 0.32 per cent. in the kidneys in one case. In another case the liver contained 2.1 per cent. The iron was seen in the liver cells as small granules. Iron has also been found in the tissue of the lungs and of the pancreas, and in the peritoneum. Purser found the dried kidneys to yield 0.0352 per cent. of iron. This increase of iron goes hand-in-hand with diminution of hæmoglobin. Oidtman (quoted by Rosenstein) found, on analysis, the healthy liver to contain 0.08 per cent. and the spleen 0.15 per cent. of iron.

The blood, extremely small in amount, is collected in the heart and larger venous trunks. Attempts have been made to estimate the total quantity of blood, but the results are naturally uncertain. Quincke, in two cases, computed the blood to be 5 per cent. and 4.34 per cent. of the body weight (8 per cent. is considered normal). The small amount of blood in the body can be appreciated during life by attempts to secure some for examination. A deep thrust of a needle in an artificially congested finger, or even an incision, is required to obtain a few drops. It is thin and watery, stains the hands as does nitric acid, or looks like muscle washings or weak coffee. Coagula are rarely found in the cavities of the heart and the vessels. If present, they are soft, friable, and pale or light brown. The blood removed from the body to a test tube, on standing, remains uncoagulated for a long time, although a deposit of the corpuscular elements takes place. The specific gravity of the blood has been found to be as low as 1.025 (Stengle).

On microscopical examinations, the red blood corpuscles are found to be decidedly fewer in number than normal, and they are changed in color, in size, and in shape. Few, if any, changes take place in the white corpuscles. Frequently, however, their number is diminished. A leucocytosis in which the lymphocytes are in excess (sixty per cent.) occurs not infrequently toward the end of the disease. A polymorphonuclear leucocytosis indicates a complication, such as pneumonia or suppuration. Litten recorded a case of pernicious anæmia which passed into leukæmia, and Stengel has observed typical myelocytes in the disease.

The diminution in number of the red corpuscles sometimes goes on to an extreme degree. Quincke records a case in which the number fell to 143,000 per cubic millimetre. Cases are said to have recovered when the red cells were reduced to 360,000 (Worm, Müller); in fact, recovery occurred in the case of Quincke, just mentioned. The smallest number the writer has seen in any case which subsequently recovered was 570,000. The amount of reduction in fatal cases varies from 400,000 to 1,000,000 corpuscles per cubic millimetre. The reduction very often takes place with great rapidity. Thus, in one of Lepine's cases, in ten days the number fell to 378,750. The increase in number is not so rapid when improvement takes place. In the case of Quincke, mentioned above, the cells increased in ten weeks from 143,000 to 1,234,000 per cubic millimetre. In one of the writer's cases the number rose from 570,000 to 1,600,000 in about nine months; a gradual recovery followed.

The red cells vary greatly in size. They are spoken of as microcytes, normocytes, and megalocytes, according to their size. The megalocytes occur in large numbers and may constitute one-eighth of all the erythrocytes. They vary in size from 9 to 14 μ in diameter and have been observed as large as 18 μ in diameter. They do not show the normal biconcave form, but appear globular. Small cells, called microcytes, occur frequently but less constantly. They vary in size from that of a blood plaque up to a normocyte. The normal-sized cells, as well as the larger and smaller ones, frequently show bizarre shapes—oval, bowl-shaped, tailed or pear-shaped, and other forms. Quincke has called them poikilocytes. They occasionally show amœboid movements.

Nucleated corpuscles identical with those occurring in embryonal life occur quite constantly, though seldom in large numbers. They vary in size as do the non-nucleated cells and are correspondingly named microblasts, normoblasts, and megaloblasts. They occasionally show karyokinetic figures. During the course of the disease there are occasional periods, called blood crises, when the number of nucleated cells is greatly increased, and after such a period there is an increase in the number of normal erythrocytes.

The amount of hæmoglobin in the blood is greatly reduced. It is not, however, reduced in the same proportion as are the red blood cells. The amount of hæmoglobin in each corpuscle is increased. The relatively high percentage of hæmoglobin is due chiefly to the large average size of the red blood cells. Eichhorst states that he has observed cases in which the hæmoglobin value of the corpuscles was not above normal. Ehrlich has observed certain erythrocytes whose protoplasm fixes both the acid and the basic stain; these he calls polychromatophile cells. He has called attention to other cells that show fine pigment granules scattered through the protoplasm,—"dotted cells." Both are supposed to be indications of degeneration, though the appearances may signify simply an embryonal condition.

Chemical analyses of the blood have yielded no results that throw any light on the nature of the disease, nor have they detected any changes that would aid in diagnosis. The alkalinity is lessened, the total solids and the albumin are diminished. Probably the loss of albumin from the red cells is greater than from the plasma. Marshall found in one case the total quantity of iron to be one-third the normal.

Cytogenic Organs.—The spleen is recorded as variable in size—from shrivelled up or very small, through all gradations to enlarged, weighing in one instance 453.5 gm. It generally is more charged with blood than is any other organ. It is not pulpy, but soft and congested, and on microscopical examination there is found an absence of pathological change, save an excess of fibrous tissue in a few cases. Granules of ferruginous pigment have been met with. The lymphatic glands are usually normal. In a few instances the lymphatic glands of the mesentery have been recorded as enlarged, this change being due, as Pye-Smith suggests, to a previous diarrhœa. In one case the lumbar lymphatic glands were enlarged. The marrow of the long bones in a considerable number of cases shows very interesting changes. The appearances described by many observers correspond in the main. The marrow is red or violet colored, and is soft or pultaceous. Its fatty appearance has disappeared, and under the microscope the fat is seen to be replaced by colored corpuscles, non-nucleated, varying in size and in the amount of hæmoglobin which they contain; by nucleated red corpuscles of various size and considerable number; and by cells containing red blood corpuscles. In addition to this, the myeloplaxes, which belong normally in this region, are generally found, though Purser noted their absence. These changes are best studied in the marrow of the shafts of the long bones.

Circulatory Apparatus.—More marked pathological changes take place in this apparatus than in any other. The heart is normal in size or dilated; the muscular tissue is soft, flabby, pale in color; often the cavities are empty, or they contain soft brown or fawn-colored clots. To the naked eye the appearances of fatty degeneration are most striking. There are some cases in which this change has not been seen; when present, it is most marked on the musculi papillares and columnæ carneæ, and appears as yellow dots, "zigzag striations," or "tabby mottling." The subpericardial fat generally is abundant (Eichhorst). The ventricles are more degenerated than the auricles, it is said, although the writer has observed in two cases an extreme degree of wasting of muscular fibre in the auricles. So marked was it that they transmitted light, the fasciculi of the muscle could be separated, and the endo- and pericardium seemed to make up the auricular wall. The left heart is more markedly degenerated than the right. In one case of the writer's the converse was true. Wilks first de-