the large central sinuses the reticular meshwork may at times be very scanty.

The reticulum of the sinus appears, in part at least, to be lined with endothelial cells, but these are with great difficulty made out, and in many places the blood seems to be in direct contact with the reticular surfaces. The circulation is therefore of the type described as sinusoidal. The nuclei of the cells of the reticulum stain much more lightly than those of the neighboring lymphoid tissue. There is apparently a direct continuation of the sinus reticulum with the reticulum of the lymphoid areas; and the latter may be regarded as the same structure enclosing in its meshes masses of lymphocytes. The number and size, as well as the general arrangement of the blood sinuses, vary greatly, so that scarcely any two glands resemble each other in these respects.

The lymphoid tissue lying between the blood sinuses resembles that of the spleen or ordinary lymphatic gland. It varies very much in amount, sometimes forming a mere network between the sinuses, while in other cases it may form the chief part of the gland. Usually the greater mass of lymphoid tissue is toward the periphery, forming the inner border of the peripheral sinus; but frequently extending to the capsule, breaking up the peripheral sinus into small sections that run for a short distance only. Small round collections of lymphoid cells resembling splenic follicles are often seen. These occur more frequently at or near the periphery, but they may occasionally be found near the central portion of the gland. They may be partly or wholly surrounded by the blood sinus. The cells in the central portion of the follicle stain more lightly than those at its periphery. Serial sections show that these nodes are almost perfectly round in the majority of cases. Usually they possess no arterial relations, but occasionally a small capillary is found in them which under certain pathological conditions may become gradually converted into a small arteriole with thickened walls. The resemblance in this case to the splenic follicle is very complete.

The cells of the lymphoid area are for the greater part small lymphocytes. These vary greatly with respect to the relative size and staining power of the nucleus and the relative amount of protoplasm. Next to the small lymphocytes the large mononuclear leucocytes are the most common form present. These also vary much in size, form, and staining power. Transitional and polynuclear leucocytes are also present in varying numbers. A small number of basophile and mononuclear eosinophiles is also usually present; mast cells are rare in the majority of cases, but occasionally a gland may be found in which the majority of the cells of the central portion are mast cells, as is so frequently the case in the hæmolymph glands of the steer and sheep.

The reticulum of the lymphoid areas resembles that of the blood sinuses, and is directly continuous with it. In its meshes lie the cells of the lymphoid tissue and also numerous red blood cells. The latter fact suggests the presence in the lymphoid tissue of very fine blood spaces similar to those in the spleen pulp, but differing from the latter in that the blood spaces are smaller and the reticulum is more dense. The reticulum of the large sinuses is much more abundant and of a coarser mesh than that of the lymph sinuses of the lymphatic glands. Small fibrillæ of elastic tissue and unstriped muscle may be scattered through it. In its meshes there are constantly present large mononuclear phagocytes containing disintegrating red cells and blood pigment. These cells are also found in the reticulum of the lymphoid tissue in connection with free pigment; but they are always more numerous in the reticulum of the medullary sinuses than elsewhere. Under normal conditions their number in individual glands varies greatly, the appearances suggesting a possible cyclical function of hæmolysis. Glands containing many of these cells may be found side by side with others whose reticular spaces contain but few. The same appearances are found in the hæmolymph glands of the lower animals, particularly in those of the dog and rat. Multinuclear giant cells, eosinophile, basophile, and mast cells may at times be found in the reticular meshes. The origin of the phagocytes has not yet been definitely determined; they may arise either from leucocytes or from the endothelial cells lining the reticulum.

Scattered masses and droplets of a fuchsinophile hyaline substance are often found throughout the lymphoid tissue; they are usually most numerous toward the periphery of the gland. They are frequently seen as highly refractile spherules lying in the meshes of the reticulum or enclosed in phagocytes. They are evidently the product of the destruction of red cells, as all stages of their formation can be found. In some cases the spherules are seen partly extruded from the phagocyte. They frequently give an iron reaction, especially those found in phagocytic cells.

Marrow-lymph Glands.—This type of hæmolymph gland is of very much less frequent occurrence in the normal body; but is much more prominent in certain pathological conditions, suggesting the possibility of resting glands or new formations. In some cases they appear to arise directly out of adipose tissue. They have been found only in the retroperitoneal region, along the vertebræ and brim of pelvis, and always in close proximity to the large vessels, abdominal aorta, vena cava, common iliacs, adrenal and renal vessels. They are present most frequently behind the aorta or between it and the vena cava. These glands are usually flattened and elongated, their greatest dimension lying parallel to the axis of the neighboring vessel. They may possess a distinct hilum, but the number of vessels entering is not so great as in the case of the splenolymph gland. Lymph vessels are also found in connection with these glands. Not rarely the marrow-lymph gland is found as a slender cylinder several centimetres in length embedded in fat. On section these glands are white or pinkish in color with fine red streaks corresponding to the course of the blood sinuses. Their consistence is very soft, and on section they present an almost homogeneous surface.

The capsule is thin and contains but little unstriped muscle and yellow elastic tissue. Delicate trabeculæ run from it toward the centre of the gland. Beneath the capsule there is a peripheral blood sinus of small size which usually runs entirely around the gland, and from this there are narrow branching sinuses accompanying the trabeculæ toward the centre of the gland. All of the sinuses are filled with a coarse reticulum through the meshes of which the blood circulates. Dilated sinuses as in the splenolymph glands are not present. The course of the sinuses is distinctly shown by the lighter staining nuclei of the reticulum and the presence of red cells. Lymph sinuses may also be present. Between the sinuses lies the lymphoid tissue arranged in irregular lobules. It is in much greater amount than in the case of the splenolymph glands. Throughout the lymphoid tissue, near the central portion of the gland, fat cells are present, either singly or in small groups. This may be regarded as one of the most striking characteristics of this type. Collections of cells resembling follicles are not present. The reticulum of the lymphoid areas is more delicate and scanty, and contains but little elastic tissue. The cells of the lymphoid areas present a much more striking variety of form and staining properties than in the splenolymph glands. Mononuclear eosinophiles and mast cells are more numerous; and multinuclear as well as large mononuclear forms with deeply staining knobbed nuclei may be present. Giant cells resembling those of the bone marrow are occasionally found, and in certain pathological states of the blood may be very numerous. No nucleated red cells have been found under normal conditions. Phagocytes containing red cells, pigment, fuchsinophile, hyaline bodies, and leucocytes occur to a less extent than in the splenolymph glands. Numerous red cells are found scattered throughout the reticulum of the lymphoid tissue suggesting the presence of smaller blood spaces.

Transition forms between spleno- and marrow-lymph glands are found, and also between the latter and ordinary lymphatic glands. The various forms found are such as to suggest the idea that hæmolymph glands are not permanent structures in any one form, but possibly show a certain amount of fluctuation. Thus the blood sinuses may become increased in size by a decrease of the lymphoid portion, while, on the other hand, an increase of lymphocytes may occur at the expense of the blood sinuses.

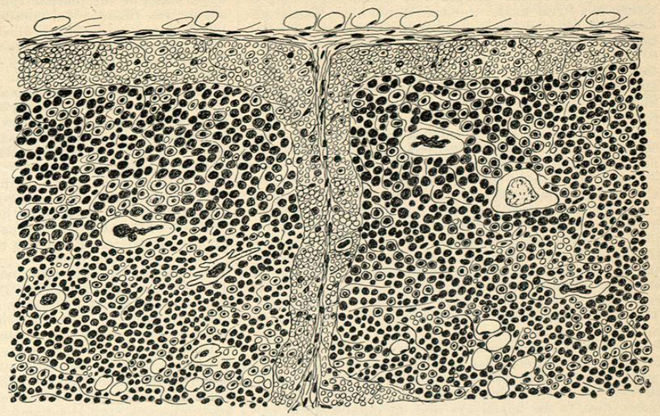

Fig. 2438.—Portion of Human Hæmolymph Gland (Marrow-lymph Gland) from Retroperitoneal Region of an Individual who had Died of Hemorrhage from the Nose. In the lymphadenoid tissue are giant cells resembling those of the marrow, nucleated red cells, mononuclear eosinophiles, etc. A number of fat cells are also seen scattered through the lymphadenoid tissue. Leitz objective No. 7; eye-piece No. IV. Reduced one-third.

Circulation. — The exact mode of circulation in the hæmolymph glands has not yet been worked out. It is probable that the arteries entering the hilum quickly divide into smaller branches which, passing toward the periphery, empty into the blood sinuses from which the blood is again gathered into veins which pass out at the hilum or obliquely through the capsule. The circulation in the sinuses is of the type known as sinusoidal, only the endothelium separating the blood from the cells in the reticular meshes. The current in these spaces must be very slow, and a long period of time must be required for the complete circulation through the intricate meshes of the reticulum crossing the sinuses. The relations of the lymphatic and blood systems in these glands are also unknown. It is possible that, in the human body at least, a mixture of blood and lymph, the so-called hæmolymph, may be present in the sinuses, and that direct communication between the two systems occurs in these glands.

Development.—No work has yet been done upon the development of these structures. They are found as fully developed organs in the new-born child, and have been found at an early period in the fœtal calf. They are without doubt to be regarded as individual organs whose early stage of development runs parallel with those of the lymphatic glands. Under certain pathological conditions it is possible that they may be developed from ordinary lymphatic glands or from adipose tissue in compensation for the spleen or bone marrow.

Function.—The hæmolymph glands are so numerous in the steer and sheep that their function is obviously of importance. In other animals and in man, while constantly present, they do not under ordinary circumstances attract attention through either their numbers or their size. The constant presence of phagocytes containing disintegrating red cells and pigment would indicate that extensive hæmolysis is one function carried on in these structures. As before mentioned, the presence of glands containing many phagocytes in their sinuses side by side with those whose sinuses contain only red cells would indicate a cyclical function; and there are many other appearances to suggest this. Under normal conditions no evidence of the formation of red cells has been observed, unless the occasional presence of bone-marrow giant cells may be taken as an indication of this process. The presence of these in the sinuses may, however, be explained on the assumption of giant-cell embolism. Under pathological conditions, such as anæmia and leukæmia, the hæmolymph glands, particularly those described as marrow glands, show evidences of increased functional activity in the hyperplasia of all the glandular elements and the increased number of mitoses in the lymphoid cells. In addition large numbers of giant cells may be found in the reticulum of the sinuses and in the lymphoid areas, evidently formed in the gland; also nucleated red cells, myelocytes, etc., may be present, so that the gland may come to resemble lymphoid marrow. These changes are not shared by the other lymph glands of the body. The hæmolymph glands are also to be regarded as important centres of leucocyte formation. After splenectomy or in certain pathological conditions of the spleen the splenolymph glands may compensate for this organ through hyperplasia and increased hæmolytic activity. In short, the hæmolymph glands normally possess a hæmolytic function and give rise to leucocytes; under pathological conditions they may also become centres of red-cell formation.

Pathology.—The more common pathological processes, such as congestion, inflammation, tuberculosis, metastases of malignant tumors, etc., have been found affecting these glands in common with the ordinary lymphatic glands. In a limited group of conditions such striking changes occur that they must be regarded as specific in character. These changes are confined entirely to cases showing more or less marked pathological alterations of the blood.

Anæmia.—In all of the cases of anæmia examined either the splenolymph or the marrow-lymph glands showed changes of greater or less extent. These changes varied with the nature and degree of the anæmia.

Post-hemorrhagic Anæmia.—In a case of fatal anæmia following repeated and prolonged attacks of epistaxis the only lymph glands showing change were those of the retroperitoneal region, particularly those in the neighborhood of the solar plexus. These were moderately enlarged, of a pink color and soft consistence. On microscopical examination they presented a structure resembling in the most striking way the lymphoid marrow. Throughout the reticulum of the sinuses and lymphoid areas were numerous giant cells in all respects resembling those of the marrow. The findings admitted of but one interpretation: these giant cells must have been formed within the gland, most probably from the reticulum or the endothelium lining it. Large numbers of mononuclear eosinophiles, nucleated red cells of large and small

size, large mononuclear leucocytes corresponding to myelocytes, and all possible varieties of transitional forms were also present. The bone marrow of this case showed scattered areas of lymphoid marrow, and in both the liver and spleen changes were found suggesting a return to a fœtal mode of blood formation. Numerous nucleated red cells were present in the blood. The remaining lymph glands showed only a fibroid hyperplasia.

Secondary Cachectic Anæmia.—In a large number of cases examined showing a more or less severe cachectic anæmia both marrow- and splenolymph glands showed increased hæmolysis, but no evidences of the formation of red blood cells were present.

Splenic Anæmia.—In a case of splenomegaly with severe anæmia, the patient dying after splenectomy, numerous minute nodes of lymphoid tissue were found scattered throughout the adipose tissue of the mesentery and retroperitoneal region. The majority of these possessed a small arteriole showing a much thickened wall; in some cases the lumen was completely obliterated by the proliferation of the intima. The new tissue blocking the vessel in many cases showed a hyaline change, and the concentric arrangement in some instances bore a strong resemblance to the thymus corpuscles. In some cases the hyaline tissue had undergone calcification. This new formation of lymphoid tissue resembles very much the changes found in the omentum of animals whose spleens had been experimentally removed, and is probably to be interpreted as compensation for the diseased spleen. The splenolymph glands in this case showed also such changes that they resembled splenic tissue, both to the naked eye and on microscopical examination, being regarded at the autopsy as accessory spleens.

Pernicious Anæmia.—In five cases of pernicious anæmia examined the changes in the hæmolymph glands were so constant and so marked that the writer regards them as specific in nature. In the more rapidly progressing forms the number of splenolymph glands is so great that they must be regarded either as new formations or as resting glands become active. In one case over sixty of these glands were removed from the cervical, thoracic, and retroperitoneal regions; and in another over thirty from the retroperitoneal region alone. The glands are enlarged and darker in color, often a chocolate brown. On microscopical examination the central and communicating sinuses are found almost filled with large phagocytes containing red cells and pigment. The processes of hæmolysis are increased to an extraordinary degree, particularly in the rapidly progressing forms. The spleens in these cases showed but little evidences of hæmolysis, while liver and kidneys showed marked hæmosiderosis. No evidences of increased activity on the part of the bone marrow were found; on the contrary, in all of the cases there was marked atrophy of the red marrow associated with osteoporosis and the formation of cystoid cavities filled with liquid fat.

In one case of progressive anæmia extending over three years, characterized by repeated severe attacks of epistaxis, hæmatemesis, and bloody stools, the only pathological changes of importance found on autopsy were in the retroperitoneal lymph glands. These were enormously enlarged, forming an almost continuous double row on each side of the abdominal aorta and diverging below along the brim of the pelvis. Each gland was 3 to 4 cm. in length and 1 to 2 cm. in thickness. They were almost cylindrical, somewhat flattened, and were dark red in color, almost black. On section the blood flowed freely from the greatly dilated veins. On microscopical examination a great hyperplasia of the lymphoid tissue was found, extending beyond the original capsule of the gland into the surrounding fat tissue. The appearances suggested strongly the possibility of a direct conversion of fat into lymphoid tissue. Numerous mononuclear eosinophiles, nucleated red cells, and occasional giant cells were present throughout the reticulum of the lymphoid areas. Mitotic figures were numerous. The presence of blood sinuses proved these glands to be hæmolymph glands of the marrow-lymph type, and the process was interpreted as a compensatory hyperplasia for the bone marrow which was atrophic and cystoid.

Leukæmia.—In a case of mixed leukæmia an enormous hyperplasia of the marrow-lymph glands similar to the above was found. On microscopical examination the blood sinuses were found filled with giant cells which were also scattered throughout the lymphoid areas. Mononuclear eosinophile cells, nucleated red cells, myelocytes, and an almost infinite variety of leucocytes, especially well shown in specimens stained with the tri-acid stain, made up the lymphoid portions. The resemblance to lymphoid marrow was very close, as in the case of fatal anæmia following epistaxis. The other lymph glands showed but slight enlargement due to the increased number of leucocytes present. The bone marrow showed but little lymphoid increase; the spleen was greatly enlarged. The changes in the marrow-lymph glands are to be interpreted in this case also as being evidence of the ability on the part of these glands to take up the blood-forming function of the bone marrow.

Leucocytosis.—In cases of pyæmia showing marked leucocyte increase the hæmolymph glands exhibit evidences of increased activity in the cells of the lymphoid areas, as shown by numerous mitoses. The mononuclear eosinophiles are also increased in number, and nucleated red cells and giant cells may also be found.

Experimental Pathology. — In animals whose spleens have been removed the hæmolymph glands show hyperplasia and evidences of increased hæmolysis. In poisoning with hæmolytic agents such as pyrogallic acid, muscarin, toluylendiamin, etc., these glands show greatly increased hæmolysis, the sinuses being packed with phagocytes containing red cells and pigment.

Summary.—By the above cases it is shown that under pathological conditions of either the spleen or bone marrow, the hæmolymph glands may assume either a hæmolytic or a hæmatopoietic function; and that in all conditions characterized by increased hæmolysis the chief seat of the blood destruction appears to be located in the sinuses of these organs. *Aldred Scott Warthin.*

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HÆMOPERICARDIUM.—Blood in the pericardium is a rare condition and of small clinical interest.

Etiology.—In tuberculous and malignant diseases of the pericardium, just as in similar diseases of the peritoneum, the exudate is usually bloody. By hæmopericardium is meant a hemorrhage into the pericardium. This accident occurs under the following conditions:

(1) As a result of traumatic injury from without, or by foreign bodies penetrating the œsophagus from within.

(2) Such hemorrhages have been found associated with scurvy, purpura, leukæmia, and allied conditions.

(3) From rupture of the heart or a cardiac aneurism.

(4) From rupture of an aneurism of the aorta or pulmonary artery. The first part of the aorta is usually involved and it may be by only a pinhole rupture.

(5) From rupture of smaller vessels, namely, one of the coronary arteries, or of vessels in a new growth.

Anatomical Characters.—The quantity of blood varies much. It is greater when the opening in the aorta is small. When an aneurism bursts into the pericardium the average amount of blood usually found is said to be about seven ounces. When the hemorrhage takes place through a small hole, it may reach twenty-four ounces. A traumatic case has been reported in which over six pints of thin, dark, fluid blood were removed from the pericardium in the course of three hours. The patient recovered. The blood may appear as a soft, red, jelly-like clot. A variable amount of serum may have separated from it.

Clinical History.—The condition may occur suddenly. The associated disease, such as aneurism, may have been previously demonstrated. When the hemorrhage takes place through a large rent, immediate or very rapid death usually occurs, either from the effects of the hemorrhage, or from paralysis of the heart. The fatal event may be preceded by grave cardiac symptoms. When the accumulation takes place gradually the patient may live for some time, complaining of cardiac oppression or pain, dyspnœa, and faintness.

Physical Signs.—These are not likely to be noted in the sudden cases. When the progress is slower there is a more or less rapid increase in the area of cardiac dulness; the apex beat disappears and the heart sounds become weak.

Treatment.—In the majority of cases treatment is limited to the relief of symptoms. Hæmostatics are useless. In the protracted cases cardiac stimulants may prolong life. A few patients recover as a result of aspiration of the pericardial sac. *James Rae Arneill.*

HÆMOPHILIA.—(Synonyms: Hemorrhagic Diathesis or Idiosyncrasy, Hæmorrhaphilia, Hæmatophilia, Hereditary Hemorrhage; Ger., *Hämophilie, Bluterkrankheit, Blutsucht, Blutungssucht;* Fr., *Hémophilie.* Otto, an American physician, gave the name Bleeder [Ger., *Bluter;* Fr., *Homme saignant*] to an individual patient.)

Definition.—An hereditary and congenital disease, characterized by a tendency to frequent, obstinate, and prolonged hemorrhages, external or interstitial, spontaneous or traumatic, associated with swelling of the joints.

History.—Our knowledge of this disease is modern. Its historians have been able to find the records of but few probable cases or families prior to the present century, and even these, with the exception of the cases reported by Hochstetter and Sir W. Fordyce, may all be considered doubtful examples, and Legg cannot admit Banyer's case to be beyond doubt. It was left for American physicians accurately to fix the characteristics of the disease. Otto, E. H. Smith, Hay, the Buel brothers, and Coates, in the early part of the last century, and Hughes, Gould, Harris, Hutchinson, Holton, and Dunn, in the past thirty years, have been the chief contributors to its literature. The early writers first demonstrated its hereditary nature. In the second and third quarters of the last century the Germans were prolific workers. Nasse, Rieken, Schönlein, and others, were of the earlier writers. Wachsmuth's monograph, Lange's statistics, Virchow's complete description in his "Handbuch," the monograph of Grandidier, the most complete published, and the article in "Ziemssen's Handbuch," by Immermann, familiarized modern German physicians with the affection. The exhaustive monograph of Legg is the principal contribution made by any English physician.

Etiology.—Sex and heredity are the most important factors in the etiology of hæmophilia. It occurs with greatest frequency in the male, the ratio having been put as high as eleven males to one female. Females do not usually present typical cases, and danger to life is less in the latter sex.

Hereditary disposition is so essential that its absence in a supposed case is sufficient to negative the diagnosis, although, it is true, it is difficult, often impossible, to trace genealogy among the lower classes. Legg believes all or nearly all cases may be traced to an hereditary origin. It has been suggested that this hereditary tendency is the result of the intermarriage of near relations. The fact that it occurs largely among Germans and Jews favors this argument, for in both classes such marriages are common. A common ancestry for all bleeders has been assumed by some authors.

While the females are not the bleeders of a hæmophilic family, the disposition is transmitted through them. The mother, not a bleeder, will transmit the tendency to her sons. They in turn are not likely to conduct the disease to their children, but the tendency passes through the daughters to the grandson. The females that transmit the tendency are usually in perfect health, although cases have been reported, in rare instances, in which the mother, a bleeder, transmitted it to the children of both sexes. The cases are still more rare in which the father, a bleeder, will pass down the tendency to either the sons or the daughters, respectively. A male non-bleeder, in a hæmophilic family, seldom transmits the disease to his descendants. Transmission through the female line is the rule. It is said that the first-born of a family are less liable to become bleeders. This tendency to bleeding may continue for many generations. The Clitherow family, reported by Legg, have exhibited the tendency for two hundred years. The families of Tenna, Switzerland, trace the disposition through five generations.

One peculiarity of bleeder families that has been noted is the marked intellectual power of the individuals; another, the great fertility of the families. Although they have many children, few reach adult age, as the number is much lessened by death from hemorrhages in early life, the mortality at that period being very great.

The disposition to bleed, Grandidier believes, may gradually be lost in a family. He has himself seen one such example, and another has been reported by Legg.

It was noted above that among Germans hæmophilia is common. In fact, some think it a disease peculiar to the Anglo-Germanic races. Dunn's analysis of 219 families shows its distribution about as follows: Germany, 94; Great Britain, 52; North America, 23; France, 22; Prussia and Poland, 10; Switzerland, 9; and the remainder in other European countries. The condition is rarely found in the negro, as has been pointed out recently by Steiner (Johns Hopkins Hosp. Reports, 1900) who reports one case and refers to one other decribed by Hadlock.

Hæmophilia spares no social class, though cases are reported more frequently from the middle and lower classes. Its presence or absence is not influenced by geographical position, and the nature of the food is also without effect on it.

While it has been asserted of many cases of hæmophilia that they arose spontaneously, yet nothing is known of the circumstances contributing to their origin. Legg rightly criticises the case of Mutzenbecher, in which the disease was reported to have arisen *de novo*. A mother, suckling her child, received a great fright, after which the child nursed. Shortly afterward symptoms of hæmophilia developed. Two other sons, also bleeders, were subsequently born, a fact which renders very probable the hereditary transmission in this case.

The circumstances, aside from traumatism, influencing the occurrence of hemorrhage, or which may be the predisposing or exciting causes of the accident, in a person belonging to a hæmophilic family, are the age, the constitution, and the temperament of the individual; the time of day, the season of the year, and the climate. Hemorrhages have not appeared for the first time after the twenty-second year; it is rare for them to appear after the twelfth year, and in the larger number of instances the first attack occurred before the fifth year. Its most usual appearance is about the end of the first year. Hemorrhage from the umbilicus, after sloughing of the cord, is very rare.

Bleeders are always in good health except that they suffer from anæmia. They often have blue eyes, light hair, a thin skin, and prominent veins.

Instances are recorded in which the hemorrhages occurred most frequently at night. The winter season and a cold, damp climate favor attacks of hemorrhage.

Those who consider the disease to be an infectious condition have scanty evidence to support their view. Bacteriological examinations have been entirely negative,