THE HUMAN SPLEEN AS AN HÆMATOPLASTIC ORGAN, AS EXEMPLIFIED IN A CASE OF SPLENOMEGALY WITH SCLEROSIS OF THE BONE-MARROW.[1]

By J. L. DONHAUSER, M.D.

Resident Pathologist, Pennsylvania Hospital, Philadelphia.
(From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

PLATES XXXII AND XXXIII.

This paper has been written for the following reasons:

1. To present a case of splenomegaly with very unusual pathological findings.

2. To show the similarity which may exist between bone-marrow changes and splenic transformation, and the relation of the one to the other.

3. To consider certain types of splenomegaly as being compensatory processes dependent upon and due to bone-marrow disease.

History of the Case.—The patient, Samuel K., an oiler, aged 58 years, was brought into the Pennsylvania Hospital, August 5, 1907, in the ambulance during the service of Dr. J. C. Wilson, whom I wish to thank for the following notes.

He complained of malaise, weakness, dyspnœa, shortness of breath, insomnia, loss of appetite, nausea, constipation and œdema of lower extremities. His father died of "debility"; his mother, as result of an accident. Three brothers and two sisters are dead, the causes unknown. Three brothers and three sisters are living and well. There has been no chronic illness in family. The patient was born in County Dongon, Ireland. He lived there until he was thirteen years old; he came to the United States when fourteen, worked on a farm for three years and then was employed by Traction Company as driver and conductor for twenty-three years. He was employed as "workman on road" up to 1902. Since then he has done odd jobs. During the last two years he has been employed as an oiler in an engine room. He has always been a healthy individual. He had measles, mumps and whooping cough when a child. Patient states that as far as he knows he has never been sick before the present illness (with the exception of diseases of childhood). There is no history of malaria, syphilis or gonorrhœa. He drinks a fair amount of tea and coffee. He occasionally drinks

[1] Read before the Pathological Society of Philadelphia, March 12, 1908. Received for publication April 3, 1908.

whiskey and gin as well as considerable beer—15 to 20 glasses a day. He has taken no liquor for past three years.

Patient thinks that his illness began about the first of this June, 1907, with a swelling of the lower extremities, dyspnœa and shortness of breath which gradually increased; he was unable to sleep or lie down with any degree of comfort. Appetite was poor; he was nauseated and vomited once or twice; bowels were regular; there was no cough nor pains in chest. There was occasionally slight vertigo. There was no abdominal pain, distension or tenderness. Patient worked until the middle of June when he was compelled to stop as his condition was becoming worse. He went home and remained there but did not go to bed. Symptoms gradually became more marked; his feet and legs became more œdematous, dyspnœa and shortness of breath increasing with slight precordial pain; appetite became poorer. He began to notice that the abdomen and scrotum were becoming swollen. He was unable of late to lie down on account of dyspnœa. Sleep was very poor. On admission to the hospital temperature was 99° F.; pulse, 108; and respiration, 36.

Physical examination shows a fairly well developed though emaciated man, past middle age. He sits up in bed and is unable to lie down. He breathes with difficulty and is swollen and anemic looking. Abdomen and extremities are moderately swollen and œdematous and pit on pressure. Pupils are equal and react to light and accommodation. Conjunctiva is clear though anæmic looking. The tongue is moderately coated, moist and not tremulous; the breath is offensive. There are some pulsations of vessels of neck. There are no enlarged glands; no rigidity. Brownish pigmentation is present at the root of the neck. Chest is fairly well developed and symmetrical; expansion is poor. At the base of both lungs there are some crepitant and mucous rales, with slight impairment to percussion; breath sounds are somewhat suppressed and distant, but otherwise the lungs are clear. There is normal vesicular breathing with no impairment of resonance; vocal fremitus is fair.

The area of cardiac dullness is slightly enlarged, extending to the upper border of the third rib and 3 cm. to the right of the mid line; the heart beat is circumscribed and moderately forcible. There is also seen and felt just at the edge of costal margin 1.5 cm. to left of the mid line, an impulse. Heart sounds are heard fairly well at all the cardiac areas; they are somewhat forcible but not clear and distinct, and seem to lack muscular tone. At apex there is heard, at times, a soft systoic murmur transmitted to the base. The pulse is moderately rapid, fairly soft and compressible and at times slightly irregular. The arteries are slightly sclerotic. The abdomen is quite distended and tense and pits on pressure in the lower quadrants. On percussion there is dullness in the flanks, and the lower quadrants are slightly tympanitic below costal angle; there are definite succussion splash and movable dullness. There is a large mass in left upper and lower quadrants, apparently projecting from below the costal margin. It is quite hard, apparently solid and smooth, and tender to palpation. The mass extends from the costal margin into the pelvis, approximately measuring 23 cm. and from the median line to left flank, 23 cm. It does not move with respiration and moves only slightly on change of position. Coils of intestine can be felt floating over the mass. Liver reaches from the fourth rib in mid-clavicular line to the costal margin and is tender on palpation. There is no pulsation. The

mass in the left quadrant is apparently the spleen or else is fused with it. Pelvis and scrotum are somewhat swollen and œdematous. There is moderate œdema of the lower extremities.

On admission the hæmoglobin was 85 per cent. (Dare). The blood count was as follows:

Leucocytes, 11,550 per cu. mm.

Polymorphonuclear leucocytes	71.6 per cent.
Large mononuclear leucocytes	13.2 per cent.
Small mononuclear leucocytes	8.4 per cent.
Transitional leucocytes	6.0 per cent.
Eosinophile leucocytes	0.4 per cent.
Basophile leucocytes	0.4 per cent.

Urine is reddish yellow, acid, sp. gr. 1023; there is a large amount of albumin; no sugar; hyaline and granular casts, a few leucocytes, epithelial cells, and mucous cell detritus are found.

Patient improved for a time but gradually became worse and died of asthenia September 10, 1907. After the first day the temperature never advanced above normal point.

The blood was examined from time to time while the patient was in the hospital but apart from the fact that there were evidences of a gradual decrease in the hæmoglobin, a slight decrease in the number of red blood corpuscles and a moderate increase in the large mononuclears, the blood picture showed nothing unusual. The lowest percentage of hæmoglobin was 50 per cent.; the minimum number of red blood cells 3,220,000; of white blood cells 8,950. The differential counts were suggestive of nothing. At no time in the course of the disease were nucleated red blood cells found.

An autopsy was performed seven and one half hours after death. The report is as follows:

A. 1013 D. The body is that of a well built, rather poorly nourished adult male, measuring 155 cm. in length. Rigor mortis is present to a slight degree. Bluish red discoloration of dependent parts. Pupils are equal, clear and widely dilated. No lymph glands palpable. External genitalia apparently normal. The abdomen is protuberant.

Abdominal cavity contains approximately 500 c.c. of a clear straw-colored fluid. The bowels are in a collapsed condition and the omental fat is scanty. The parietal and visceral peritoneal surfaces are smooth and glistening with well-injected vessels. The mesenteric glands are enlarged. The appendix is directed downward, inward and upward in the right iliac fossa: it measures 5 cm. in length, is patent throughout and apparently normal. The spleen is seen to extend 5 cm. below the costal margin.

Each pleural cavity contains approximately 1,000 c.c. of a yellow-brown, clear fluid. There are a few adhesions over the right pleura; the left lung is bound to the chest wall by numerous adhesions. The pericardial cavity contains about 50 c.c. of a clear straw-colored fluid. The visceral pericardium is covered, in numerous areas, by large white plaques which are firmly adherent to the underlying tissue.

Heart.—Weight, 450 grm. The right ventricular wall measures 8 mm. in

thickness, the left ventricular wall 3.25 cm. in thickness. The heart's flesh is of a pale red color, very firm in consistency and there is evidence of an increase in the interstitial connective tissue. The coronary arteries are patent throughout and free from sclerosis. Tricuspid, aortic and pulmonic valves are negative. The anterior leaflet of the mitral valve is somewhat hard in consistency and apparently slightly thickened. Five millimeters above one of the aortic cusps is a calcareous area measuring 1 cm. in diameter.

Lungs.—The right lung is voluminous, crepitant in some portions and boggy in other areas. It is of a purple color. No nodules are felt. On section a grey fluid exudes from a cut surface which is of a gray-black color dotted with small areas of a dark red. A few white fibrous plaques are found in the right pulmonary artery. The left lung is somewhat smaller than the right one and is tougher to the feel. The external surface is purplish grey in color. On section the upper lobe resembles the right lung. The lower lobe is, however, entirely collapsed and is of a dark red-brown color; on pressure it exudes a slight amount of frothy red fluid. There are a few sclerotic patches in the left pulmonary artery.

Mesenteric glands are greatly enlarged throughout and on section present areas of caseation and calcification.

Spleen.—22 x 15 x 8.5 cm.; weight, 1,470 grm. Its external surface is covered with small and large fibrous tags. The organ is very firm and regular to the feel. Small whitish plaques, varying in size from that of a millet seed to a split pea, are noted over its entire surface. On cut section the capsule is seen to be somewhat thickened and the organ, as a whole, of a dark red color. The trabeculæ are very distinct. The Malpighian bodies are barely visible. Scattered throughout and indiscriminately arranged are small, rather soft areas of a light red color, spherical in form, varying in size from a pin point to that of a large bean. These soft nodules stand out prominently as light red areas in contradistinction to the surrounding tissue which is of a much darker red. The above described portions do not appear to be encapsulated, though they are definitely spherical.

Kidneys.—The right kidney measures 8 x 6.5 x 4 cm. The capsule strips quite readily though it is slightly adherent in areas. A small retention cyst is noted. On section the cut surface is gray-red in color. The cortex measures 8.5 mm. in thickness. The glomeruli are rather prominent; the pyramids and striæ very distinct. The pelvic fat is normal in amount.

The left kidney measures 10 x 4.5 x 3 cm. It is somewhat lobulated and rather soft in consistency. The capsule strips with difficulty. On section the cut surface is gray-red in color. There is an evidence of confluency of cortex with the pyramids, no distinct line of demarcation being seen. The glomeruli are quite distinct, as are also the striæ and pyramids. There is a small cortical retention cyst.

Liver.—23 x 12 x 9 cm.; weight, 2,130 gms. It is very hard to the feel. The external surface is free from adhesions and is of a pink-gray color. The edges are slightly rounded. On section the cut surface is reddish yellow in color, studded with small patches of yellow-red, especially noted toward the center of the liver lobules. There is a marked engorgment of the capillaries. The portal connective tissue is apparently slightly increased in amount. The bile ducts are patent; no stones are found. Vessels are apparently normal.

Gall bladder contains approximately 50 c.c. of a viscid brown fluid.

Adrenals are apparently normal.

Urinary bladder is apparently normal.

Testicles are somewhat œdematous but there are no signs of orchitis. There is a small cystic tumor of the right epididymis.

Prostate and seminal vesicles are apparently normal.

Aorta is apparently normal.

Gastric mucosa shows congestion and is covered with thick mucus; otherwise it appears normal.

Pancreas is apparently normal.

The intestinal mucosa especially in the neighborhood of the big gut shows a marked hyperplasia and is covered by thick mucus such as is seen in the stomach. In the neighborhood of the jejunum there is marked vascular injection.

Bone marrow removed from the middle portion of the right femur shows a very firm dark brown-red tissue.

Anatomical Diagnosis.—Acute œdema of lungs. Dilatation and hypertrophy of right and left ventricles. Chronic myocarditis. Chronic splenic tumor. Atelectasis of lower lobe of right lung. Chronic parenchymatous nephritis. Cloudy swelling of liver and kidneys. Tuberculosis of mesenteric lymph glands. Sclerosis of bone marrow. Fibrinous pleurisy.

MICROSCOPICAL EXAMINATION.

Heart.—Muscle fibers are of normal size but are quite granular and contain a fair number of vacuoles. There is some increase in the interfibrillar connective tissue.

Lung.—Pleura is somewhat thickened. Many of alveoli are filled with a serous-like material. Capillaries are engorged; no large giant cells are seen.

Liver.—Capsule shows moderate thickening. The liver cells are swollen and granular and show a well advanced grade of vacuolization. Some areas show so high a degree of granulation that the liver cords have completely lost their contour and appear piled upon one another. Extending from the center of many of the lobules and in some portions almost to the periphery, are areas of necrosis with complete disappearance of the liver parenchyma; they have been filled with red blood corpuscles, vast numbers of polymorphonuclear leucocytes and an occasional round cell. The connective tissue around the bile ducts shows slight thickening with round cell infiltration. The periportal connective tissue is somewhat increased. The inter- and intralobular connective tissue does not appear to be increased in amount. The blood vessels and capillaries are filled with red blood cells. Their walls are normal. No multinucleated or large vesicular cells are found in any sections.

Kidneys.—Attached to the cortex are bands of connective tissue which show a moderate degree of round cell infiltration. At the juncture of the cortex with these fibrous bands, are large clusters of round cells. Many of the glomeruli appear normal in all respects, others are atrophied and still others have undergone a complete hyaline change. The epithelium of the tubules is swollen and granular and many of the lumina are almost occluded by the swollen and desquamated cells. There is a slight increase in the intertubular connective tissue. The blood-vessel walls are slightly thickened. The capillaries and larger vessels are filled with red blood cells. No multinuclear or large vesicular nucleated cells are found.

Pancreas.—The gland is apparently normal.

Mesenteric Lymph Glands.—Capsule shows moderate thickening with extensive round cell infiltration. The sinuses are in areas entirely obliterated by the proliferative and desquamative endothelial cells of the lymph spaces. Many of the lymphoid follicles have been entirely replaced by a necrotic tissue surrounded and infiltrated by large epithelioid, round cells and giant cells of the bipolar and mural type. Scattered within the tissue are polymorphonuclear leucocytes, especially seen around the areas of necrosis. Many of the germinal follicles seem to be the starting point for the tuberculous process. No bone marrow giant cells or vesicular nucleated cells (except the epithelioid cells) are seen.

Bone Marrow.—There is an enormous hyperplasia of the cellular and connective tissue elements. The types of cells seen are of all the varieties seen in the bone marrow under normal conditions (Fig. 3). Thus the types seen are, neutrophilic and eosinophilic myelocytes, polynuclear leucocytes, giant cells, large and small mononuclear cells, normocytes, normoblasts and megoblasts, together with large numbers of fibroblasts of the connective tissue. The cells as a whole lie embedded in a very much thickened and well-formed connective tissue membrane containing well-developed blood vessels and capillaries (Mallory's connective tissue stain). The neutrophilic myelocytes are for the most part arranged in clusters and are occasionally seen, bunched together in spaces lined with endothelium. The cells described as myelocytes are the fairly large mononuclear cells which appear to contain neutrophilic and eosinophilic granules; no true basophilic myelocytes are seen. Scattered indiscriminately throughout the tissue are large giant cells which appear in two forms (though their nuclei which often contains a nucleolus and their nuclear fibrillar network together with their hyaline appearing protoplasm, are the same) : one type of cell possesses numerous nuclei, arranged generally in the center, and is composed of large vesicular nuclei and nucleoli with a well-defined network and surrounded by a hyaline appearing protoplasm. To this type is applied the term polykaryocyte; the other type or megokaryocyte possesses but one singular lobulated nuclear cast, possessing a nucleolus, well-defined nuclear membrane and surrounded by a large amount of hyaline appearing protoplasm. Throughout the section are noted enormous numbers of very large cells with vesicular nucleus about which is a small, apparently non-granular, rim of protoplasm, which has a tendency toward taking the alkaline stain. These cells contain often a well-developed nucleolus. They have a tendency toward cluster arrangement, and some definite masses of these cells are seen in spaces lined by endothelial cells. Arranged among erythrocytes and also scattered indiscriminately among the other cells are fairly large numbers of normoblasts, some of whose nuclei are in the process of extrusion. An occasional megoblast with dividing nucleus may be seen. The polynuclear cells are scarce as compared with those of normal bone marrow, though here and there are noted some. They have no tendency toward arrangement in clusters. There are definite large masses of small mononuclear cells or lymphocytes seen in different portions of the sections. An occasional polynuclear eosinophile with no definite position is seen. Coursing everywhere are enormous numbers of fibroblasts and larger and more developed connective tissue cells. The blood vessels are large and well developed with thickened walls. The capillaries are markedly increased also. There are no organisms seen in sections. A

noticeable feature is the presence of very large numbers of small mononuclear cells and fibroblasts with a relative decrease in the normal functionatory marrow cells.

Spleen.—Capsule is somewhat thickened, is infiltrated with round cells and has attached to it small and large strands of connective tissue. The trabeculæ and blood vessels show a slight hyperplasia; there is a marked increase in the reticulum. Many of the Malpighian bodies appear intact though the majority of them show some atrophy, many of them having disappeared. The splenic pulp is markedly hypertrophied and is found to contain large clusters of well-formed and well-preserved red blood corpuscles. Scattered here and there among the pulp cells are seen very large cells with vesicular nuclei, some cells containing but a rim of a homogeneous protoplasm, while in others the protoplasm is more extensive and apparently contains what are perhaps neutrophilic granules. There is a marked tendency on the part of these cells to cluster together and lie within spaces lined by epithelial cells. An occasional multinucleated giant cell of the bone marrow type is seen, many normoblasts are visible. There is an extraordinarily small amount of pigment.

Splenic Nodes.—Surrounded by a tissue which microscopically resembles the above are areas from 1 to 2 cm. in diameter, which greatly differ in some respects from the surrounding tissue. These areas (Fig. 1) are seen to be made up almost entirely of large cells, containing a vesicular nucleus and but a rim of protoplasm. They for the most part are seen in small spaces, some of which appear to be lined with endothelial cells. Bone marrow giant cells, both of the multinuclear and polynuclear forms, are seen in abundance (Fig. 2). All these cells are supported by a connective tissue meshwork, which contains also large numbers of nucleated red cells and erythrocytes arranged in no particular fashion. No pigment is seen.

Microscopic Diagnosis.—Œdema and congestion of lungs. Fibrinous pleurisy. Chronic interstitial myocarditis. Fatty metamorphosis of heart and liver. Chronic splenic tumor, with bone marrow cell hyperplasia. Cloudy swelling of heart, liver and kidneys. Chronic diffuse nephritis. Primary tuberculosis of mesenteric lymph nodes. Sclerosis of bone marrow.

As the term splenomegaly is now applied it has especial reference to a splenic hypertrophy which has extended over a period of months, perhaps years. Some writers include under the word splenomegaly only those conditions in which there is an idiopathic enlargement of the spleen, accompanied by an anæmia or perhaps an anæmia with a cirrhotic liver. Others apply the term to a condition in which there is an enlarged spleen with known or unknown etiology. The causes of many of the splenomegalies is still so uncertain that to formulate any definite classification from an etiological standpoint is wholly impossible. It is not the purpose of this report to discuss all of the various conditions which may give rise to an enlarged spleen. The main interest arises as to the

etiology of these cases grouped under the term " splenic anæmia." At the present time their origin is attributed to some intoxication, chronic in form, which principally affects the spleen, though sclerosis of the splenic and portal vessels and thrombosis of the splenic sinuses have been given as possible causative agents. That a diseased bone marrow might be the contributing cause in some of the cases has not been suggested, and it is important, therefore, to present an example in which the bone marrow is as extensively affected as the spleen.

This appears to be the condition in the case just described. What toxin, if any, caused the chronic inflammation of the bone-marrow in this case is not known. It should be remembered, too, that from the histological examination the bone-marrow presents a more intense and, perhaps, more advanced sclerosis than does the spleen, and that the greater part of the bone-marrow elements, as seen in the sections, are not the true blood-forming cells of the body, but are principally lymphoid cells and fibroblasts. Associated with this intense sclerosis of the bone-marrow are the definite foci composed of true bone-marrow elements in the spleen.

It is needless to add that a differential diagnosis from the other splenomegalies is not necessary. From a review of the literature it has been seen that the case described above does not resemble the types heretofore reported.

The pathological changes which take place in the various forms of splenomegaly, particularly of the primary types, are not uniform and the relative bearing of the bone-marrow upon cases of splenomegaly has been but briefly commented upon. It is, therefore, only by careful examination of individual cases and by experimentation upon animals that we may hope to arrive, some day, at conclusions as regards the physiologic and pathologic properties of the splenic hypertrophies.

In consideration of all cases of enlarged spleen, especially when the etiology is entirely unknown, we must of necessity turn to the so-called hæmopoëtic organs in which group are included, besides the spleen, the bone-marrow, lymph glands, liver and hæmolymph glands. That a decided relationship exists between the first three has been proved by all who have spent much time in study of the

subject. The liver too undoubtedly plays an important rôle, while Warthin's (1) work on the "Anatomy and Physiology of the Hæmolymph Glands," together with W. B. Drummond's (2) monograph on the same subject, have brought these structures into an important relationship with the other tissues considered as exciting some special action on the blood's function or destruction. Bizzozero and Neuman, long ago, demonstrated the fact that the bone-marrow was the seat of formation of the red blood cells. Soon after Ehrlich not only verified this statement, but also demonstrated that the bone-marrow was the site of white cell formation. Investigators of later date have found these facts to be true, and we are now in the position to give the most important functions of the bone-marrow. The function of the lymph gland cannot be asserted as definitely, but the fact remains that the lymph glands cannot be excluded from those organs described as being hæmopoëtic. They are possibly the place of origin of the lymphocytes of the circulating blood and from chemical and experimental observations it appears that they have power to assume, at some time, perhaps a compensatory function. The liver in embryonal life aids in the blood's formation, while as age advances it gradually loses that power and helps in the carrying off of waste matter, the result of disintegration of red cells. The functions of the hæmolymph glands are still in dispute; thus Drummond (2) claims that "there is no sufficient evidence that the hæmolymph glands play any part in the formation of red blood cells, but that on the other hand they appear to perform a very active part in the destruction of red blood cells and in the liberation of pigment." On the other hand, Warthin (1) says that "the close relations between spleen, lymph glands and bone-marrow is shown by the power of the hæmolymph glands to take on a structure of either spleen or marrow and to compensate for these organs when their function is abridged by disease." And finally the spleen has perhaps caused more discussion than any of the other organs. Differences in the cellular contents and structural characters in various animals has proven a barrier for decisive experimental work. Thus in lower vertebrates and in some of the mammalia, as the mouse, hedgehog and rabbit, nucleated red cells are normally present, giving evidence of a formation of red blood

cells in the spleen. Ehrlich (3), on the other hand, states that in the human spleen nucleated red blood cells are not to be found normally. Other investigators do not substantiate this phase of Ehrlich's work and claim that under normal conditions normoblasts are often found in the human splenic pulp. It is for this reason extremely difficult in animal experiments to determine the part taken by the spleen in forming erythrocytes. It is generally believed that though the spleen may be one of the sources of origin of red blood cells, its main duty is the absorption of the material due to disintegration of red and white cells and to preserve a portion of it, at least, for the organism.

The main point of interest which concerns us is the significance that may be attached to a pathological change in the spleen in which we see definite bone-marrow elements, including giant cells arranged in isolated areas through the splenic pulp. The presence of giant cells, resembling in all respects those of the bone-marrow existing in the human spleen, has been mentioned and but slightly commented upon by Dock and Warthin (4), Rolleston (5) and Simonds (6). Dock and Warthin interpret them as being emboli, while Rolleston and Simonds offer no hypothesis. On the other hand, numerous investigators, such as Dominici, Opie, Jarotsky, Bunting and others have commented upon their presence in the hedgehog, the rabbit and the guinea pig, under normal as well as under pathological conditions. Under all normal conditions bone-marrow giant cells are absent from the human spleen. It is only during an acute or chronic intoxication that they appear in the human spleen. I have not been able to find a note on their presence in the acute infections of human beings, though in one case which I have studied the spleen from a patient dying with acute gonorrhœal endocarditis, showed definite bone-marrow cells, including the true myeloplaxes and the large granuleless mononuclears arranged in small clumps. Dock and Warthin's report on the pathology of two cases of " splenic anæmia " is interesting since in one of their cases giant cells resembling those of the bone-marrow were found in great numbers in the lung capillaries, while a smaller number were found in the liver capillaries and blood spaces of the spleen and hæmolymph glands. In the other case there were found large

numbers of these cells in the lungs, a smaller number in the spleen and a fair number in the hæmolymph glands. In both cases there was a decided decrease of giant cells in the bone marrow. As stated above, the writers considered these cells emboli.

The question now arises whether there are splenomegalies in which the bone-marrow's function has become exhausted by the action of some circulating toxin and in which the spleen exerts itself in a compensatory manner by forming new blood elements for the organism.

Osler, Sippey (7) and Simonds (6) have thoroughly reviewed the literature of splenomegaly and hence the citation of cases will be dwelt upon only so far as it may have a definite bearing on the subject under discussion. The cases of so-called " splenic anæmia " or splenic anæmia with cirrhosis of the liver (Banti's disease) form the greater part of the cases of obscure origin. In these the pathology has been quite well outlined by Rolleston (5), who says that the main pathologic changes in splenic anæmia are: (1) Fibrosis of the organ, (2) atrophy of the lymphoid elements and (3) fibrosis of the Malpighian bodies. In addition there is usually no evidence of exaggerated hæmolysis such as excessive pigmentation of the spleen. He notes also that there is usually a red marrow transformation, though the yellow marrow may persist.

The pathological changes seen in the present case are entirely different from those which have been described previously. Macroscopically distinct small, rather soft areas, of a light red color, spherical in form, varying in size from a pin head to that of a large bean, were quite striking. Simonds (6) describes an enlarged spleen as containing " numerous round, oval or branched reddish brown areas about two millimeters in diameter." In this case the areas, containing a large amount of pigment, give an intense iron reaction. The difference is obvious, since the areas described in my case are free from pigment and are seen to be made up of collections of what appear to be definite bone-marrow cells. There was great similarity between sections of the bone-marrow and sections through these areas in the spleen. For a comparative study of the bone-marrow and the cells in the nodules the most useful stains were Duval's modification of Leishman and Wright stains,

polychrome methylene blue, hæmatoxylin and eosin, Mallory's connective tissue stain, Van Giesen's stains and Ehrlich's triacid stain. With none of these stains, however, have definite neutrophilic granules been made out in the cells, either in the spleen or bone-marrow. This is perhaps due to the fixation which unfortunately was entirely in Zenker's fluid. Some of the cells of the bone-marrow presented, what appeared to be, neutrophilic granules. There were cells in the spleen which had the same appearance, but I cannot state positively whether they were or were not myelocytes. It can be definitely said, however, that the giant cells, the megakaryocytes, were present in both tissues and that the large granuleless mononuclear cells found normally in the bone-marrow alone were present in great abundance in these nodules in the spleen.

The question now arises whether this enlargement of the spleen should be considered as an heteroplastic growth or as an hyperplastic. We meet with three hypotheses: (1) That the condition is due to a disease of the spleen *per se,* (2) that the bone-marrow foci found in the spleen are emboli and the enlargement due to an intense congestion, (3) that the enlargement depends upon the spleen assuming a dormant hæmopoëtic function with hyperplasia of the cells of the spleen pulp.

The exact determination as to whether the condition was primary in the spleen is impossible. From the examination of the bone-marrow it seems more probable that the sclerosis there is of an older form and of a greater intensity than it is in the splenic pulp. The theory that these masses of bone-marrow tissue arise from bone-marrow cell emboli cannot hastily be disposed of, for the two cases reported by Dock and Warthin, referred to above, which showed definite bone-marrow cells in the capillaries of the liver, spleen, hæmolymph glands and lungs, together with Bunting's (10) report of the finding of definite bone-marrow in the dorsal portion of the aorta, would perhaps suggest the possibility of such an emigration of cells. Bunting, however, states that one is not justified in deciding whether they were formed by a further metaplasia of connective tissue cells or by a metaplasia of emigrated cells from the blood stream, capable of differentiation into the various types of marrow cells. In my case it does not seem probable that the

bone-marrow elements have been brought to the spleen by the blood stream, for if such were the case it would seem reasonable to suppose that these same cells should be found in the lungs and liver, as in the two cases of Dock and Warthin. On the other hand, possibly such a process cannot be entirely ruled out for the clusters of marrow cells, some of which are found in blood spaces, suggest at least the idea that they may be emboli. However, from a careful study of the sections as regards the position of the bone-marrow cells and the condition of the lymph nodes, liver and lungs, I do not feel justified in stating that they are brought directly to the spleen from the bone-marrow.

Finally we come to the third proposition as to whether the enlargement may be due to the development within the spleen of blood-forming elements. This hypothesis really rests upon two conditions, namely: (1) that the bone-marrow cells are fœtal remains of cells which have been lying latent and through a stimulant, perhaps exciting the bone-marrow to activity and finally to uselessness, have increased in proportion and have taken on their original fœtal blood-forming function; (2) that the spleen has produced bone-marrow cells from the blood or lymph spaces. Before arriving at any conclusion whatsoever as regards the logic of either of these two hypotheses, it is necessary to consider the subject, as best we can, from an experimental standpoint, for it is only by this means that we may throw some light on the subject. Indeed from the sections of organs removed at autopsy no consecutive changes can be noted.

It is an accepted fact that the human and mammalian fœtal spleens contain a varying number of bone-marrow cells such as the giant and myelocytic cell together with large numbers of nucleated red blood corpuscles. As the human spleen becomes further developed the bone-marrow and normoblastic cells gradually disappear while in the spleens of many of the mammals the blood foci cells persist through life though in greatly decreased numbers.

Experiments of Pugliese (11) on hedgehogs have shown that after repeated blood lettings the giant cells increase markedly in the spleen, and that after partial splenectomy the giant cells, in the intact splenic tissue, show a decided increase; that with total extir-

pation of the spleen the bone-marrow becomes filled with giant cells and that after repeated venesections the giant cells increase in the spleen but remain unchanged in bone-marrow, whereas in the liver and lymph glands there are no traces of them. The experimental anæmias produced by Bunting (12) in rabbits throw much light on the compensatory power of the spleen. Thus after sclerosis of the bone-marrow had been produced the spleen showed a marked dilatation of the peripheral venous sinuses which were crowded with marrow cells, and especially numerous were the megakaryocytes. Myer and Heincke (13) have shown similar changes in the spleen in a case of pernicious anæmia. Bunting (12) comments upon the fact that bone-marrow, following injection of hæmolytic toxins, becomes sclerotic and there may be an almost entire replacement of the hæmopoëtic elements by the newly formed connective tissue, while hæmorrhages cause only the hyperplastic marrow of a secondary anæmia. Clinically it has been noticed that an enlargement of the spleen often causes an improvement in the general condition of the bloods.

Dominice (14) has subjected rabbits to repeated bleedings and has found practically the same histological changes in the spleen as has Bunting. He has observed, however, that in the course of experimental infections with the typhoid bacillus there takes place what may be called "a partial myeloid change." By this term Dominice means that all the elements of the bone-marrow are not present. Thus there are noted large normoblasts and basophilic and neutrophilic myelocytes, but the eosinophilic myelocytes and giant cells are very rare or entirely absent. Jarotsky's (15) experiments with white mice infected with the hog cholera bacillus further substantiates the findings of Bunting, Pugliese, Dominice and others. Jarotsky produced in twenty-four hours an enormous increase of giant cells and myelocytes in the spleen.

Opie (19) has observed the occurrence of eosinophilic myelocytes and bone-marrow giant cells, in the spleens of guinea-pigs four hours after inoculation with Bacillus pyocyaneus, Bacillus anthracis, and Bacillus mucosus capsulatus—he believes that these elements are derived from the bone-marrow and are not formed in the spleen.

With the exception of some of Bunting's work on the experi-

mental anæmias, investigations of the subject have been limited to the acute infections. It is indeed fortunate that cases have been recorded in which similar splenic changes have taken place in the course of what appears in the present state of our knowledge to be a condition of chronic intoxication or infection, namely pernicious anæmia. Careful histological study of seventeen cases of pernicious anæmia by Gulland and Goodall (16) shows that in eight of the seventeen cases cells like those of the bone-marrow were found in the liver, while in four cases myelocytes were found in the spleen, and in one case there were typical large bone-marrow giant cells in the spleen.

Dominice and Jarotsky have written at length upon the possible mode of origin of the bone-marrow cells in the spleen. Their findings, though interesting, are not at all convincing. The theories of transportation of bone-marrow cell to the various organs can be substantially upheld by anatomical evidence in the leukæmias. That the phenomenon takes place, however, in all cases, where cells resembling those of the bone-marrow are found in the various organs, cannot be supported. On the other hand, experimental and anatomical evidence go to substantiate, if not prove, the theory that the spleen under certain conditions of chronic inflammation of the bone-marrow may take up the hæmopoëtic function. What the toxin is cannot be proven in many cases; but whatever the chemical changes may be, the toxin must have some deleterious effect upon the bone-marrow, either prohibiting the growth of cells or so stimulating them as to finally exhaust their power to produce blood cells. It is but natural to suppose that the spleen lying dormant, as it were, in the body should at times be called upon to perform or at least aid in performing the activities of the marrow.

CONCLUSIONS.

1. The nodules found in the spleen are islands of active hæmatoplastic tissue.

2. The bone-marrow, at least in the case which has been described, has been the primary focus of disease; some toxin has probably produced a chronic inflammatory change.

3. The bone-marrow, owing to its enormous sclerosis, has lost

its hæmopoëtic powers totally or to a marked degree and the spleen has reverted to its fœtal power to form blood.

BIBLIOGRAPHY.

1. Warthin, *Jour. of Med. Research,* 1901, vi, 13.
2. Drummond, *Jour. of Anat. and Physiol.,* 1899–1900, xxxiv, 198.
3. Ehrlich and Lazarus, Histology of Blood, Cambridge University Press, 1900, p. 99.
4. Dock and Warthin, *American Jour. of the Med. Sciences,* 1904, xxvii, 25.
5. Rolleston, *British Med. Jour.,* 1903, ii, 573.
6. Simonds, *Jour. of Infectious Diseases,* 1908, v, 23.
7. Sippey, *American Jour. of the Med. Sciences,* 1899, cxviii, 570.
8. Bovaird, *American Jour. of the Med. Sciences,* 1900, cxx, 377.
9. Sippey, *American Jour. of the Med. Sciences,* 1899, cxviii, 570.
10. Bunting, *Jour. of Exper. Med.,* 1906, vii, 365.
11. Pugliese, *Fortshr. der Med.,* 1897, xv, 727.
12. Bunting, *Jour. of Exper. Med.,* 1906, viii, 625.
13. Meyer and Heincke, *Verhandl. der deutschen pathol. Gesel.,* 1906, ix, 224.
14. Dominice, *Arch. de méd. expér. et d'anat. path.,* 1901, xiii, 1.
15. Jarotsky, *Virchow's Arch.,* 1908, cxci, 112.
16. Gulland and Goodall, *Jour. of Path. and Bact.,* 1905, x, 125.
17. Weber, *British Med. Jour.,* 1904, i, 1416.
18. Bunting, *Johns Hopkins Hosp. Bull.,* 1905, xvi, 222.
19. Opie, *Am. Jour. Med. Sciences,* 1904, cxxvii, 988.

Explanation of Plates XXXII and XXXIII.

Fig. 1. Section from localized nodule in spleen (low magnification).
Fig. 2. Section from nodule in spleen (high magnification).
Fig. 3. Section from bone-marrow.

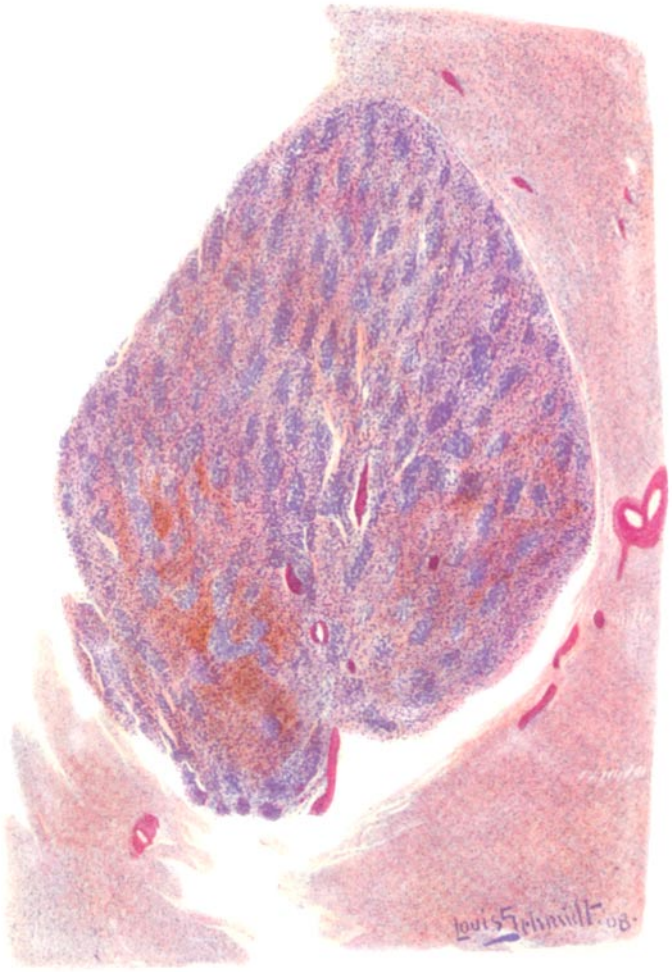

FIG. 1.

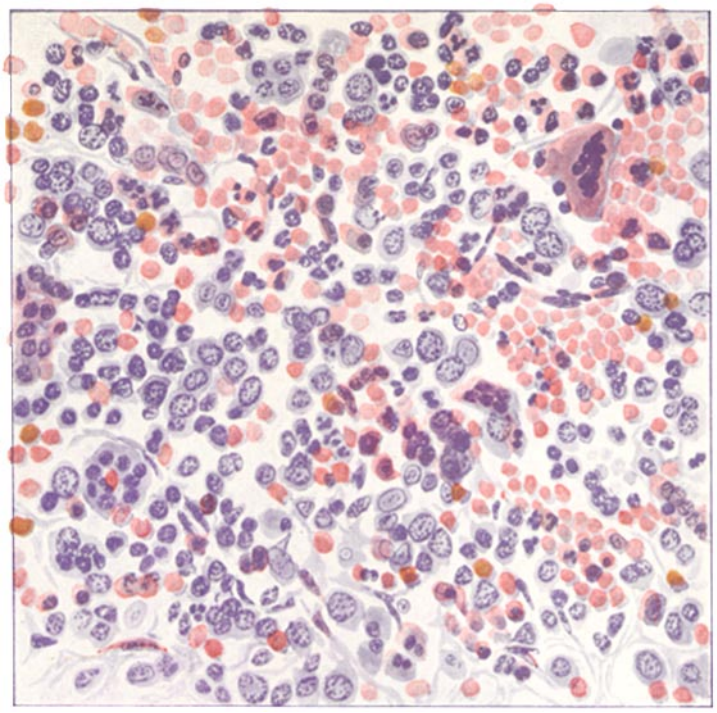

FIG. 2.

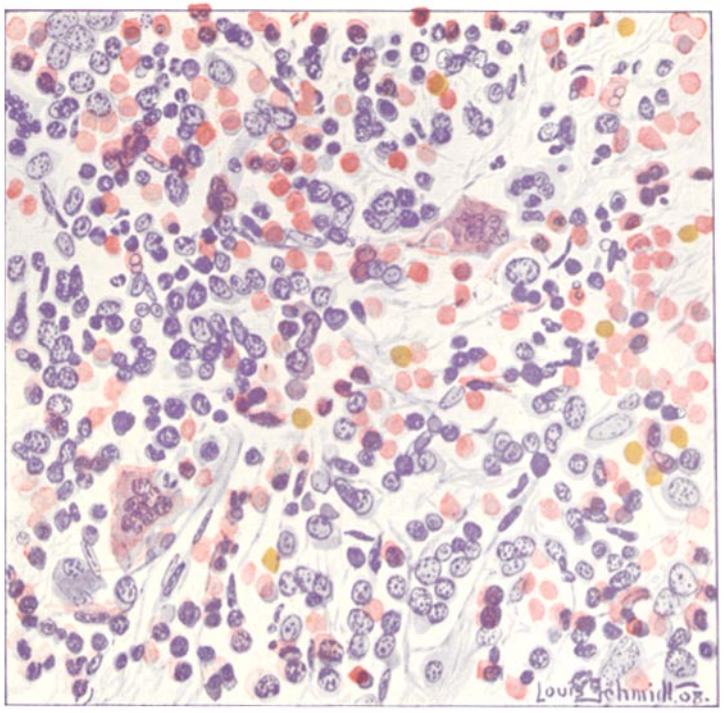

FIG. 3.