THESIS

SPLENOMEGALY, WITH SPECIAL REFERENCE TO THE OCCURRENCE OF MYELOID METAPLASIA

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TABLE OF CONTENTS

Introduction

Myeloid metaplasia of the spleen, its etiology and the etiology of various conditions associated with it have been discussed with increasing frequency in the medical literature of recent years. A confusing terminology is generally good evidence that a subject is complex and incompletely understood, and this point is well illustrated by myeloid metaplasia and its associated marrow disorders for which Heller and associates listed 24 synonyms in 1947. Numerous theories have been advanced to explain the actual method of development of extra-medullary hematopoiesis in the spleen and other organs, but so far no one has provided a solution acceptable to all hematologists and pathologists. Rosenthal (1) in 1950 summarized the current etiologic theories as follows:

(1) The theory of cellular colonization, in which it is believed that primitive cells of medullary origin are carried in the blood stream to the spleen, where they implant and develop.

(2) The theory of colonization from peripheral elements, which depends on the concept that the circulating lymphocyte retains its capacity to become a hemocytoblast which then migrates into the tissue to develop.

(3) The theory of local origin or metaplasia in which it is supposed that the hematopoietic cells develop

in the spleen (or liver, or lymph nodes) from primitive cells such as those of the reticulo-endothelial system, vascular endothelium or other mesenchymal derivatives.

Almost without exception recent work supports the last of these theories. There is much less unanimity regarding the primary or secondary nature of myeloid metaplasia. Authorities supporting the secondary status of extra-medullary hematopoiesis believe that this ectopic blood cell formation is a compensatory process found in conditions of relative bone marrow failure, such as anemia of various types, in hemorrhage, and in conditions in which there is destruction or replacement of the marrow. Those supporting the primary nature of the extra-medullary hematopoiesis believe that some unknown stimulus causes a generalized proliferation of the primitive mesenchymal cells in various organs. These cells retain the capacity to differentiate in numerous ways so that while myeloid metaplasia may occur in the spleen it may be associated with any one of a number of different pictures in the bone marrow, including those characteristic of such diseases as polycythemia vera, leukemia, aleukemia myelosis, myelofibrosis and osteosclerosis, either singly or in combination. The review of the literature which follows provides strong evidence that the question of the etiology of myeloid metaplasia in the spleen is far from answered and that much work will be required before it is finally elucidated.

We thought it possible that some insight into the incidence of myeloid metaplasia might be obtained by reviewing a large series

of cases in which the only common feature was a splenomegaly at the time of autopsy. We also hoped that a detailed study of the cases in which myeloid metaplasia was discovered would provide some information as to the etiology of the condition. This thesis therefore presents the results of such a study.

Chronological Review of the Literature

1879. In 1879 Heuch (2) reported a case of generalized osteosclerosis with marked hepato-splenomegaly, anemia, hyperplastic lymph nodes and extreme leucocytosis which he believed was an example of chronic myelogenous leukemia in which the osteosclerosis was a chance association. This was probably the first occasion on which such a combination of findings was reported.

1908. Donhauser (3) published details of a case of splenomegaly due to myeloid metaplasia associated with anemia, congestive heartfailure and fibrosis of the bone marrow. There was also active tuberculosis in the mesenteric lymph nodes. Although several case reports had appeared in the French and German literature following Heuch's publication in 1879, this appears to be the first attention given to the matter in English. Donhauser believed that the primary lesion was the fibrosis in the bone marrow, attributing this to the action of an unknown toxin. The extra-medullary hematopoiesis he considered to be secondary and in the nature of compensation for a destroyed marrow. This hypothesis of his is particularly interesting in view of

some of the recently published theories of the etiology of the condition.

1923. Minot and Buckman (4) described their findings in 15 cases of erythremia (polycythemia vera). In 3 cases which terminated in anemia there was a sudden enlargement of the spleen co-incident with the fall in red blood count. Only one patient came to necropsy but when this spleen was examined it showed marked myeloid metaplasia said to resemble the appearance of myelogenous leukemia. The marrow, however, was actively erythroblastic as well as showing an excess of myelocytes and megalomyocytes. The authors believed that more cases of erythremia would probably terminate with anemia and myeloid metaplasis if the duration of the illness was not shortened by death from other complications.

1927. Ballin and Morse (5) reported 2 cases manifesting splenomegaly, anemia and a circulating blood leuco-erythroblastosis. In both a splenectomy was done to relieve abdominal discomfort, histologic examination of the excised spleens revealing myeloid metaplasia in the pulp. Unfortunately no marrow biopsies were performed so it is impossible to be certain of the exact nature of the disease in these cases. It is interesting that the one case which was followed was living after 8 years.

1929. Weber (6) published a short abstract of a case of a 56 year old man with severe anemia, variable leuco-

erythroblastosis and a generalized osteosclerosis proved both by x-rays during life and later at autopsy. It was noted that the spleen, liver and lymph nodes were not typical of leukemia but no further description was given. At first it was thought that the osteosclerosis was probably associated with aleukemic myelosis or other type of leukemia, but an addendum (7) to this case report was published later in which it was stated that the osteosclerosis was a response to generalized skeletal metastases from a hitherto undiscovered carcinoma of the prostate.

1930. Downey, Palmer and Powell (8) reported a case showing anemia, leucopenia and leucoerythroblastosis. A splenectomy was performed, and the spleen, which weighed 2,700 gm., showed extensive extra-medullary hematopoiesis involving all three hematopoietic series. A liver biopsy showed dilated sinuses which contained immature blood cells. The platelet count following surgery remained at 420,000/cu.mm. The patient died 4 months postoperatively and no autopsy was performed. The authors believed the case was not one of leukemia because of the relative scarcity of young myeloid forms in the blood. They considered the case, in which metaplastic megakaryocytes were especially prominent, as one of thrombocythemia with secondary involvement of other myeloid lines, or as an example of atypical aleukemic myelosis. They believed they could trace the local development of megakaryocytes from reticulo-endothelial cells and from myeloblasts in

the spleen.

1933. Stephens and Bredeck (9) reviewed the literature and discovered 19 acceptable cases of generalized osteosclerosis with aleukemic myelosis. Only one of the 19 reports had appeared in the English literature, the remainder being in German. The authors added 2 cases of their own which presented with splenic enlargement and in which splenic puncture showed numerous myelocytes. In one case marrow biopsy was performed and showed fibrosis with osteosclerosis. The etiology of the osteosclerosis was not discussed but it was suggested that this condition could be compared to metastatic carcinomatosis of bone in the genesis of extra-medullary hematopoiesis as in both conditions there was invasion and replacement of the marrow spaces.

1934. Jordan (10) believed that foci of myeloid metaplasia developed in situ in an organ as a compensatory mechanism for a diseased bone marrow. He illustrated the point by 2 case reports. In the first, a case of acute leukemia, the bone marrow and spleen were largely removed from the active hematopoietic system by disease and the lymph nodes showed compensatory erythrocytic metaplasia. In the second, a case with widespread metastases to bones and lymph nodes which to a great extent destroyed their structure and function, the spleen showed erythropoietic activity.

1935. The result of a necropsy on a patient who had been known to have polycythemia vera for 31 years was published by Hirsch (11). The spleen was enlarged and the cut surface showed small nodules of red-brown tissue which histologically proved to be foci of myeloid metaplasia especially rich in megakaryocytes. The bones showed extensive osteosclerosis, some marrow spaces containing edematous fibrous tissue and other containing hematopoietic tissue. Hirsch suggested that the osteosclerosis was the end result of the polycythemia vera, perhaps on the basis of a stimulus from the abnormally hyperplastic hematopoietic tissue. The myeloid metaplasia he regarded as secondary, and compensatory in nature.

1936. McMichael and McNee (12) reported 3 cases which presented with splenomegaly. Myeloid metaplasia was proved by splenectomy in 2 cases and by autopsy in 1. In only the latter case was a marrow biopsy performed and this was normal. The authors were chiefly concerned with the clinical diagnosis of the condition and emphasized that repeated blood counts, including differential counts, were necessary to distinguish it from leukemia. In addition, they remarked that the myeloid metaplasia could develop as a synergic effect in the presence of an intensely active marrow or as a compensatory effect when the marrow was hypoplastic.

In a study of leucoerythroblastic anemia Vaughan (13) found 8 cases of this condition in 24 individuals with skeletal metastases and of these 8, 6 showed myeloid metaplasia of the spleen. An addition 3 cases of carcinomatosis had myeloid metaplasia at autopsy but no immature cells in the blood during life. One out of 18 cases of multiple myeloma and all 3 of her cases of myelosclerosis showed leucoerythroblastosis, only one of the latter group having proved myeloid metaplasia at necropsy. Vaughan did not believe that either the presence of young forms in the circulating blood or the myeloid metaplasia could be attributed to mechanical blocking of the marrow, as in her cases the red marrow had extended into normally fatty areas, so that she estimated there was probably more than the normal amount of active hematopoietic tissue. She felt there might have been a deficiency of a factor necessary for normal hematopoiesis, the condition thus being analogous to pernicious anemia.

1937. Tudhope (14) reported a case of extensive myeloid metaplasia of the spleen in which the organ showed circumscribed nodules of myeloid tissue, which could be recognized grossly, as well as the more usual diffuse infiltration of the pulp. He thought it interesting that in view of the other findings, including myelofibrosis, considered typical of the condition, no leucoerythroblastosis was present.

In the first report actually to use the term "myelofibrosis" Mettier and Rusk (15) differentiated this disease from Albers-Schonberg (marble-bone) disease. They discussed 2 cases of myelofibrosis, one of which they considered compatible with myelogenous leukemia and the other with aleukemic myelosis, the marrow picture in both being the same. An unusual feature was the fact that the extra-medullary hematopoiesis was entirely leucopoietic.

Hickling (16) reported 7 cases of splenomegaly with myeloid metaplasia. Of the two cases that came to necropsy one had a normal and the other a hyperplastic marrow, and in both the metaplasia had destroyed the Malpighian bodies in the spleen. As this latter feature differed from most case reports which indicated that the follicles were preserved the author suggested that this might represent a more advanced degree of the condition. In addition he reviewed 27 previously reported cases in which splenectomy had been performed and came to the conclusion that this operation was contra-indicated as the myeloid metaplasia was a compensatory mechanism for marrow failure. Later the same year Hickling (17) published details of a case of splenomegaly in which myeloid metaplasia occurred in tumor-like foci containing particularly large numbers of megakaryocytes. The vertebrae showed a

simple hyperplasia of the marrow while the femur showed osteosclerosis. Although this patient had pulmonary tuberculosis, with a tuberculous lesion in an accessory spleen, Hickling believed this was a coincidental rather than an etiological factor. In further discussing the etiology he noted that the osteosclerosis was not generalized and was probably a response to a hyperplastic marrow. He concluded that this was a case of myelosis affecting both spleen and bone marrow, perhaps being due to a lack of some developmental factor.

1938. Gall (18) reported a case in which there was extensive extra-medullary hematopoiesis in both spleen and liver, following exposure to benzene. There was fibrosis of the bone marrow with a few active cells remaining.

Stone and Woodward (19) discussed a case of long-standing polycythemia vera which terminated with a marked leucoerythroblastic anemia and splenomegaly. Myeloid metaplasia of the spleen was proved histologically while the marrow showed a varying picture of hyperplasia and osteosclerosis. The authors stated that although there is an associated osteosclerosis in many cases of myeloid metaplasia the remaining marrow is often so hyperplastic that it must compensate for the loss of active hematopoietic tissue. This being so, they suggested that the picture could be part of a deficiency pattern involving all organs

concerned. They also mentioned that this case had tuberculosis of the cervical lymph nodes, the possibility therefore existing that a toxin from this source had caused the early polycythemia vera and later failure of the marrow.

1939. Vaughan and Harrison (20) reported 2 cases of leucoerythroblastic anemia associated with myelosclerosis. Polycythemia had been an early finding in both cases. Necropsy on one case showed extra-medullary hematopoiesis in the spleen and other organs. Vaughan and Harrison described the fibrosis of the marrow as being obscured to a great extent by hyperplastic blood forming elements and suggested that myelosclerosis might be found terminally in all cases of polycythemia if the complete skeleton was examined. In conclusion they offered the hypothesis that leucoerythroblastic anemia, myelofibrosis and myeloid metaplasia were multiple responses to a single unknown stimulus acting on the primitive undifferentiated mesenchymal cell.

Downey and Nordland (21) published details of a case of myeloid metaplasia which not only showed diffuse involvement of the spleen but also two tumor-like nodules composed of large numbers of megakaryocytes accompanied by fewer myelocytes, normoblasts and hemocytoblasts. The liver sinusoids also contained numerous immature blood cells. There was an anemia with an elevated white cell count and

numerous immature forms. The marrow varied from hypoplastic to hyperplastic, in the latter areas being very similar to leukemia. However, the appearance of the spleen was not thought to be compatible with leukemia, so the authors suggested the case was probably of the type described as leucoerythroblastic anemia by Vaughan in 1936.

1940. Jackson, Parker and Lemon (22) described 10 cases of a condition which they called "agnogenic myeloid metaplasia". Common to all was splenic myeloid metaplasia, and although some bone marrows were aplastic, some hyperplastic and some fibrotic, in no case, according to the authors, could the marrow histopathology be confused with that of leukemia. One case appeared typical of acquired hemolytic anemia. They stated that the condition was apt to be confused clinically with leukemia in a sub-leukemic phase, but that the diagnosis could be made when a case featured a long course, splenomegaly, a comparatively low white blood count with a leucoerythroblastosis, a bone marrow biopsy not typical of leukemia, and a splenic puncture aspirate containing megakaryocytes and immature cells of the red cell and white cell series. They could not reconcile the extreme variation in the marrow picture, which did not always include sclerosis, with the theory of Vaughan and Harrison (20) that the leucoerythroblastic hyperplasia, marrow sclerosis and myeloid metaplasia were processes which occurred simultaneously as a reaction to a single stimulus.

One year after publication of this article Rawson, Parker and Jackson (23) reported 6 cases of myeloid metaplasia. All the patients had been exposed to industrial solvents including benzol and carbon tetrachloride. Apparently these cases represent 6 of the 10 originally described, and so it would appear that their designation as "agnogenic" would no longer be valid.

1941. Carpenter and Flory (24) reported a case of chronic non-leukemic myelosis and stated that this condition should be distinguished from myelogenous leukemia by the diversity of cell types in the foci of metaplasia and in the bone marrow, by the commonly low white blood count with a low proportion of immature cells and the almost constant presence of nucleated red cells, by the frequency with which osteosclerosis and myelosclerosis are encountered, and by the absence of characteristic leukemia infiltrations. They believed there was some pathologic stimulus which caused the myeloid metaplasia rather than a compensatory one resulting from a damaged marrow. They point out that their case had a terminal acute miliary tuberculosis but that the axillary nodes were caseous and the disease might have been present there for sometime. While admitting the possibility of a tuberculous toxin damaging the marrow, they decided the co-existence of the two conditions was more likely to be a co-incidence. They agreed with the theory of Vaughan and Harrison (20) that chronic non-leukemic myelosis was probably due to an unknown

stimulus acting on the multipotential mesenchymal tissues.

In presenting a case of myelosclerosis associated with widespread extra-medullary hematopoiesis Taylor and Smith (25) stated that marrow sclerosis belongs to the group of dyscrasias of the reticulo-endothelial system. They believed that some unknown toxin, bacterial or chemical, acts on the marrow causing either inactivity, or else proliferation of fibroblasts and osteoblasts. As a consequence, there is reversion to fetal type hematopoiesis in the spleen, liver and lymph glands as a compensatory measure.

1942. A further 5 cases of agnogenic myeloid metaplasia were described by Reich and Rumsey (26). Four of the cases had typical extra-medullary hematopoiesis in the spleen while the description of one was more nearly that of Hodgkin's disease, a fact that was noted by the authors. In considering the results of splenectomy and irradiation in their cases Reich and Rumsey support the contention that both procedures are harmful and should be avoided in myeloid metaplasia.

1943. Rosenthal and Erf (27) reported 1 case of osteopetrosis and 7 of myelofibrosis. They noted that leuco-erythroblastic anemia could be the first sign of several diseases including skeletal carcinomatosis, multiple myeloma, osteopetrosis, myelosclerosis and polycythemia. They found a reciprocal relationship between the liver and spleen on the one hand, and the marrow on the other hand, as far as hematopoiesis

was concerned. In other words, they endorsed the theory that myeloid metaplasia was compensatory for an inactive marrow.

Mendeloff and Rosenthal (28) reported a case of leuco-erythroblastic anemia with myeloid metaplasia of the spleen and liver, and diffuse osteosclerosis. The metaplastic areas contained numerous large, irregular megakaryocytes. They emphasized that the anemia and metaplasia developed first and the osteosclerosis later, as a splenectomy had been performed 5 years before x-rays of the bones showed osteosclerosis.

1944. A clinical and pathologic study of 13 cases of fibrosis of the bone marrow was made by Erf and Herbert (29). They included 3 examples of fibrosis due to metastases in which the spleens showed varying degrees of myeloid metaplasia. The remainder included 7 autopsied cases of primary myelofibrosis, of which 3 showed unequivocal extra-medullary hematopoiesis. They suggested that estrogens - perhaps incompletely conjugated in the liver - may have caused the myelofibrosis as it has been proved experimentally that estrogens do cause marrow fibrosis. In some cases of myelofibrosis they believe local factors such as occlusion of vessels and low temperature may provoke the fibrotic process.

1947. Heller, Lewisohn and Palin (30) reported 3 cases of proved extra-medullary hematopoiesis and leuco-erythroblastosis associated with hyperplastic marrows. They noted

that the condition was known by 24 different synonyms at that time. They presented strong arguments to support their belief that the process is a leukemic one, in which proliferation and differentiation of reticulo-endothelial cells in the spleen, nodes, liver and marrow occurs in response to an unknown etiologic factor. The process is modified in aleukemic myelosis (which is their term for this condition), in that its intensity is reduced and its course is longer than in overt myelogenous leukemia. They do not believe that examination of one area of bone marrow is necessarily representative of the entire organ and see no reason why an area of frank leukemia should not exist in one site and myelofibrosis in another. This view is supported to some extent by the findings of Churg and Watson (31) who discovered 6 cases of myelofibrosis in a review of 97 cases of myelogenous leukemia. Heller and his associates cannot understand why myeloid metaplasia is not present in other types of anemia if it is purely a compensatory process. They do not believe that the absence of an elevated white blood count is valid evidence in favor of a non-leukemic etiology for this condition, as it is widely known that undisputed cases of leukemia exist with a white blood count within normal limits. They state that it is not surprising that cases of aleukemia myelosis respond poorly to irradiation or splenectomy, as cases of myelogenous

leukemia would react similarly if irradiation were continued beyond the point when the white blood count approaches normal. They believe undue emphasis has been given to the presence of immature red cells in the circulating blood in aleukemic myelosis. These are also invariably found in frank leukemia but are not so obvious as the smear is flooded by so many immature granulocytes.

1948. Crail, Alt and Nadler (32) reported 4 cases of miliary tuberculosis associated with myelofibrosis and extra-medullary hematopoiesis. These cases probably represented a terminal dissemination of a long-standing granulomatous tuberculosis. As there was fibrosis of other organs such as the spleen, pancreas and adrenals, the authors considered that the myelofibrosis might be part of the general disease and that its extent could possibly depend on the duration of life of the patient. They mentioned other reports which showed that miliary tuberculosis is accompanied at first by a hyperplastic and later by a hypoplastic or aplastic marrow.

1949. In discussing 6 cases of chronic non-leukemic myelosis, Mersky (33) agreed with Heller, Lewisohn and Palin that the difference between this condition and myelogenous leukemia was merely that of degree. He felt that if the process affected the red cell series polycythemia vera would result; if it affected the white cell series only slightly chronic non-leukemic myelosis would result; and if it affected the white

cell series to a great extent then myelogenous leukemia would occur. Merskey quoted a report by Rowlands and Vaizey (34) of a case characterized by a thrombocythemia with raised white and red cell counts as evidence that if the unknown stimulus chiefly affected megakaryocytes a leukemic-like picture of them could result.

1950. Rosenthal (1) presented an excellent discussion of the various theories which have been advanced to explain the phenomenon of myeloid metaplasia of the spleen and other areas of extra-medullary hematopoiesis (see introduction). He did not attempt to do more than present the current arguments on the subject, but in doing so he remarked that a primary involvement of the multipotential mesenchymal cell offered an attractive explanation for the puzzling and frequent interassociation of polycythemia vera, leukemia, osteosclerosis, myelofibrosis and thrombocytosis. He suggested that, as in other neoplastic processes, there need not be one particular stimulus common to these diseases, but that a combination of many factors could be at work.

Wyatt and Sommers (35) reported their findings in 30 cases of extra-medullary hematopoiesis associated with chronic marrow failure or myelosclerosis. They described the histology of the condition in detail, noting that the earliest change in the bone marrow was a hyperplasia of all cell types associated with pyknosis and necrobiosis of many individual immature cells. Later, hematopoietic cells

atrophied, leaving intact islands surrounded only by the reticulo-endothelial framework. Fibrosis and osteosclerosis were still later developments. They attributed the necrobiosis to the action of an unknown toxin and believed the hyperplasia was reactive in type. Their cases fell into 5 main groups associated with 1) An extrinsic toxic agent, 2) Liver dysfunction, 3) Endocrine disease, 4) Hemorrhage or hemolysis, 5) Cardiovascular disease. They also suggested a source for the etiologic toxin as follows: phenol and quinone groups are known to exert a toxic action on hematopoiesis. These compounds are not only found in many industrial solvents but also in endocrine steroids. If, for some reason, the liver fails to conjugate these substances to sulfates and glycuronates, the marrow may be exposed to a higher concentration of them than usual. This could result in the break-down of the lipid-containing immature cells, the products of which might then act as trophic stimuli causing hyperplasia of the remaining marrow cells, and also extramedullary hematopoiesis.

Taylor and Simpson (36) reported a case of aleukemia myelosis in which they were able to show by biopsy the presence of myeloid metaplasia in the spleen and liver before the development of fibrosis in the marrow. At the time of the splenic biopsy the sternal marrow was hyperplastic but 8 months later there was definite fibrosis, although even at

autopsy considerable areas of hyperplasia remained. In view of these findings they suggested that a case of myelofibrosis reported by one of them in 1941 (25) had really represented the end stage of a leukemia.

Twelve cases of myeloid metaplasia proved by splenic and/or liver biopsy were described by Block and Jacobson (37). They divided their cases into those in which the etiology was unknown and those in which the metaplasia was secondary to carcinomatosis, myelofibrosis and tuberculosis. They regarded myeloid metaplasia as a non-specific response of immature multipotent cells of the liver and spleen to a wide variety of stimuli. To this extent they agreed with authors such as Heller and associates (30), and Merskey (33), but then they emphasized their belief that the condition was fundamentally different from leukemia.

1951. Dameshek (38) discussed the relationship which several diseases characterized by myeloproliferative phenomena bear to each other. He was of the opinion that too much attention is paid to minor variations in type and that it would be more logical to consider diseases such as chronic myelogenous leukemia, polycythemia vera, idiopathic myeloid metaplasia of the spleen, megakaryocytic leukemia and erythroleukemia as different manifestations of proliferative activity of the bone marrow cells, perhaps due to some as yet unknown stimulus. He mentioned the possibility of the stimulus being

hormonal or steroid in type, but stated that there is no definite foundation for this theory.

1952. An interesting case of myeloid metaplasia was reported by Claman and Collier (39). It occurred in a spleen removed at surgery from a patient with acute hemolytic anemia. The marrow showed megakaryocytic hyperplasia but no fibrosis. The post-operative course of this patient was good in contradistinction to one previously reported by Jackson and associates (22).

1953. Green, Conley, Ashburn and Peters (40) reported 5 cases of proved myeloid metaplasia of the spleen in which splenectomy was performed. Four of the bone marrows showed myeloid and megakaryocytic hyperplasia plus fibrosis and one showed only the hyperplasia. The authors favored the view that the condition was due to stimulation of the mesenchymal precursors of the hematopoietic system, and was not a compensatory process arising in the spleen as a consequence of marrow failure. They based this belief on the results of 5 splenectomies which indicated that the course of the patients following the operation was little different from the natural history of the disease. If the myeloid metaplasia had been compensatory in nature, the authors felt that splenectomy should have had an adverse effect on the prognosis. They noted, however, that their view of the results of splenectomy was in opposition to the majority opinion at that time, although there was evidence

that with the advent of improved surgical technique the antipathy towards the operation in such cases was gradually vanishing.

Hutt, Pinniger and Wetherley-Mein (41) endeavored to show the close relationship between the various myeloproliferative disorders. This they did by selecting 10 cases, one of myelogenous leukemia, one of definite myelofibrosis and 8 miscellaneous in type. All showed myeloid metaplasia in the spleen. They showed that in cases which had been diagnosed clinically as myelogenous leukemia there was frequently a proliferation of reticulum and fibroblasts in the marrow as well as the overgrowth of the granulocytic series. The proportion between the processes varied from case to case and sometimes there was also proliferation of megakaryocytes. In a case diagnosed as polycythemia vera the marrow showed increased proliferation of all three series plus reticulum and collagen formation. Not all their cases evidenced splenomegaly, although undoubted myeloid metaplasia was present.

Eight cases of myelofibrosis were described by Cook, Franklin, Hamilton and Fowler (42). All were associated with myeloid metaplasia of the spleen. These authors believe that the syndrome of myelofibrosis has reasonably characteristic features enabling it to be differentiated from myelogenous leukemia. They suggest that a relative polycythemia may be

the initial phase of myelofibrosis rather than myelofibrosis the terminal phase of polycythemia vera. Their experience with splenic irradiation led them to believe that this treatment is not so dangerous as commonly supposed, and that it can be used to relieve abdominal distress due to splenomegaly when there is evidence of other extra-medullary hematopoiesis.

Beattie and Withey (43) described 3 cases of polycythemia which later developed a leucoerythroblastosis, myelosclerosis and myeloid metaplasia. In discussing the pathogenesis they agreed with Vaughan and Harrison that the sclerosis of the marrow was due to the same stimulus which produced the extra-medullary hematopoiesis. In other words, one process was not the result of the other but both developed simultaneously from the action of an unknown factor, possibly a deficiency in some nutritional substance or the presence of an abnormal metabolite.

Three cases of myelosclerosis with myeloid metaplasia of the spleen were included in a study of 11 cases of bone marrow failure undertaken by Loeb, Moore and Dubach (44). They were especially interested in the capacity of the marrow for regeneration, and also in the presence of a hemolytic component in the anemia causing increased blood destruction. The former was estimated by administering corticotropin and cortisone, and the latter by measuring red cell survival times. Two of the three cases of myelosclerosis were shown to have a hemolytic component to their anemia and responded well to

splenectomy. The remaining case, in which there was a history of exposure to benzene, did well on maintenance doses of cortisone. As a result of their observations the authors suggested the possibility of a splenic inhibition of the bone marrow. They did not recommend splenectomy unless both the capacity of the marrow to respond and the presence of a hemolytic factor had been established.

A report of 17 cases of myelosclerosis with myeloid metaplasia of the spleen was published by Robson (45). Ten of his cases were examples of "primary myelosclerosis", although islands of hematopoietic elements were present in the marrow of 3 of them, while the others were found in patients with polycythemia, myelogenous leukemia or long-standing hemolysis. As a result of studying these cases and of reviewing the literature, the author subscribed to the belief that both the myeloid metaplasia and the myelosclerosis were the result of the stimulatory action of some unknown substance. He quoted the experiments of Mallory, Gall and Brickley (46) who showed that, while acute poisoning by benzene led to marrow aplasia, long-continued exposure to lower concentrations led to hyperplasia of bone marrow elements. The inference from this was that repeated or prolonged exposure to small doses of myelotoxic agents might produce hyperplasia of any of the cell types derived from the primitive mesenchymal reticulum cell. Agents of a myelostimulatory nature mentioned included hemolysis, chronic hemorrhage, chronic sepsis as in

tuberculosis and the presence of metastatic tumor in the marrow spaces.

Peace (47) agreed with Wyatt and Sommers (35) that focal necroses in the marrow, followed by reactive hyperplasia, are the first stages in a process ending as myelofibrosis. He illustrated his paper by 4 cases in all of which myeloid metaplasia was present. He stated that at first the maturation of the newly formed cells in the hyperplastic areas is quite advanced but as the process continues the cells revert to more primitive types. This proceeds until even the hemocytoblasts disappear, leaving reticulo-endothelial cells which proliferate to form fibrous tissue and later perhaps take part in bone formation. He believed that the causative cytotoxins may be of the nature suggested by Wyatt and Sommers, but also pointed out that nucleoproteins, which are released during cell destruction, have been proved experimentally to have a myelostimulatory action both on hematopoietic elements and on primitive mesenchymal cells. Newly formed cells resulting from this stimulation would be more vulnerable to the action of the original toxin, and so a vicious cycle would be initiated. He also presented some evidence that the mesenchymal system is an end-organ participating in the general adaptation syndrome, and that the myeloproliferative disorders are one result of pituitary-adrenal dysfunction.

1954. Chatterjea and Das Gupta (48) described what was probably the first case to appear in the literature of myeloid meta-

plasia of the spleen associated with classical aplastic anemia. Splenic enlargement first developed following an attack of benign tertian malaria and was proved by aspiration biopsy to be due to myeloid metaplasia. In spite of the fact that slight myeloid metaplasia has been reported in association with chronic malaria the authors felt that it was most unlikely that malarial infection was responsible for extensive extra-medullary hematopoiesis in a patient who had aplastic anemia prior to the attack. In discussing the possible etiology they suggested that it would be conceivable that a mild toxic agent applied over a short period of time could be active enough to depress the differentiated bone marrow elements sufficiently to cause aplastic anemia, and yet not be active enough to depress the entire reticulo-endothelial system. As a result the primitive cells in the spleen might differentiate and become hematopoietic as a compensatory measure. Experimental support for this theory was available from irradiation experiments of Jacobson, Marks, Gaston, Robson and Zirkle (49) who found that the survival rate of irradiated mice was higher when the spleen was protected from irradiation injury by an appropriate shield. The protected spleens were shown to contain extensive foci of myeloid metaplasia.

1956. Another case of myeloid metaplasia associated with a hyperplastic marrow and occurring during the course of an infection was reported by Hemsath and Pinkerton (50). The

infection was a double one due to the salivary gland virus (cytomegalic inclusion disease) and to Toxoplasma organisms. The authors felt that the hematologic picture was probably "agnogenic" but also mentioned the possibility that it might have been due to toxic products elaborated as a result of the infections. In this connection they thought it interesting that myeloid metaplasia had been seen in chronic malaria (the plasmodium of malaria being an organism of the same class as Toxoplasma) and also in a few cases of adults infected with salivary gland virus. Also, the pathologic picture of cytomegalic inclusion disease in children often resembles that of erythroblastosis fetalis.

Materials and Methods

The information for this study was obtained from the records of 923 patients who died while patients in one of the hospitals associated with the Mayo Clinic, or who died at their homes in Rochester, Minnesota. The cases were taken from the years 1945 through 1955, an autopsy having been performed in every instance. The requirement for admission to the study was a splenomegaly of at least 200 gm., either at autopsy or at the time of a previous splenectomy. Although the weight of the normal spleen is known to be extremely variable, it was believed that most pathologically enlarged spleens would exceed 200 gm., and that the number of abnormal spleens under this weight would be negligible. When a patient was under 16 years of age at the time of death, the normal average weight

of the spleen was obtained from a table of standards (61).

The study was carried out in four stages as follows:

Stage 1. Sections of spleen were examined microscopically and the 923 cases were classified according to the local condition which was considered most likely to have caused the splenomegaly. No attempt was made to specify the immediate cause of death. Sections of bone marrow were obtained and were studied in approximately two thirds of the cases, but proved to be of value chiefly in differentiating the various types of leukemia. The routine slides prepared following autopsy were used for this stage of the study and in all but a few cases provided adequate information.

Stage 2. The 53 cases showing myeloid metaplasia in the spleen were studied in detail. Sections of spleen and bone marrow were re-cut as required, and when necessary new tissue was obtained from stock so that at least 2 specimens of spleen and 1 of bone marrow were examined in every case. More sections were examined when material permitted. All were stained with hematoxylin and eosin. In 2 cases the marrow was poorly preserved and not suitable for study. The specimens of bone marrow were obtained from several different sites according to the material available. The origin was unknown in 24 cases; from the vertebrae only in 7; from the sternum only in 5; from the ribs only in 1; and from a combination of these sites in 16. At least 2 sections of

liver were studied in every case.

Stage 3. The clinical histories of the 53 cases were reviewed to ascertain the age and sex of the patients, the duration and type of the primary disease, and any pertinent laboratory data.

Stage 4. A correlation of the accumulated data was undertaken.

Results

Table I presents a detailed analysis of the histology found in the 923 enlarged spleens originally examined. As stated before, the diagnosis listed is a descriptive one and it is coincidental that in some cases, such as the leukemias, the picture in the spleen reflects the appearance of the disease which was the immediate cause of death. The various subdivision of this table will now be considered briefly.

Congestion

Three hundred and one of the enlarged spleens (32.6 %) showed a varying degree of congestion and in this group no other pathology was present to account for the increased weight. The degree of congestion varied from slight to marked. Of these 301 cases 16 had associated infarcts in the spleen which were in all stages of development, from the recent type in which the area was packed with blood to old scars with marked fibrosis and deposition of hemosiderin pigment. In another 5 of the cases circumscribed fibrotic, and sometimes calcified, lesions were present in the pulp. They measured

only a few millimeters in diameter and probably represented healed granulomas, most likely indicating a healed infection with tuberculosis or histoplasmosis. Many of the spleens showed a mild degree of fibrous capsular thickening but as this condition was found indiscriminately throughout the entire series of enlarged spleens no attempt was made to group such cases separately.

Fibrosis

Spleens showing fibrosis of the pulp numbered 103 (11.16 %). Of these 6 showed resolving infarcts or old scars. All gradations in the degree of fibrosis were present. It seemed probable that most of the cases in this and in the following group were examples of chronic congestive splenomegaly due to portal hypertension. Moschcowitz (51) in 1948 gave an excellent description of the development of fibrosis in the spleen in portal hypertension, and without making any attempt to sub-divide this present group into early and late cases, it was evident that the histology closely followed the pattern outlined by him. The important features included an increase and broadening of the trabeculae with an associated capsular thickening. Fine septa of fibrous tissue were seen branching from the trabeculae to spread through the pulp. There was an increase in the amount of reticulum present, and the sinusoids were often dilated and lined by prominent and swollen endothelial cells. In advanced cases the sinusoids appeared as an open network separated from each other by rather densely fibrosed cords of pulp. The lymph follicles were generally small but except in late cases seemed to escapte the fibrotic process which surrounded them.

Fibrosis with Congestion

There is little question that from the etiologic point of view the 81 cases (8.78 %) in this group should be placed in the same category as the fibrotic spleens. However, as in all the cases there was a considerable degree of congestion, it was thought better to classify them separately rather than to attempt to decide in which of the first two groups they should be included. The histology was that of a fibrotic spleen of varying severity in which both sinusoid and remaining pulp spaces contained an excess of blood. Old or new infarcts were present in 7 of the cases.

Septic Splenomegaly

Ninety-three cases (10.08 %) were classified as septic splenomegaly. According to Richter (52) other terms for this condition are acute splenitis or acute splenic tumor. The characteristic feature of this group was a marked increase in the cellularity of the pulp. Usually the increase was due to the presence of large numbers of polymorphonuclear leucocytes, both in the sinusoids and in the pulp, but in some cases plasma cells and large mononuclear cells were also prominent. Frequently there was an associated increase of erythrocytes in the pulp spaces, but the increase in the number of polymorphs was too great to be accounted for by those normally present in blood. In 5 of the spleens there was frank abscess formation with necrosis of the tissue. In another 14 of the cases infarcts were present. Some of these were very recent and none were old enough to have become fibrotic.

Acute Leukemia

The number of cases of acute leukemia amounted to 101 (10.94 %). In this group it was necessary on occasion to obtain the results of peripheral blood counts and bone marrow biopsies from the clinical history before a definite classification of the type of leukemia could be made. Even with this assistance 34 cases remained unclassified. Of the remainder, 42 were called acute lymphatic leukemia, 10 acute myelogenous leukemia and 15 acute monocytic leukemia. As far as could be determined 13 of the monocytic leukemias were of the Naegeli type and 2 of the Schilling variety. The amount of infiltration of the spleen with leukemic cells showed a wide degree of variation. In a few cases the picture under a low power objective was very similar to that of myeloid metaplasia, but the resemblance was easily resolved on inspection with higher power, when it became evident that the infiltrating cells were all in a very primitive stage of development and that they were confined to the white cell series. In addition, single cells tended to be widely scattered throughout the pulp whereas in myeloid metaplasia the cells generally occurred in clusters of similar cell types. However, these confusing cases of leukemia were much in the minority, the remainder showing a uniform infiltration of the splenic pulp with destruction of the normal architecture.

Chronic Leukemia

Twenty-seven cases of chronic lymphatic and 34 cases of chronic myelogenous leukemia were found in the series making a

total for the group of 61 (6.61 %). Generally, the cases of chronic myelogenous leukemia were easily recognized as the masses of leukemia cells had completely replaced the normal splenic architecture. This massive infiltration was also normally seen in chronic lymphatic leukemia but in a few cases the outline of follicles and germinal centers remained visible with cords of small lymphocytes spreading outwards from them into the pulp. It was impossible to distinguish chronic lymphatic leukemia from lymphosarcoma without knowledge of the presence or absence of a leukemic blood picture during life.

Lymphomas

In all, 55 cases (5.96 %) were classified as lymphomas. It was rarely difficult to diagnose a case as belonging to the lymphoma group, but frequently careful examination of the section was necessary before a more specific classification could be made. The method used to distinguish the 12 cases of lymphosarcoma from chronic lymphatic leukemia is described in the preceding paragraph. Nine cases of typical reticulum cell sarcoma and 7 cases of typical Hodgkin's sarcoma were found. The 24 cases of Hodgkin's disease (paragranuloma and granuloma types) varied in appearance from small deposits of tumor cells adjacent to the Malpighian corpuscles through those in which the entire pulp was infiltrated by a pleomorphic mass of cells to those in which only scanty tumor cells were seen surrounded by dense collagenous fibrous tissue.

Granulomas

Seventeen cases (1.84 %) were listed under this classification. There were 7 cases of tuberculosis affecting the spleen; 5 of the

miliary variety, 1 tuberculoma and 1 massive caseating lesion. All were proved either by acidfast stain or by culture. The organisms in the 4 cases of histoplasmosis and the 1 case of cryptococcosis were visible microscopically and were also cultured at the time of autopsy. Two spleens contained granulomatous lesions in which large fat vacuoles were visible and in which numerous giant cells contained fat droplets in their cytoplasm. Miliary granulomas were scattered throughout the spleen in 3 other cases, in which special stains and cultures failed to reveal a causal organism.

Amyloid Disease

Diffuse amyloid disease, as proved by congo red and methyl violet stains, was present in 7 cases (0.76 %). There were no cases in which the amyloid deposit was confined to the lymph follicles, the type known from its characteristic gross appearance as the "sago spleen". One case of diffuse amyloid disease occurred in a patient with multiple myeloma and the clusters of myeloma cells present in the pulp probably contributed to the splenic enlargement.

Benign Tumors

Two of the 4 spleens (0.43 %) in this group contained multiple cysts which probably represented cystic lymphangiomas. One spleen showed a similar lesion plus a large cavernous hemangioma, while the final one contained numerous discrete cavernous and capillary hemangiomas.

Metastatic Tumors

The spleen is relatively infrequently involved by secondary tumors and of the 923 cases of splenomegaly only 4 (0.43 %) spleens contained metastatic lesions. The primary tumor was in the tail of the pancreas in 2 cases, in the liver in the form of a cholangioma in 1 case, and in the fourth case was a primary peritoneal mesothelioma.

Reticulo-endothelial Hyperplasia

The 15 cases (1.63 %) of reticulo-endothelial hyperplasia presented an almost uniform histologic appearance. The Malpighian bodies were little affected although the germinal centers were unusually large and active in a number of cases. The sinusoids were collapsed and there appeared to be a reduction in the number of lymphocytes in the pulp. There was marked proliferation of the reticulo-endothelial cells which frequently formed broad bands transversing the pulp. The individual cells were elongated and had abundant swollen cytoplasm with large oval pale nuclei.

Hemosiderosis

The 2 cases (0.22 %) so classified showed a moderate degree of fibrosis in the spleen with a very large amount of hemosiderin pigment present in mononuclear phagocytes in the pulp and sinusoids. Smaller accumulations of hemosiderin lay free in the fibrous tissue of the trabeculae and capsule.

Erythroblastosis Fetalis

Fourteen examples (1.52 %) of this condition were found. The sinusoids and pulp spaces generally contained large numbers of erythroblasts and normoblasts. Myelocytes were also present but in fewer numbers. No megakaryocytes were seen. While one of the major characteristics of erythroblastosis fetalis is extra-medullary hematopoiesis, it was decided to exclude this group from detailed consideration with the 53 other cases of myeloid metaplasia in view of the age at which it occurs and of the fact that the etiology has been quite adequately elucidated.

Multiple Myeloma

In the 12 cases (1.3 %) in this group the microscopic picture in the spleen varied from irregular small foci of myeloma cells in the pulp to a diffuse infiltration of the sinusoids and pulp with the malignant cells.

Cases of Myeloid Metaplasia. General.

The 53 cases (5.74 %) in which the spleen showed evidence of myeloid metaplasia fell into several groups when classified according to the primary disease or diseases with which they were associated. Such a classification is given in Table II. Two cases were examples of aleukemic myelosis; 12 had tumor involvement of the bone marrow; 18 had cirrhosis of the liver; 6 had some other liver disease; 11 had cardio-renal disease; 2 had purpura; and 2 remained in a miscellaneous group. The several groups will be discussed in the above sequence.

Group 1. Cases of aleukemic myelosis. (Figures 1, 2, 3, 4)

The clinical and pathologic findings in the two cases in this group are summarized in Table III A, and the blood counts are detailed in Table III B. The first case of aleukemic myelosis was found incidentally at autopsy in a 78 year old woman who died from a terminal lobar pneumonia following 8 months of congestive cardiac failure. During life she had a slight anemia, and the white blood count was at the upper limit of normal (11,900 per cu.mm. and 9,200 per cu.mm. on two samplings). There was no leucoerythroblastosis and the differential count was not otherwise remarkable. At autopsy the liver weighed 2,125 gm., was congested and showed dilated sinusoids containing megakaryocytes. The spleen weighed 1,630 gm., and the cut surface showed a deep purple, circumscribed nodule measuring 2.5 cm. in diameter. A small infarct was also present. Microscopically the nodule resembled hyperplastic bone marrow. No trace of normal splenic pulp remained in this area. Cells of the granulocytic series, at all stages of development from myeloblasts to mature polymorphonuclears, were abundant. Numerous foci of erythropoiesis were seen and a striking feature was the very large number of megakaryocytes. The nodule was quite sharply demarcated from the remainder of the pulp which showed moderate fibrosis and congestion. The follicles were all well preserved but in the intervening pulp there were numerous poorly defined areas of myeloid transformation, which chiefly contained cells of the granulocytic series. The sinusoids also contained a few small clusters of myeloblasts and myelocytes; also some erythroblasts. Four sections of marrow from the sternum and vertebrae all

showed the same picture. There was extreme hyperplasia of the granulocytic and megakaryocytic elements with a definite reduction in erythrocytic activity. A few fat cells remained. Many of the megakaryocytes were large and contained irregular and sometimes hyperchromatic nuclei. There was no fibrosis or necrosis. No myeloid elements were seen in the other organs.

The second case occurred in a 25 year old man who complained of left upper quadrant pain of 3 months' duration. A blood count performed 3 years previously, when the patient was seen for an unrelated minor complaint, had showed a slight leucocytosis with a few promyelocytes and myelocytes in the smear. On examination a mass was palpated in the left upper quadrant and a laparotomy was performed to determine its nature. An enlarged spleen was found and this, together with an acessory spleen, was removed, the surgical pathologic diagnosis being myeloid metaplasia. A sternal marrow aspiration after surgery showed active myelopoiesis, many platelets and a few normoblasts. A fixed section of marrow showed a few marrow cells, numerous megakaryocytes and fibrous tissue. A very marked thrombocytosis developed post-operatively, and this later dropped somewhat, although remaining considerably above normal levels. The white blood count reached 40,100 per cu.mm. and there was a slight leucoerythroblastosis. X-rays showed an area of rarefaction in one rib and increased density in the pelvis, said to be compatible with myelofibrosis and early sclerosis. Another laparotomy was performed three months later for recurrent left upper quadrant pain, but no abnormality was found. He was given a course

of radiation to the paravertebral area but later developed thrombophlebitis of legs and arms and died of multiple pulmonary emboli. At autopsy the liver weighed 3,700 gm., was congested and showed dilated sinusoids containing many megakaryocytes which were frequently very irregular with bizarre and hyperchromatic nuclei. The surgically removed spleen weighed 1,850 gm. One section near the hilum contained a re-canalized thrombus in a medium sized artery. The follicles were well preserved and the pulp was moderately fibrotic with dilated sinusoids. Throughout the pulp there were poorly demarcated areas of myeloid change containing myeloblasts, myelocytes and mature polymorphonuclears. There were numerous megakaryocytes and scanty foci of erythropoiesis in the sinusoids. The histology of the accessory spleen was similar. Four sections of marrow were available, two from vertebrae, one from the sternum and one from a rib. In all of them there was a tremendous hyperplasia of cells of all three series. The megakaryocytes were particularly abundant and showed distorted and hyperchromatic nuclei. A few fat cells remained but there were no areas of fibrosis or necrosis. Apart from a few megakaryocytes impacted in the capillaries of the kidneys and lungs the other organs showed no myeloid change.

Groups 2 to 7. General

To avoid unnecessary repetition some of the general aspects of the cases in these 6 groups will be considered here. The weight of the spleens in the 51 cases varied from a low of 226 gm. to a high of 1300 gm., the average being 430 gm. (Tables IV, VIII A, IX A, X, XI, XII).

The gross appearance of the spleens as described at autopsy was of little help in this study, no mention having been made in any of the protocols of an abnormality which could be attributed to the presence of foci of myeloid metaplasia. Moreover, it seemed doubtful, after studying the microscopic sections, that any such gross lesions would have been visible, except perhaps in a few of the most extensively involved cases. Nor was much information obtainable from the autopsy protocols about gross abnormalities in the bone marrow except in some of the cases with skeletal metastases, although it must be presumed that any striking abnormality would have been recorded.

Histology of Spleen (Figures 5, 6, 7)

While the histologic appearance of the spleen in these 51 cases varied widely, it was noted that this variation was caused by differences in the degree of congestion, amount of fibrosis, presence or absence of infarcts and other similar factors rather than by a qualitative difference in the myeloid metaplasia present. There was, however, considerable quantitative difference in the degree of metaplasia, and for ease in discussion it was decided to classify the process as scanty, moderate or widespread. In the scanty group the foci of hematopoiesis were small and widely spaced; in the moderate group clusters of metaplastic cells appeared in every low power field; and in the widespread group the foci of metaplasia were definitely larger and several were present in each high power field. The earliest stage in the process was the appearance of small clusters of hematopoietic cells in the splenic sinusoids. The first cells to

appear were generally myeloblasts and myelocytes and these were present in every case. Cells of the erythroid series, erythroblasts and normoblasts, were sometimes as numerous as those of the myeloid series but occasionally they were rather scanty and had the appearance of more recent development. In only two cases were erythrocytic cells completely absent and in both of these the metaplasia was classified as scanty. Each cluster of immature blood cells in the sinusoids was limited to cells of one series, the younger forms lying in the center surrounded by the older. Megakaryocytes were seen in varying numbers in 31 of the 51 cases; but their presence could not be related to any particular primary disease. Although they were occasionally distorted by the shape of the sinusoid there was no hyperchromaticity of the nuclei. When the myeloid metaplasia became more extensive the immature cells were found in the pulp spaces surrounding the sinusoids. At first this extension took the form of individual cells but in widespread cases actual clusters appeared. In no case was more than the outer rim of a Malpighian body involved by the myeloid metaplasia. The trabeculae were invariably well preserved.

Histology of the Bone Marrow (Figures 8, 9, 10)

In any study involving the bone marrow it is necessary for complete accuracy to obtain specimens from as many different sites as possible. In this series lack of material frequently rendered this impossible, but it was found that multiple specimens differed little from each other in the cases in which they were available. Hence, it was considered that in cases where only one specimen was available this was probably, but not definitely, representative of the rest of

the marrow. A marrow was classified as normally active if it contained approximately equal amounts of hematopoietic tissue and fat; as hyperplastic when the proportion of fat was decreased; and as hypoplastic when the proportion of fat was increased. These standards were necessarily interpreted rather freely taking into consideration the activity evident in the hematopoietic cells. It was noted that in the few cases in which there was a relative hyperplasia or hypoplasia of erythrocytic, granulocytic or thrombocytic elements there was no corresponding increase or decrease in the proportion of cells of that particular series in the metaplastic areas of the spleen.

Group 2. Cases associated with tumor involvement of the marrow.

Table IV contains a detailed summary of the findings in these 12 cases. Four patients had multiple myeloma. In 3 of these the spleens contained a moderate degree of metaplasia and in one the amount was scanty. Two of the cases had hyperplastic marrows, and in 2 only tumor tissue was visible. There was no correlation between the amount of metaplasia in the spleen and the degree of activity of the bone marrow. In the 2 cases in which a differential blood count was done, a leucoerythroblastosis was present. The remaining 8 cases were examples of metastatic tumor replacing bone marrow. The primary lesions were in the large bowel, stomach, lung, liver and uterine cervix. In this group the degree of myeloid metaplasia was generally more extensive than any other except Group 1. Five cases had widespread involvement of the spleen, 2 moderate and 1 scanty. Apart from 3 specimens in which only tumor was visible the picture in the marrow was one of hyperplasia. No relationship was evident between the amount of metaplasia and the state of the bone marrow, as the

latter was hyperplastic with both scanty and moderate, as well as widespread metaplasia. Leucoerythroblastosis was present in 5 cases, absent in 2, and not examined for in 1. It was noted that the metaplasia was generally more extensive in cases which showed immature cells in the peripheral blood. No relation between the known duration of the primary disease and the degree of metaplasia was evident, but it must be remembered that many of the tumors had undoubtedly been present for much longer than the period shown in Table IV which indicates the duration between the first symptom and death.

Group 3 through 7. Summary of some features.

The primary diseases in the 39 cases in these 5 groups have only rarely been reported in the literature as being associated with myeloid metaplasia. To this extent these cases resemble each other and differ from those in the 2 groups already described. Some general features of these remaining cases will, therefore, now be considered before describing them individually in detail. Table V shows the relation between the degree of myeloid metaplasia in the spleens and the degree of activity of the bone marrow. The 3 cases which showed widespread metaplasia also showed a hyperplastic marrow. Of the 14 cases with moderate metaplasia, 8 showed a hyperplastic and 4 a normal marrow. Similarly, of the 22 cases with scanty metaplasia, 13 had a hyperplastic marrow and again approximately half that number, namely 7, had a normal marrow. Only 2 cases had a hypoplastic marrow, while in 2 cases the state of the marrow was unknown. Considering all degrees of metaplasia together, approximately twice as many cases were associated with a hyperplastic as with a normal marrow. Also, it can be seen from Table VI, which relates the degree of marrow

activity to the 5 primary disease groups, that the hyperplastic, normal, and hypoplastic marrows were proportionately distributed among the groups, so that no single group had a monopoly of one particular degree of marrow activity. In addition, Table VII shows that cases in which an anemia (under 12 gm. % of hemoglobin) was present did not have a disproportionate number of hyperplastic marrows.

Group 3. Cases associated with cirrhosis of the liver.

The detailed findings in this group of cases are given in Table VIII (A and B). There were 10 cases of portal cirrhosis, 4 of cirrhosis resulting from a preceding hepatitis, and 3 of biliary cirrhosis. In the remaining case the liver was almost completely replaced by a cholangioma, and although small areas of parenchyma were present and indicative of a pre-existing cirrhosis, it was impossible to classify this as to type. Five cases of portal, 1 of post-hepatitic, and 1 of biliary cirrhosis showed a moderate amount of splenic myeloid metaplasia, and the remaining 11 cases had scanty metaplasia. Signs of portal hypertension as evidenced by the presence of esophageal varices or ascites were noted in all but 4 cases. It proved impossible to relate the degree of metaplasia to the age and sex of the patient or to the duration of the disease from the time the first symptom became evident. With one exception (case No. 15), the livers showed an advanced degree of cirrhosis on histologic examination. Reference to Table VIII B will confirm that, in those cases in which they were performed, liver function tests also

indicated severe damage. Anemia, if present at all, was slight and no relation could be seen between either the state of the peripheral blood or the liver function tests and the degree of metaplasia. Hyperplastic and normal bone marrows were found in both moderate and scanty degrees of myeloid metaplasia.

Group 4. Cases associated with various liver diseases.

Table IX (A and B) outlines the main findings in this group. All but one case were females. Cases 1, 2 and 6 were characterized by obstruction to the biliary tree either by calculi or post-operative stricture. There was associated cholangitis and necroses of liver cells in all three. Case 3 was similar in that a carcinoma of the gall-bladder had caused obstruction to the bile ducts with resulting suppurative cholangitis and portal vein thrombosis. In cases 4 and 5 there was fairly extensive replacement of the liver parenchyma with metastatic tumor, the primary lesion in one being in the gall-bladder and in the other in the rectum. The myeloid metaplasia was widespread in one case, moderate ir two and scanty in three. In the case with widespread metaplasia and in one in which it was moderate there was no leucocytosis in the peripheral blood, which seemed to eliminate infection as the etiologic factor in causing the more extensive extra-medullary hematopoiesis. Conversely, peripheral blood leucocytosis was present in two cases with scanty metaplasia. Four marrows were hyperplastic, 1 normal and in 1 the condition was unknown. In comparing the state of the marrow with that of the peripheral blood, it did not appear as if either anemia or infection had caused the hyperplasia of the marrow. Liver function tests were very incomplete

(Table IX B). However, 2 cases, 1 with widespread and the other with scanty metaplasia, had raised blood ureas, which links them with the group to be discussed next.

Group 5. Cases associated with cardio-renal disease.

This group of 11 cases includes 7 in which there was known to be uremia of varying degree (Table X). It is possible that in at least one other case (No. 7) uremia existed although no estimations of the blood urea were carried out. In case number 4 there was a subacute bacterial endocarditis, the spleen showed widespread metaplasia, and the marrow was hyperplastic. There was also a leucocytosis of 20,800 cu. mm. and it is possible that infection played a part in stimulating the marked hematopoiesis both in the bone marrow and the spleen. Of the remaining 10 cases, 3 had moderate and 7 scanty metaplasia. Six of the marrows were hyperplastic, 3 normal and 1 hypoplastic. Again, no relationship existed between degree of metaplasia and activity of the bone marrow. Many of these cases were also associated with liver destruction in the form of chronic passive congestion. Three grades of congestion were recognized: The first, or slight, when necrosis of liver cells was present up to one-third of the distance from central vein to portal tract; the second, or moderate, when necrosis was present in the entire central half of the lobules; and the third, or severe, when necrosis existed in the entire central two-thirds of the lobules. In cases 2 and 3 the livers were normal and the metaplasia was moderate while the marrow of one was normal and of the other hypoplastic. In the other 9 cases showing varying degrees of chronic passive congestion of the liver there was no relationship evident between the severity of the liver destruction,

the degree of metaplasia or the activity of the marrow. As expected, most of the cases in this group were anemic, and although the three cases with moderate myeloid metaplasia had a rather more severe degree of anemia than those in which it was scanty, it was very doubtful if this feature was striking enough to be etiologically significant. In addition to the primary cardio-renal disability, case 11 had evidence at autopsy of destruction to the biliary tree in that stones were found in the bile ducts and bile retention was seen microscopically in the liver. This case, therefore, formed a link with those in group 3.

Group 6. Cases associated with purpura. (Figure 11)

Table XI describes the details of the 2 cases in this group, in which the myeloid metaplasia was associated with purpura. Both patients were young females and were ill for only a few months. Case 1 showed widespread metaplasia and case 2 a moderate amount. In the former, an emergency splenectomy was performed 8 days before death and was followed by massive intra-peritoneal hemorrhage. The latter was a case of thrombotic thrombocytopenic purpura associated with a malignant thymoma. This case has previously been reported by Cooper and associates (53). Both cases had severe anemia, with a leuco-erythroblastosis and hyperplastic marrows. Blood transfusions amounting to 16,000 ml. and 3,000 ml. had been given to the two cases respectively.

Group 7. Miscellaneous cases.

The findings in these 2 cases are presented in Table XII. Case 1 showed a moderate degree of myeloid metaplasia associated with a leukopenia, leucoerythroblastosis and a hyperplastic bone marrow. This patient gave a history of typical symptoms of diabetes mellitus,

accompanied by increasing dyspnea, starting 3 months before admission. One week before admission she developed fever, night sweats, became disoriented, and was brought to the hospital in coma where she died two days later. Her fasting blood sugar was 611 mgm. % and her blood urea was 80 mgm. %. At autopsy, miliary non-caseating granulomas were found widely scattered through the liver, spleen and lymph nodes. All special stains and cultures were negative, but the appearance was not typical of sarcoidosis. This case, therefore, is one of diabetes mellitus complicated by an infective disease of unknown etiology.

Case 2 showed scanty metaplasia associated with a slight leucoerythroblastosis and a hypoplastic marrow. There was no leucocytosis and the fasting blood sugar was 245 mgm. %. This case was a typical example of Cushing's syndrome of 18 months' duration. Two months before death a right nephrolithotomy was done for the removal of renal calculi. Following this a cutaneous urinary fistula developed. Sixteen days before death a left sub-total adrenalectomy and left pelvilithotomy was performed. Sixteen days later she underwent a right pelvilithotomy with drainage of a perinephric abscess. She died in pulmonary edema one hour after completion of the final surgery. Autopsy permission did not include the head so the state of the pituitary was never discovered.

Although these two cases did not fit into any of the other groups previously described, they bear a certain resemblance to each other in that both were primarily endocrine abnormalities and that both had diabetes mellitus.

Discussion

Most of the case reports of myeloid metaplasia appearing in the literature have approached the problem from the clinical standpoint, paying particular attention to the relationship of the condition to myelosclerosis, polycythemia vera and other diseases or syndromes. In many instances the presence of myeloid metaplasia was proved by splenic aspiration biopsy, while in other reports histologic examination following splenectomy or necropsy was available. Occasionally, the presence of extra-medullary hematopoiesis in the spleen was presumed on the basis of clinical findings of leucoerythroblastosis, splenomegaly and sclerosis of the bone marrow as shown by x-ray examination or by biopsy. It was, therefore, our hope that the investigation of the occurrence of myeloid metaplasia in the spleen in an autopsy series, followed by the correlation with clinical findings during life, might help to elucidate the etiology of the condition.

It has proved disappointing that none of our cases of myeloid metaplasia was associated with myelofibrosis. There are three possible reasons why this was the case:

1. Areas of fibrosis may have existed but sampling was not wide enough to encounter it. This seems unlikely as when numerous marrow specimens were available little difference was noted in their various histologic appearances.

2. Hyperplasia of the marrow seen in many of the cases may conceivably have given way to fibrosis if the course of the disease had been more prolonged.

3. The most probable reason is concerned with the type of medical practice at the Mayo Clinic. Patients are drawn to the Clinic

from the entire mid-western section of the United States and their homes are often at a considerable distance from Rochester, Minnesota. The course of the majority of cases of myelosclerosis associated with myeloid metaplasia is a prolonged one, and it is probable that most of the patients seen at the Clinic return to their homes after this diagnosis has been made and treatment has been recommended, so that autopsy material is not available to us for study. Our belief that this is the correct explanation is supported by a recent report (54) from this institution describing 25 cases of myelofibrosis and myeloid metaplasia seen clinically.

In the preceding section it has been shown that myeloid metaplasia of the spleen may be associated with several different disease processes. This diversity of primary diseases would lead one to suspect that multiple factors may be concerned in the production of this extra-medullary hematopoiesis. In an attempt to discover what factors may be at work each group of cases will be considered in turn.

From a review of the clinical and pathologic findings in the two cases in Group 1, it is clear that in many ways they are very similar. For example, both had an insidious onset, splenomegaly, slightly raised white blood count and minimal leucoerythroblastosis. In addition, the general architecture of the spleen was well preserved, the myeloid metaplasia chiefly taking the form of poorly demarcated nodules of granulocytic cells with numerous megakaryocytes. The bone marrows were uniformly hyperplastic, megakaryocytes being especially prominent. On the other hand, there was a marked difference in age,

sex and amount of marrow erythropoiesis. Also, the tumor-like nodule of myeloid tissue in the first case and the thrombocythemia in the second case were both features peculiar to only one case.

We believe that both cases are examples of an atypical form of chronic myelogenous leukemia. The almost complete absence of fat from the marrow spaces, together with the intense hyperplasia of the granulocytic elements, provides strong evidence in favor of this view. A striking feature in both cases is the large number of megakaryocytes present in the marrow, and that this is not a rare finding in leukemia was shown by Minot and Buckman (55) in 1925. Erythrocytic hyperplasia, which was present in the second case, is not usually seen in myelogenous leukemia. However, if one accepts the view of Dameshek (38), Rosenthal (1) and others (33, 41) that diseases such as leukemia, polycythemia vera and erythroleukemia are different manifestations of proliferative activity on the part of the multipotent mesenchymal cell, it is not difficult to explain the erythroid hyperplasia in the marrow. We do not feel that the absence of a high leucocyte count in the first case militates against the concept of a leukemic nature for the disease as it is a well-known fact that cases of proven myelogenous leukemia not infrequently retain a normal, or even a leukopenic, count throughout the entire course of the disease. The two differential counts which were performed on this case failed to reveal a leucoerythroblastosis, but McMichael and McNee (12) emphasize that not infrequently repeated examination must be made before this is detected. The reason for the development of a tumor-like nodule of myeloid tissue in the spleen of the first case remains obscure, but it is interesting to note that

several reports (14, 16, 21) of cases manifesting similar lesions have appeared in the literature. In discussing three cases of aleukemic myelosis, Heller, Lewisohn and Palin (30) state that they believe them to be examples of myelogenous leukemia in which the disease process had a reduced intensity and prolonged course. In this way they explain the absence of leukemic infiltrations throughout the body. Esentially, the same concept was stated by Merskey (33), and also Taylor and Simpson (36), a few years later, and it would appear that our two cases are adequately explained on this basis.

As none of our cases was characterized by myelofibrosis we are not in a position to discuss the relationship between myeloid metaplasia and this condition from our experience. However, several authors (20, 30, 33, 41) believe that the hyperplastic marrow present in aleukemic myelosis and sometimes even in leukemia, may later in the course of the disease become fibrotic on the basis of an alteration in the response of the mesenchymal cells to the unknown leukemic stimulus, so that fibroblasts are formed instead of hemocytoblasts. Heller and associates (30), in particular, believe that at any one time some areas of the marrow may be leukemic while others are fibrotic or sclerotic. Several writers (1, 20, 33, 38) state that a similar relationship also exists between polycythemia vera and myelofibrosis. Finally, Wyatt and Sommers (35), and also Peace (47), have presented evidence that many cases of myelofibrosis result from the action of various toxins on the marrow. While they do not claim to know the nature or mode of action of the toxins they believe that

the latter are responsible for small areas of necrosis to which the marrow reacts by compensatory hyperplasia of the undamaged cells. In time, if the action of the toxin continues, the marrow is no longer able to respond by increased hematopoiesis, and fibrosis results. It is not clear whether the accompanying myeloid metaplasia in the spleen and other organs is an attempt to compensate for a damaged marrow or if it is due to the same toxin stimulating the entire mesenchymal system to produce blood forming elements.

It has been known for many years that some cases characterized by skeletal metastases develop foci of extra-medullary hematopoiesis in the spleen and lymph nodes. In addition, Vaughan (13) has reported cases of multiple myeloma with similar myeloid metaplasia. It is surprising that our series does not include at least one case of carcinoma of the prostate which so commonly metastasizes to bone. However, this is probably merely fortuitous as both Weber (6, 7) and Erf and Herbut (29) have described cases in which myeloid metaplasia was associated with prostatic skeletal carcinomatosis.

Authors such as Jordan (10) believe that the myeloid metaplasia in such cases represents an attempt on the part of the spleen and lymph nodes to revert to their fetal state as blood-forming organs, in an effort to compensate for destruction of the marrow. It is difficult to accept this view because, as Vaughan (13) points out, there is an actual increase in the total amount of red marrow in cases of skeletal carcinomatosis as a result of its extension into portions of medullary cavity normally containing only fat. It is conceivable that a case could exist in which all the fatty marrow had become converted into active hematopoietic tissue, the latter then being

replaced by neoplasm so that eventually a diminution in the amount of total active marrow might occur. Cases such as this must be exceedingly rare, but it is only in some such circumstances that we could accept the validity of this compensatory theory for the etiology of the myeloid metaplasia.

The marrow surrounding the nodules of tumor is almost always hyperplastic and it, therefore, appears more likely to us that the destruction of marrow cells causes the release of some substance which not only stimulates the undamaged cells in the marrow to undergo hyperplasia, but also may act on the mesenchymal cells in the spleen causing them to differentiate into hematopoietic elements. It is interesting, in this regard, that Peace (47) quotes experimental evidence which shows that nucleoproteins have a myelostimulatory effect not only in the bone marrow but also in the spleen. The reason why myeloid metaplasia occurs in some cases and not in others in which skeletal carcinomatosis is as widespread, or even more widespread, is not clear. One can only suppose that some individual susceptibility exists. The fact that extra-medullary hematopoiesis in our cases tended to be more extensive in cases showing a leucoerythroblastosis suggests that the immature cells in the circulating blood may have originated in foci of metaplasia in the spleen rather than in the bone marrow itself.

It will be convenient to discuss Groups 3 and 4 together as the cases in both are characterized by some form of liver disease. In the former the pathologic lesion is cirrhosis, while in the latter focal necroses, cholangitis and tumor metastases are represented. Anemia is not a striking feature of these cases and when it does exist

it is not necessarily accompanied by a hyperplastic marrow. Therefore, it does not appear that the hyperplasia of intra-medullary or extra-medullary elements can be explained on the basis of a response to anemia. Nor, as was seen earlier, can the hyperplasia be accounted for by a response to infection.

In describing the histologic changes that occur in the spleen in portal hypertension, Moschcowitz (51) found small intra-sinusoidal foci of extra-medullary hematopoiesis in 10 out of 86 cases. In 5 of these cases the portal hypertension was due to extra-hepatic thrombosis of the portal or splenic vein, and in the other 5 liver disease was present in the form of portal cirrhosis, hemachromatosis and schistosomiasis. Moschcowitz emphasized the fact that the portal hypertension was of prolonged duration in all ten cases and he attributed the presence of myeloid metaplasia to a phylogenetic reversal of the tissue to fetal type, presumably as a result of the hypertension. One cannot deny that such an explanation is a possibility but it certainly would not suffice to explain the occurrence of myeloid metaplasia in the cases in Group 4, or in the 4 cases in Group 3 in which there was no clinical evidence of portal hypertension. Nor did several of the cases of post-hepatic and biliary cirrhosis fulfill the requirement of a prolonged course. However, it should be recorded that several other authors (56, 57) have remarked on the presence of megakaryocytes in the sinusoids of the spleen in cases of Banti's disease.

In discussing chronic marrow failure, myelosclerosis and extra-medullary hematopoiesis, Wyatt and Sommers (35) described 6 cases in

which liver disease and myeloid metaplasia were associated. Two of their cases showed liver dysfunction by liver function tests, one was a post-necrotic cirrhosis and three were examples of hemosiderosis, only one of which had a co-existent cirrhosis. The myeloid metaplasia varied from small foci to complete inundation of the pulp, while the marrow at first showed hyperplasia of all elements with fibrosis developing later. The authors suggest that partial failure on the part of the diseased liver to conjugate substances containing phenol and quinone groups may result in the exposure of the bone marrow to higher concentrations of these compounds which are toxic to immature hematopoietic cells. They note that, as well as various extrinsic chemicals and drugs, adrenal cortical and estrogenic compounds contain phenol & quinone groups. To complete their theory these authors suggest that the breakdown products of marrow cells stimulate both a hyperplasia of surviving cells and also the formation of extra-medullary hematopoiesis. In view of this hypothesis of Wyatt and Sommers, one wonders if the five cases described by Moschowitz (51) in which no mention was made of liver disease might not indeed have had some dysfunction, perhaps as a result of the thrombosis of the portal vein.

Unfortunately, a discrepancy exists between the cases of Wyatt and Sommers (35) and those in Groups 3 and 4, in that marrow fibrosis is absent from all our cases. It is possible that in some cases fibrosis might have developed if the patient had lived longer, but this would not be a valid reason for its absence in many of the other cases in which liver disease had undoubtedly been present for

many years. Moreover, not all our cases showed a hyperplasia of the marrow and thus could not be considered in an early stage of the process. It would, therefore, seem that the theory of Wyatt and Sommers does not adequately explain the myeloid metaplasia in all our cases. It may be that several factors are involved but the nature of these remains obscure at this time.

The cases in Group 5 are characterized by valvular heart disease, renal disease with uremia, and in one case cardiac failure due to hypertension. In Wyatt and Sommers' (35) series of 30 cases of chronic marrow failure with myeloid metaplasia 3 cases had valvular heart disease. They have no hypothesis to offer in explanation of this association and state that it remains to be determined whether or not abnormal abdominal and bone-marrow hemodynamics can be responsible for chronic marrow failure. It is well-known that chronic renal disease is frequently associated with a refractory anemia which, according to Wintrobe, becomes more severe as the nitrogen retention increases. The etiology of this anemia is unknown but it has been suggested that retention in the blood of some substance which is toxic to the bone marrow may be a major factor. In this regard a report by Becher and Litzner (quoted by Wintrobe) (58) is interesting in that they have detected an increase in blood phenols in chronic nephritis with nitrogen retention. It is possible that exposure of the bone marrow to an excess of phenols may be important in the manner outlined by Wyatt and Sommers (35) and described above. In addition, it should be noted that many of our cases in this group showed rather extensive

destruction and necrosis of liver tissue due to chronic passive congestion. This may have resulted in failure of the liver to conjugate completely phenolic, and possibly other substances, which are toxic to bone marrow. It may be that liver dysfunction and retention of toxic substances act synergistically in some cases, while in other cases only one of these factors may be operative.

It is difficult to find an explanation for the occurrence of myeloid metaplasia in the two cases of purpura. Wyatt and Sommers (35) state that myelofibrosis and myeloid metaplasia can develop following prolonged blood loss or destruction and this view is substantiated by reports (22, 39, 45) of myeloid metaplasia occurring in hemolytic anemia. It is conceivable that in thrombotic thrombocytopenia purpura the plugging of small vessels in the bone marrow by thrombi could cause minute infarction with necrosis of hematopoietic cells and release of nucleoproteins which have a myelostimulatory effect. Similar nucleoproteins may also possibly be released from extravasated blood in purpuric hemorrhages or from the breakdown of transfused elements. It seems more likely, however, that the myeloid metaplasia in the spleen represents an effort on the part of that organ to assist the bone marrow, which may be completely hyperplastic and expanded to its limits, in producing enough blood cells to meet the demands caused by constant hemorrhage. These theories are merely conjecture and obviously fail to explain why myeloid metaplasia occurs in some cases of purpura while in the majority there is no specific splenic lesion. It must, therefore, be admitted that at this time the definitive etiology is not known.

The first case in Group 7 was characterized by diabetes mellitus complicated by a widespread granulomatous disease of unknown etiology. It is interesting that endocrine abnormalities, including diabetes mellitus and bilateral orchidectomy, have previously been described (35) in association with myeloid metaplasia. Crail, Alt and Nadler (32) have reported that myeloid metaplasia is found in some cases of miliary tuberculosis. While their cases tended to have a fibrotic marrow, they remark that studies in miliary tuberculosis have indicated that the first reaction is one of hyperplasia followed later by hypoplasia or aplasia. Other authors too (3, 17, 19, 24) have reported on the association of myeloid metaplasia and tuberculosis, particularly of the miliary type, while protozoal (48, 50) and viral (50) diseases have also been implicated. Crail and associates (32) suggest that the tuberculous toxin may act as a stimulus causing differentiation and hyperplasia of the mesenchymal cells in both spleen and bone marrow. On the other hand, Hickling (17), and also Carpenter and Flory (24), believe that the co-existence of myeloid metaplasia and tuberculosis is co-incidental. Provided that the former belief is correct, it seems possible that the myeloid metaplasia in our case might also be the result of a toxin elaborated in the granulomatous lesions.

The second case in Group 7 was an example of Cushing's syndrome in which there was bilateral hyperplasia of the adrenal cortices but in which limited autopsy permission prevented examination of the pituitary. Selye and Stone (59) have shown that when a crude preparation of anterior pituitary extract, which is rich in corticotrophin, is injected into rats there is an intense proliferation of lymphoid and myeloid elements in the spleen, accompanied by the formation of giant

megakaryocytes. As this response does not follow the injection of pure corticotrophin the authors suggest that it may be due to the combined action of the hormone and the products of tissue necrosis caused by the crude preparation. Although Sprague (60) has been unable to demonstrate corticotrophic activity in the blood of patients with Cushing's syndrome, it seems logical to suppose that in cases exhibiting this syndrome in which the primary lesion is in the pituitary some excess corticotrophin might be present. While it is realized that a primary pituitary basis for Cushing's syndrome is very rare and that we have no proof that our case was of this type, it is interesting to speculate that the myeloid metaplasia may be a result of corticotrophic activity. In addition there is the possibility that the condition may have resulted from the excess secretion of adrenal cortical hormones with their content of phenol and quinone groups as discussed under the cases of liver dysfunction above.

From this discussion it is apparent not only that myeloid metaplasia of the spleen is associated with a number of different diseases but also that probably multiple factors are concerned in its production. The majority of these factors are incompletely understood at this time and it would appear that much further study of the problem will be necessary before the etiology is finally elucidated.

Summary

The histologic appearance of 923 spleens weighing over 200 gm. has been studied, the cases being classified according to the condition considered most likely to have caused the splenomegaly. The histologic characteristics of the 53 spleens (5.74 %) which

showed evidence of extra-medullary hematopoiesis have been described in detail. It was found that these 53 cases could be classified in the following groups according to the primary disease from which the patient suffered:

	No. of Cases
1) Aleukemic myelosis	2
2) Skeletal metastases	12
3) Cirrhosis of the liver	18
4) Other liver disease	6
5) Cardio-renal disease	11
6) Purpura	2
7) Miscellaneous	2

Each of these groups have been described in detail, an attempt being made to correlate the extent of the myeloid metaplasia both with the degree of activity of the bone marrow and also with the various clinical and laboratory findings, including blood counts and liver function tests. In this regard the most constant result was the discovery that approximately two-thirds of the cases were associated with a hyperplasia of the bone marrow. Various theories purporting to explain the etiology of myeloid metaplasia have been discussed. It has been concluded that while the probable etiology is known in some of the cases, it remains obscure in others, and certainly no single etiologic factor applicable to all cases is evident at this time.

TABLE I

Causes of splenic enlargement in 923 cases of splenomegaly

Cause of enlargement	No. of cases	%	No. of cases	%
Congestion only	280	30.33		
Congestion plus infarcts	16	1.73		
Congestion plus healed granulomas	5	0.54		
TOTAL CONGESTION			301	32.61
Fibrosis only	97	10.51		
Fibrosis plus infarcts and scars	6	0.65		
TOTAL FIBROSIS			103	11.16
Congestion plus fibrosis only	74	8.02		
Congestion plus fibrosis plus infarcts	7	0.76		
TOTAL CONGESTION PLUS FIBROSIS			81	8.78
Septic only	74	8.02		
Septic plus abscesses	5	0.54		
Septic plus infarcts	14	1.52		
TOTAL SEPTIC			93	10.08
Acute leukemia - type unknown	34	3.68		
Acute leukemia - lymphatic	42	4.55		
Acute leukemia - monocytic	15	1.63		
Acute leukemia - myelogenous	10	1.08		
TOTAL ACUTE LEUKEMIA			101	10.94
Chronic leukemia - lymphatic	27	2.93		
Chronic leukemia - myelogenous	34	3.68		
TOTAL CHRONIC LEUKEMIA			61	6.61
Lymphosarcoma	12	1.30		
Giant follicle lymphoma	3	0.33		
Reticulum cell sarcoma	9	0.98		
Hodgkin's - paragranuloma and granuloma	24	2.60		
Hodgkin's - sarcoma	7	0.76		
TOTAL LYMPHOMAS			55	5.96
Miliary tuberculosis	5	0.54		
Caseous tuberculosis	1	0.11		
Tuberculoma	1	0.11		
Histoplasmosis	4	0.43		
Cryptococcosis	1	0.11		
Lipid granulomas	2	0.22		
Granulomas - etiology unknown	3	0.33		
TOTAL GRANULOMAS			17	1.84
Amyloid disease only	6	0.65		
Amyloid disease plus myeloma infiltrate	1	0.11		
TOTAL AMYLOID DISEASE			7	0.76
Cystic lymphangiomas	2	0.22		
Hemangioma plus cystic lympangioma	1	0.11		
Multiple hemangiomas	1	0.11		
TOTAL BENIGN TUMORS			4	0.43
Metastatic carcinoma - tail of pancreas	2	0.22		
Metastatic cholangioma	1	0.11		
Metastatic peritoneal and pleural mesothelioma	1	0.11		
TOTAL METASTATIC TUMORS			4	0.43
RETICULO-ENDOTHELIAL HYPERPLASIA			15	1.63
HEMOSIDEROSIS			2	0.22
ERYTHROBLASTOSIS FETALIS			14	1.52
MULTIPLE MYELOMA			12	1.30
MYELOID METAPLASIA			53	5.74

TABLE II

Primary diseases associated with 53 cases of myeloid metaplasia of the spleen

Group	Primary disease	No. of cases
1	Aleukemic myelosis	2
2	Tumor involving bone marrow	12
3	Cirrhosis of liver	18
4	Other liver disease	6
5	Cardio-renal disease	11
6	Purpura	2
7	Miscellaneous	2

TABLE III A

Clinical and pathologic data in 2 cases of aleukemic myelosis

No.	Sex	Age	Duration since 1st symptom	Assoc. diseases	Spleen		Liver		State of bone marrow
					Spleen wt. in grams	Degree of myeloid metaplasia	wt. in grams	State of liver	
1	F	78	8 months (edema)	Congestive card. failure; lobar pneum.	1630	Widespread, one nodule of myeloid tissue	2125	Congest. megakaryocytes in sinusoids	Hyperplastic except erythrocytic
2	M	25	7 months (luq pain)	Thrombophleb.; pulm. emboli; splenectomy	1850	Widespread very little erythropoiesis	3700	Congest. megakaryocytes in sinusoids	Hyperplastic, all elements

TABLE III B

Laboratory data in 2 cases of aleukemic myelosis

No.	Time from blood count to death	Hb.	RBC in mil.	WBC	Neut. %	Lymph. %	Mono. %	Eos. %	Promyelo. %	Myelo. %	Meta-myelo. %	Platelets	Remarks
1	8 mo.	78%	4.01	11,900	84	15	1	-	-	-	-	-	-
	2 mo.	73%	3.56	9,200	78	22	-	-	-	-	-	-	-
2	3 yr. 1/2	13.9 gm.	5.01	13,100	82	7	8	1	1	1	-	232,000 1,923,000	- Postoper.
	1 1/2 - mos.		4.22	40,100	89	5	4	-	-	1	1	949,000	Rare normobl. white series immat. to promyelocyte

TABLE IV

Clinical and pathologic data in 12 cases of myeloid metaplasia of the spleen associated with tumor involvement of the bone marrow

Sex	Age	Type & site of primary tumor	Known dur. since 1st symptom	Spleen wt. in grams	Degree of myeloid metaplas.	Bones showing tumor deposits grossly	Bone mar.	Peripheral blood
M	48	Multiple myeloma	4 months	430	moderate	vertebrae, ribs	only tumor visible	anemia, leuco-erythro-blastosis
M	44	multiple myeloma	8 weeks	330	moderate	vert., ribs, skull, pelvis	hyperpl.	anemia, leuco-erythroblast.
M	61	multiple myeloma	found at autopsy	610	scanty	none	hyperpl.	normal, no differential
M	78	multiple myeloma	found at autopsy	630	moderate	none	only tumor visible	anemia, no differential
M	65	adenocarc. rectum	4 months	380	scanty	vert., ribs, sternum	hyperpl.	slight anemia
F	48	adenocarc. sigmoid	1.5 yrs.	260	widespr.	vertebrae	only tumor visible	anemia, leuco-erythroblast.
F	30	adenocarc. sigmoid	2.25 yrs.	355	widespr.	vertebrae, sternum	hyperpl.	anemia, leuco-erythroblast.
M	45	adenocarc. stomach	1 month	375	widespr.	vertebrae, ribs	hyperpl.	anemia, leuco-erythroblast.
M	42	small cell carc. lung	3 months	345	widespr.	none	only tumor visible	anemia, leuco-erythroblast.
M	54	adenocarc. of lung	5 months	410	moderate	vertebrae	hyperpl.	anemia, no differential
M	50	hepatoma	2 months	340	moderate	vertebrae	hyperpl.	anemia
F	41	squam. cell carc. of cervix	5 months	290	widespr.	vertebrae, sternum	only tumor visible	slight anem., leuco-erythroblast.

TABLE V

Relation of the degree of myeloid metaplasia in the spleen to the state of the bone marrow in 39 cases associated with various diseases

Myeloid metaplasia	Marrow hyperplastic	Marrow normal	Marrow hypoplastic	Marrow state unknown	No. of cases
Widespread	3	-	-	-	3
Moderate	8	4	1	1	14
Scanty	13	7	1	1	22
Totals	24	11	2	2	39

TABLE VI

State of marrow in 39 cases of myeloid metaplasia in the spleen associated with various diseases

	Cirrhosis	Other liver disease	Cardiorenal disease	Purpura	Miscellaneous disease	Total
Normal marrow	7	1	3	-	-	11
Hyperplastic marrow	10	4	7	2	1	24
Condition of marrow unknown	1	1	-	-	-	2
Hypoplastic marrow	-	-	1	-	1	2
Total cases	18	6	11	2	2	39

TABLE VII

Relation of anemia to state of marrow in 39 cases of myeloid metaplasia in the spleen

Hb. gm./100 cc.	Marrow hyperplastic	Marrow normal	Marrow hypoplastic	Marrow unknown
Under 12 gm.	14	5	2	1
Over 12 gm.	10	6	-	-

In one case neither the hemoglobin nor the state of the marrow was known.

TABLE VIII A

Clinical and pathologic data in 18 cases of myeloid metaplasia of the spleen associated with cirrhosis of the liver

No.	Sex	Age	Duration since 1st symptom	Primary diseases	Liver wt. in grams	Spleen wt. in grams	Degree of myeloid metaplasia	State of marrow
1	M	77	1 year	Portal cirrhosis, small hepatoma	1080	496	Moderate	Normal
2	M	53	2 mos.	Portal cirrhosis, hepatoma	4500	550	Moderate	Hyperplastic
3	M	54	1 year	Portal cirrhosis, ruptured varices	2390	340	Moderate	Normal
4	M	54	15 mos.	Portal cirrhosis	1850	480	Moderate	Hyperplastic
5	M	56	5 yrs.	Portal cirrhosis, pneumonia	4100	390	Moderate	Hyperplastic
6	M	38	6 wks.	Portal cirrhosis, ruptured varices	1917	430	Scanty	Hyperplastic
7	M	45	6 mos.	Portal cirrhosis, septicemia	3373	965	Scanty	Hyperplastic
8	M	45	5 mos.	Portal cirrhosis, ruptured varices	2660	765	Scanty	Normal
9	M	67	2 mos.	Portal cirrhosis, hepatoma	Large	250	Scanty	Normal
10	F	40	2 yrs.	Portal cirrhosis, peritonitis	710	440	Scanty	Normal
11	F	27	9 mos.	Posthepatitic cirrhosis; pneum.	960	260	Moderate	Hyperplastic
12	M	41	4 wks.	Posthepatitic cirrhosis	3000	315	Scanty	?
13	M	50	3 mos.	Posthepatitic cirrhosis	1425	380	Scanty	Normal
14	F	34	6 mos.	Posthepatitic cirrhosis	1520	385	Scanty	Hyperplastic
15	F	49	2 yrs.	Early biliary cirrhosis	?	500	Moderate	Normal
16	F	43	6 yrs.	Biliary cirrhosis uremia	2075	1300	Scanty	Hyperplastic
17	F	32	6 wks.	Biliary cirrhosis acute cholangitis	1600	550	Scanty	Hyperplastic
18	F	61	4 mos.	Cirrhosis (? type) cholangioma	450	290	Scanty	Hyperplastic

TABLE VIII B

Laboratory data in 18 cases of myeloid metaplasia of the spleen associated with cirrhosis of the liver

No.	Hb. in gm. %	RBC in mil.	WBC	Serum alb. gm/100 cc.	Serum glob. gm/100 cc.	Total prot. gm/100 cc.	Bilirubin Direct mgm/100 cc.	Bilirubin Indir. mgm/100 cc.	Alk. phos. (Bodan. units)	Thymol turbid. units	Ceph. flocc.	Prothr. time in sec.	Blood urea mgm/100 cc.
1	8.9	2.26	3,000				No tests available						
2	15.4	4.88	11,400	2.9	3.6	6.5	14.4	3.4		6	4+		
3	10.0	3.20	11,100	2.8	4.4	7.2	5.3	3.5	4.1	7	3+	36	
4	13.6	3.68	5,100				0	2.2		6	4+	30	
5	15.8	5.06	6,900	In hepatic coma			No tests available						
6	13.1		10,300				No tests available						
7	10.9	3.22	7,200				No tests available						
8	13.8	3.80	6,000				No tests available						
9	12.9	3.70	19,700	2.3	4.1	6.5	3.4	1.2		6		25	
10	12.4		7,200	1.6	3.8	5.4	1.8	1.6		6	4+	32	
11	11.6	3.97	9,400				43.0	13.4				43	
12	11.1	3.41	11,900	2.8	3.6	6.4		5.2			3+	31	
13	15.3	3.80					17.3	4.7		15	4+		
14	13.2	4.25	7,500	2.7	2.9	5.6	3.6	1.9	23.3	4	1+	22	
15	12.0	3.55	6,800	3.0	3.5	6.5	28.0	6.8		2	0		
16	11.6	3.49	4,200	4.3	4.2	8.5	41.0	8.3	11.1	5.5	3+		78
17	11.2	3.45	2,700	2.7	4.0	6.7	6.9	2.0					110
18	11.0	3.52	5,300	2.3	2.6	4.9	5.6	1.8				21	

TABLE IX A

Clinical and pathologic data in 6 cases of myeloid metaplasia of the spleen associated with various diseases of the liver

No.	Sex	Age	Duration since first symptom	Liver disease	Liver wt.in grams	Spleen wt. in grams	Degree of myeloid metapl.	State of marrow
1	F	48	1 year	Necrosis of central zones; bile retent.; pericholangitis; uremia	3400	585	Widespr.	Hyperplastic
2	F	35	6 weeks	Necrosis central zones; postop. strict. bile duct	2800	360	Moderate	?
3	F	60	21 mos.	Carc. g. b., suppur. cholang., bile retent. port. vein thrombosis	2250	665	Moderate	Hyperplastic
4	M	56	5 mos.	Carc. rect.; liver met. focal necr. liver cells; pericholang.	2370	280	Scanty	Hyperplastic
5	F	52	1 mo.	Carc. g. b. with mult. liver met.	2390	390	Scanty	Hyperplastic
6	F	69	1 mo.	Acute cholangitis; postop. choledocholith. uremia	?	325	Scanty	Normal

TABLE IX B

Laboratory data in 6 cases of myeloid metaplasia of the spleen associated with various diseases of the liver

No.	Hb. in gm. %	RBC in mill.	WBC	Serum alb. gm/100 cc.	Serum glob. gm/100 cc.	Total serum prot. gm/100 cc.	Bilirubin Direct mgm/100 cc.	Bilirubin Indir. mgm/100 cc.	Thymol turb. units	Ceph. flocc.	Prothr. time in sec.	Blood urea mgm/100 cc.
1	12.9	4.35	7,500	No tests available								214
2		1.89	26,000				63.6	18.4			76	
3	10.8		8,500	2.7	3.7	6.4	19.6	4.2	6	3+		
4	13.7	4.42	8,400	No tests available								
5	15.0	5.60	18,900					0.6				
6	10.6	3.71	16,100	4.3	3.5	7.8	0.4	0.2			21	130

TABLE X

Clinical, pathologic and laboratory data in 11 cases of myeloid metaplasia of the spleen associated with cardio-renal disease

No.	Sex	Age	Duration since first symptom	Primary disease	Spleen wt. in grams	Degree of myeloid metapl.	State of marrow	State of liver	Blood urea mgm/ 100 cc.	Laboratory data
1	M	22	9 yrs.	Chr. glomerulonephr.; uremia	290	Moderate	Hyperpl.	Sl. cpc	222	Hb.7.6;rbc2.8; wbc 8,600
2	M	55	6 mos.	Malig. nephro-sclerosis; uremia	330	Moderate	Hypopl.	Normal	248	Hb.8.4;rbc 2.57 wbc 8,400
3	F	38	11 d.	Acute malig. nephro-sclerosis; uremia	250	Moderate	Normal	Normal	270	Hb. 9.3; rbc 3.29
4	M	22	5 mos.	Mitr. & aortic sub-acute bacterial endo-carditis	540	Widespr.	Hyperpl.	Mod. cpc	?	Hb. 6.9; rbc 3.21; wbc 20,800
5	F	69	6 mos.	Calcific aortic sten. with failure	370	Scanty	Hyperpl.	Mod. cpc	?	Hb. 13.3; rbc 4.30; wbc 5,900
6	M	26	3 yrs.	Calcif. aortic steno-sis with failure	350	Scanty	Hyperpl.	Severe cpc	?	Hb. 11.4; rbc 3.36; wbc 10,700
7	M	47	5 mos.	Acute L.E. with glomerulonephr.; pneum.	245	Scanty	Normal	Mod. cpc	?	Hb. 9.7; A 3.4; rbc 3.20; G 3.1; wbc 9,400; T 6.6
8	M	63	1 yr.	Calcific aortic stenosis; uremia	226	Scanty	Hyperpl.	Mod. cpc	256	Hb. 15; rbc 5.10; wbc 13,600
9	M	42	15 mo.	Mitral stenosis with failure	260	Scanty	Hyperpl.	Mod. cpc	108	Hb. 10.9; rbc 3.59; wbc 8,500
10	M	66	6 days	Postop. anuria; uremia; cor. scler. pneumonia	270	Scanty	Normal	Severe cpc	228	Hb. 14.0
11	F	50	6 mo.	Hypertension with fail.; jaund.-stones in bile duct at autopsy	365	Scanty	Hyperpl.	Mod. cpc; bile re-tention	136	Hb. 10.0; A 3.3; rbc 4.60; G 4.4; wbc 8,200; T 7.7 thym. turb. 6.5; sl. leuco-erythro-blast.; bil. dir. 6.4, indir. 1.2; alk. phos. 6.4, Bodansky units

TABLE XI

Clinical, pathologic and laboratory data in 2 cases of myeloid metaplasia of the spleen associated with idiopathic purpura

No.	Sex	Age	Duration since first sympt.	Primary disease	Spleen wt. in grams	Degree of myeloid metapl.	State of marrow	State of liver	Peripheral blood
1	F	14	6 mos.	Thrombocytopenic purp.; splenect.; intra-perit.hem.	475	Widespr.	Hyperpl.	Normal apart from mod.myel. metaplasia	Hb.6.8;rbc 2.95 wbc 8700; platelets 46,000;leuco-erythroblast.
2	F	22	2 mos.	Thrombotic thrombocyt. purp.;malig.thymoma spread to nodes and lung	510	Moderate	Hyperpl.	Normal apart from moderate myel.metaplas.	Hb. 7.5; rbc 1.80; wbc 8,400;platelets 32000;leuco-erythroblasto-sis

TABLE XII

Clinical, pathologic and laboratory data in 2 cases of myeloid metaplasia of the spleen associated with miscellaneous diseases

No.	Sex	Age	Duration since first symptom	Primary disease	Spleen wt. in grams	Degree of myeloid metapl.	State of marrow	State of liver	Peripheral bl.	Laboratory data
1	F	41	3 mos.	Diab.mell.;mult. gran.all org. - etiol. unknown; coma	680	Moderate	Hyperpl.	Noncaseating gran chr. peri cholang.	Hb.10.0;wbc 2000;leuco-erythro-blastosis	Blood urea 80 mgm/100 cc; bl.sug. 611 mgm.100 cc.
2	F	22	18 mo.	Cushing's syndrome; perinephric absc.; renal calculi	365	Scanty	Hypopl.	Sl.fatty change	Hb.11.4;rbc 4.08;wbc 4600;leuco-erythro-blastosis	A 3.4; G 2.8; T 5.6; bl. sug. 245 mgm/100 cc.

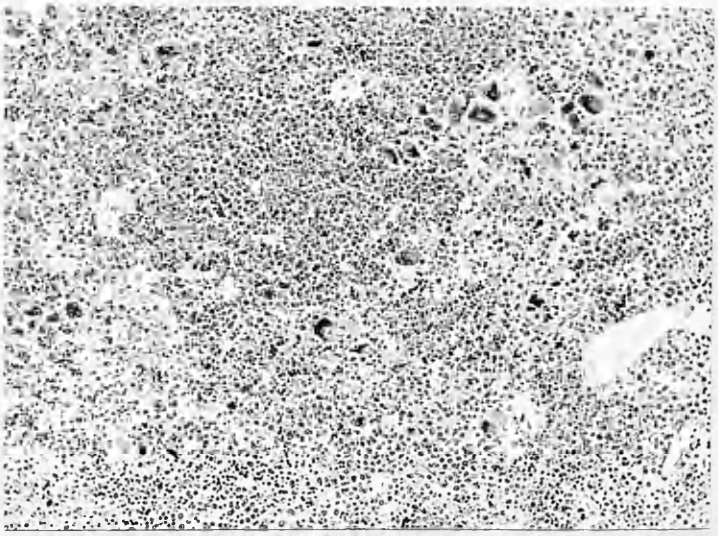

Figure 1. (H & E, x110). Spleen in a case of aleukemic myelosis. (Table III, case 1). The section is of a tumor-like nodule which resembles hyperplastic bone marrow. Cells of the erythrocytic, granulocytic and thrombocytic series are present in all stages of development. No trace of normal splenic architecture remains in this area. Note the resemblance between this picture and the bone marrow in the same case (Figure 2) and in another case of aleukemic myelosis (Figure 4).

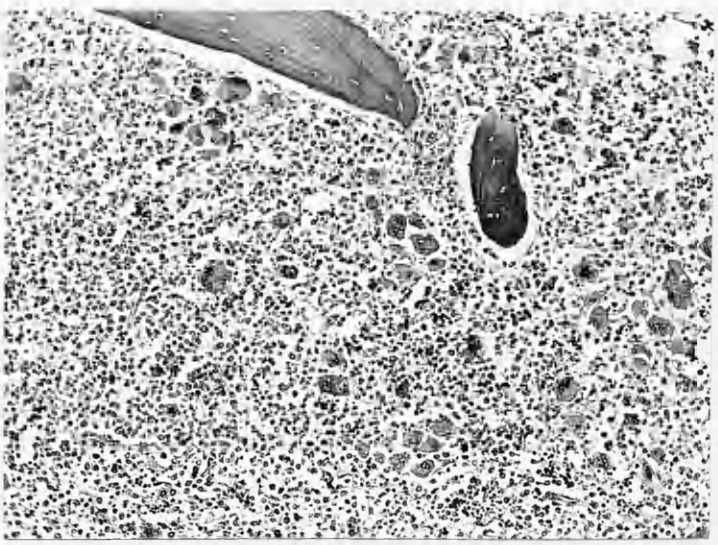

Figure 2. (H & E, x110). Vertebral bone marrow in a case of aleukemic myelosis (Table III, case 1). There is almost complete replacement of fat by hyperplastic hematopoietic elements. The hyperplasia chiefly affects cells of the granulocytic and thrombocytic series with a definite reduction in erythropoietic activity.

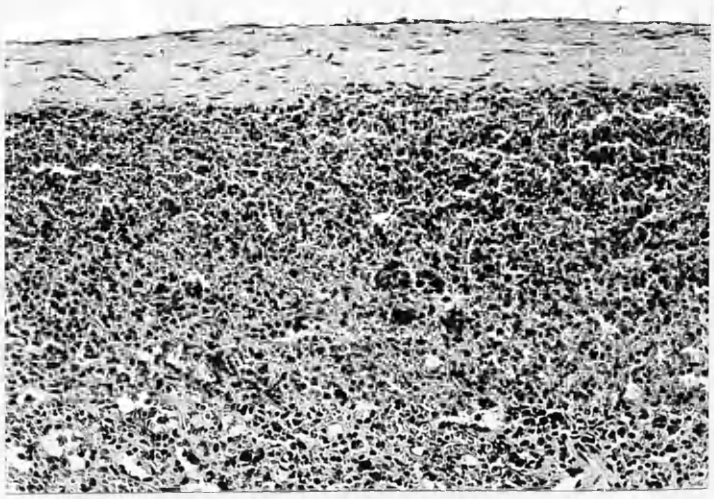

Figure 3. (H & E, x165). Subcapsular region of the spleen in a case of aleukemic myelosis (Table III, case 2). Widespread myeloid metaplasia is visible involving mainly myeloblasts and myelocytes. A megakaryocyte is visible near the center of the field.

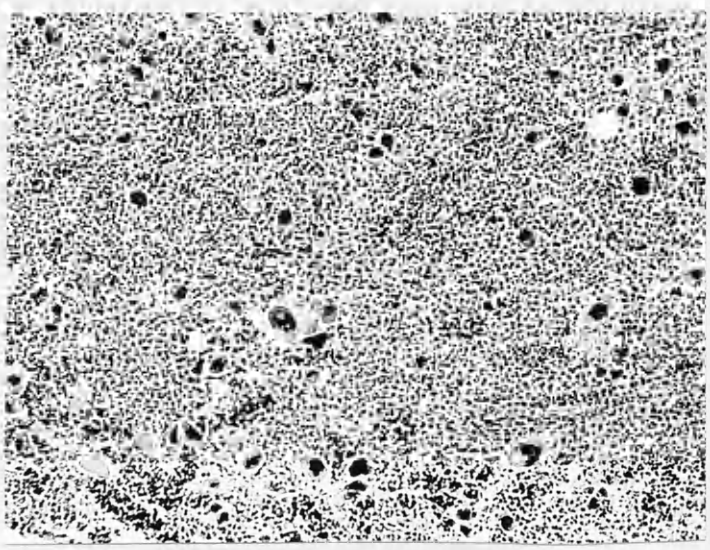

Figure 4. (H & E, x110). Vertebral bone marrow in a case of aleukemic myelosis (Table III, case 2). There is almost complete replacement of the fat by hyperplastic hematopoietic elements. While the hyperplasia affects all three series, the large number of megakaryocytes showing hyperchromatic and distorted nuclei is especially striking.

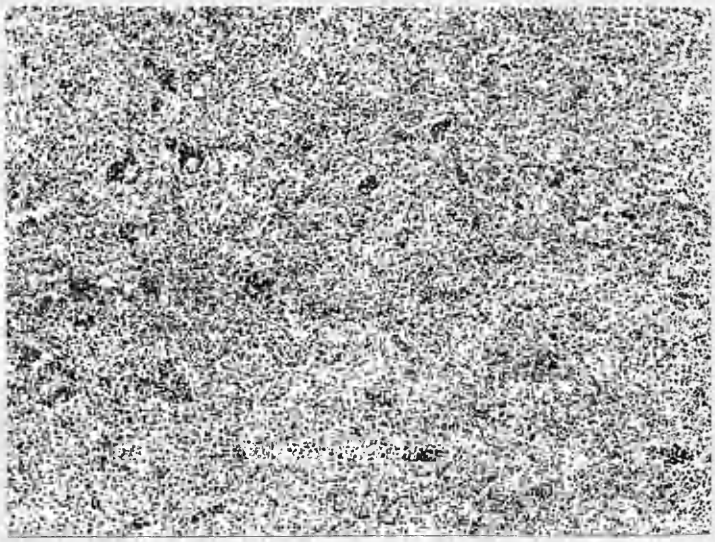

Figure 5a. (H & E, x110). Widespread myeloid metaplasia of the spleen. Clusters of hematopoietic cells are visible in the sinusoids, with widespread infiltration of the surrounding pulp.

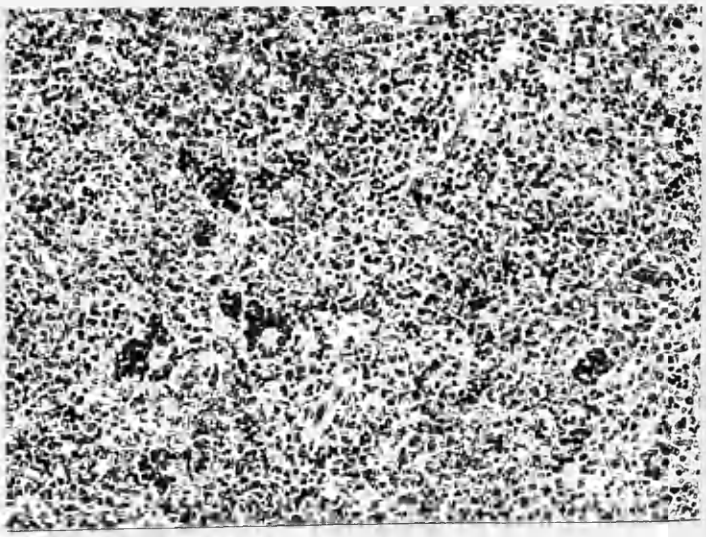

Figure 5b. (H & E, x200). Higher magnification of part of Figure 5a. Hematopoietic elements, consisting mostly of myeloblasts, myelocytes and normoblasts, are visible both in the sinusoids and extending into the pulp.

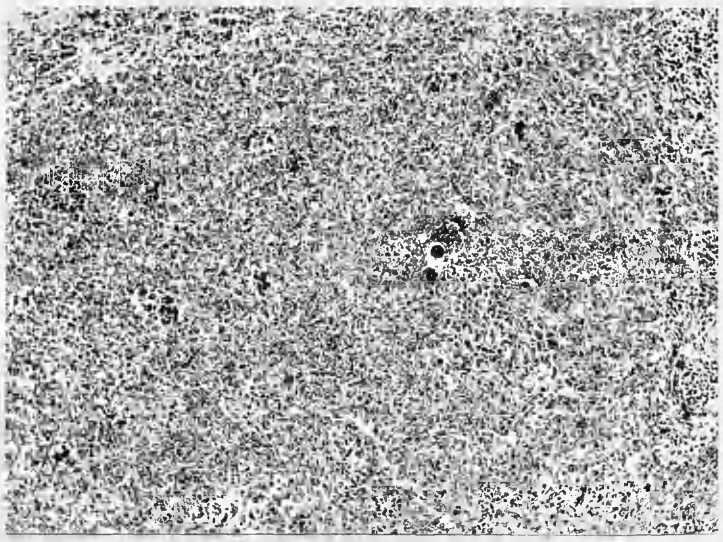

Figure 6a. (H & E, x110). Moderate myeloid metaplasia of the spleen. Intra-sinusoidal collections of hematopoietic elements are visible. Infiltration of the pulp is also present but is less extensive than in Figure 5.

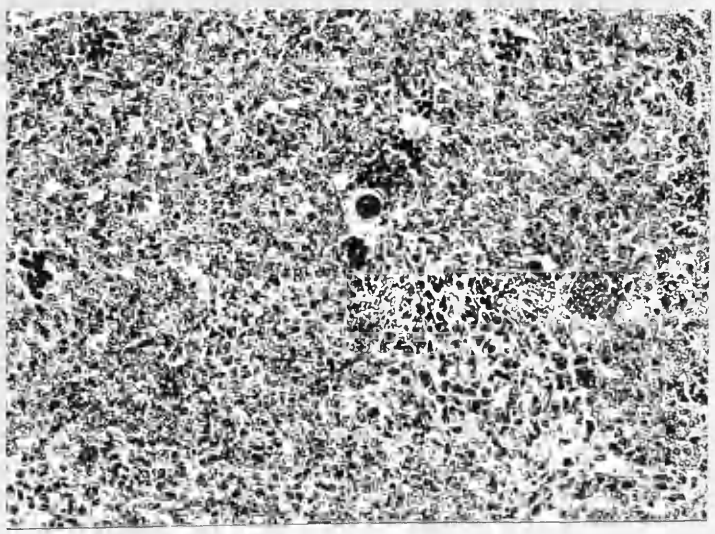

Figure 6b. (H & E, x200). Higher magnification of part of Figure 6a. A megakaryocyte and some myelocytes occupy the sinusoid in the center of the field. Just above this a cluster of normoblasts have infiltrated the pulp.

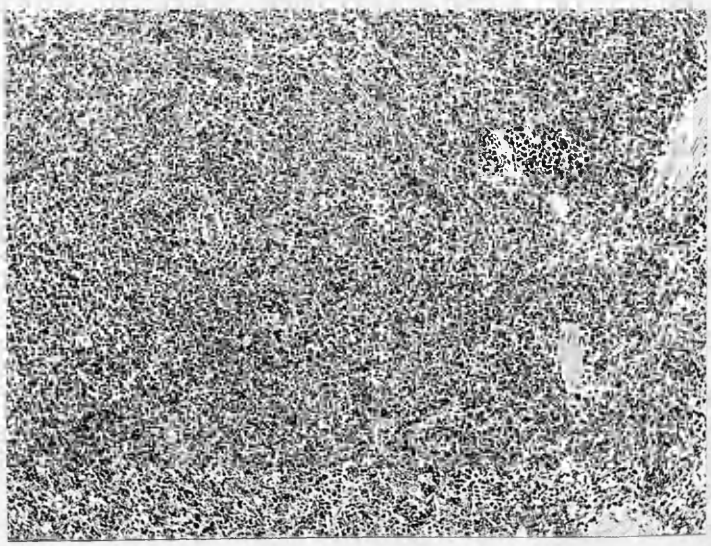

Figure 7. (H & E, x110). Scanty myeloid metaplasia of the spleen. Hematopoietic cells are more widely spaced than in either Figure 5 or Figure 6. This field shows rather more infiltration of the pulp than is usual in the group classified as scanty metaplasia.

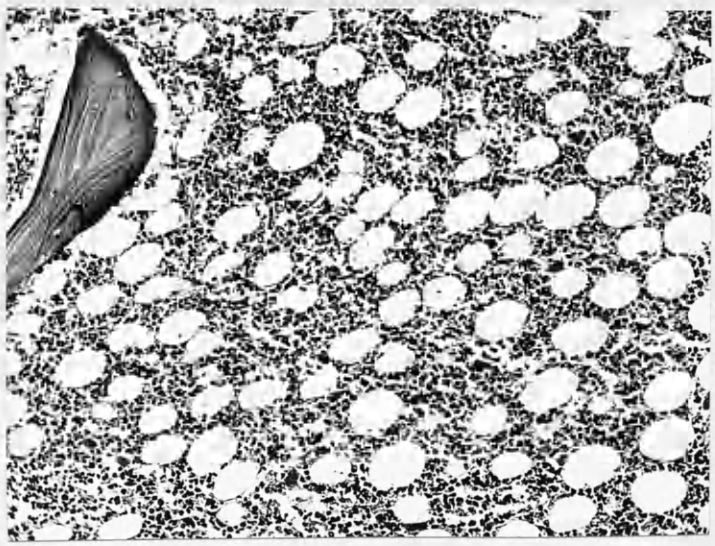

Figure 8. (H & E, x110). Sternal bone marrow showing normal activity. Approximately equal amounts of fat and hematopoietic tissue are present and cells of all three series are represented in normal proportion. Taken from a case of moderate myeloid metaplasia of the spleen associated with early biliary cirrhosis. (Table VIII, case 15).

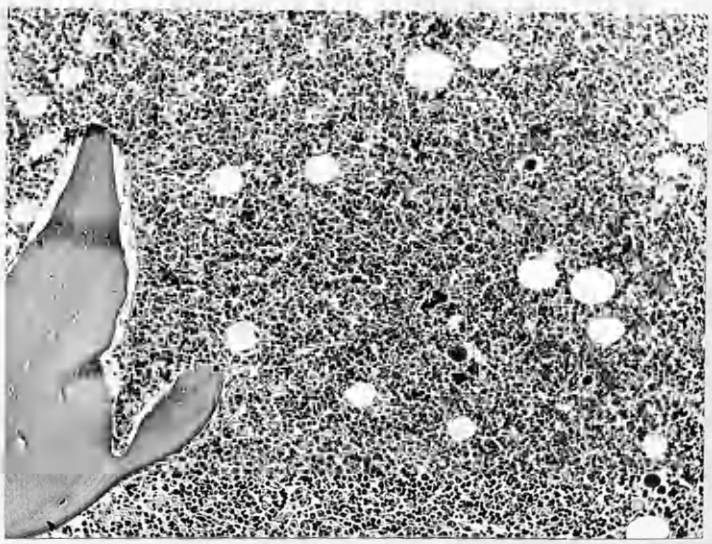

Figure 9. (H & E, x110). Hyperplasia of vertebral bone marrow. There is a marked increase in the number of cells of all three hematopoietic series, with a corresponding reduction in the amount of fat. Taken from a case showing moderate myeloid metaplasia of the spleen associated with liver disease. (Table IX, case 3).

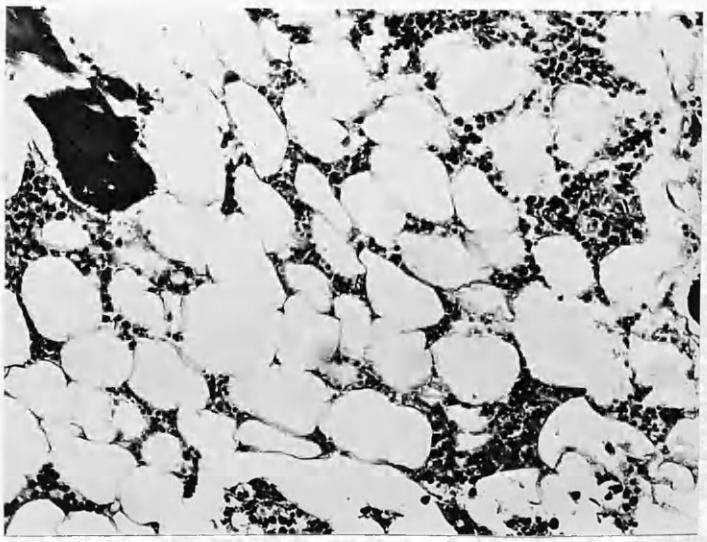

Figure 10. (H & E, x165). Hypoplastic bone marrow showing great increase of fat with reduction in all elements of the hematopoietic tissue. Taken from a case of Cushing's syndrome. (Table XII, case 2).

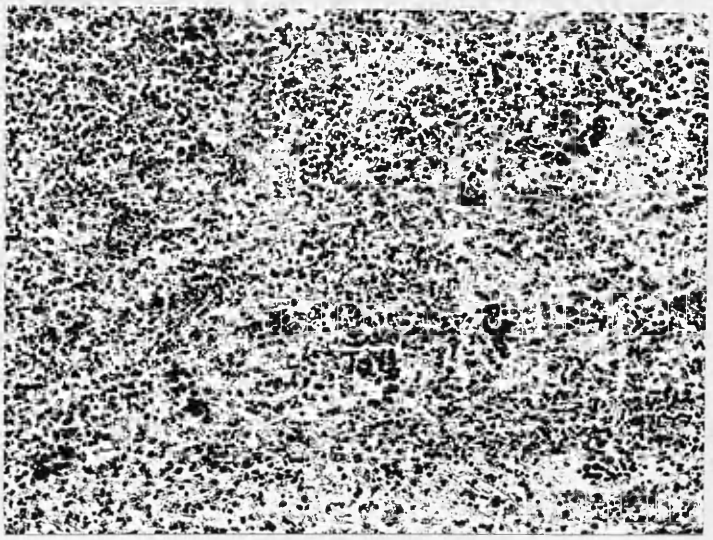

Figure 11. (H & E, x165). Very widespread myeloid metaplasia in a case of thrombocytopenic purpura (Table XI, case 1). As well as clusters of myeloblasts, myelocytes, erythroblasts and normoblasts in the sinusoids there is diffuse and marked infiltration of the pulp by these cells.

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