CHRONIC MARROW FAILURE, MYELOSCLEROSIS AND EXTRAMEDULLARY HEMATOPOIESIS

By John P. Wyatt, M.D., and Sheldon C. Sommers, M.D.

When Heuck,^ seventy years ago, reported a case of generalized osteosclerosis with marked hepatosplenomegaly, anemia, hyperplastic lymph nodes and extreme leukocytosis, a controversy began over the nature of this condition which still continues. Such clinical pictures are infrequent, most commonly discovered in investigation of a case of splenomegaly in the older age groups, and associated with anemia, leukocytosis or a leukemoid reaction. Less commonly hepatomegaly, jaundice, purpura, or gout are prominent. The erythrocyte, leukocyte and platelet counts may be low, normal or elevated, and immature cells are often present in the circulation. It is now generally accepted that the bone marrow, rather than the spleen or peripheral blood, is primarily at fault. The chief argument concerns whether the changes are reactive or neoplastic, and is reflected in a confusing nomenclature. Over twenty-five terms are extant,^ combining in different phrases anemia, erythroblastosis, hepatosplenomegaly, myelofibrosis, myeloid metaplasia, myelosis, osteosclerosis, and pseudo-leukemia.

The present study of 30 cases, including 10 autopsied, represents an attempt to find clues to the origin, morphology and nature of this clinicopathologic montage. The salient observations made were: (1) Necrosis of partly matured erythroid and myeloid bone marrow cells was the fundamental primary lesion. (2) Reactive overgrowth of the surviving, usually more immature, cells followed. (3) Extramedullary hematopoiesis identical with that in other diseases developed. (4) Integrity and eventual overgrowth of reticulum and stromal tissues were uniformly visible in marrow and sites of myeloid metaplasia. Hematopoietic cells occasionally underwent violent hyperplasia, but the invasive property of leukemic and other neoplastic cells was acquired only exceptionally. (5) Histories and retrospective analysis of laboratory data, often incomplete, pointed to the etiologic importance of the same agencies as Bomford and Rhoads^ uncovered in "refractory" anemia. (6) A logical working hypothesis of the pathogenesis could be synthesized from these data for investigative and therapeutic testing. The importance of differentiating this disease from myelogenous leukemia is no longer mainly academic, because the usual therapy of leukemia is contraindicated, as is splenectomy.

The earlier cases reported in the German literature^ were classified as leukemia. Leukemia at that time meant a leukocytosis with some immature cells, regardless of accompanying tissue alterations. These cases were considered atypical because autopsy showed no neoplastic changes of the marrow or viscera. Examples of typical lymphatic or myelogenous leukemic marrow with myelosclerosis not attributable to radiation have been recorded in the past, but they are usually
poorly documented, unconvincing and undeserving of emphasis. Neumann and Donhauser were first to consider the splenic, hepatic and other extrasosseous foci of hematopoietic cells found in such cases as representing compensatory assumption of blood formation no longer possible in the diseased bone marrow. It was appreciated that this extramedullary hematopoiesis tended to be most marked in viscera which had actively formed blood cells during embryonic life. Although it is at present generally agreed that myelocytes and nucleated red cells in the peripheral blood are not certain indicators of myelogenous leukemia, many pathologists still consider myelosclerosis with myeloid metaplasia a variant of leukemia.

**PATHOLOGIC ANATOMY AND HISTOLOGY**

Bone marrow biopsies from 10 living patients with clinical "myeloid metaplasia" studied at the beginning of the investigation showed a recognizable and rather characteristic appearance with variations attributable to different stages of the disease process. Cases seen at autopsy were also collected, which showed gross and histologic findings of the same type. Clinical diagnoses in the latter group comprised "myeloid metaplasia," myelogenous leukemia, lymphoma, benzol poisoning and refractory anemia. The original pathologic diagnoses also varied. For inclusion in this series, certain tissue changes of uniform type were required, regardless of clinical history, hematologic data or previous diagnoses.

The gross appearance of the organs in an autopsy case will suggest the presence of this condition. The spleen is enlarged from three to thirty times the normal weight, with a smooth shining capsule or one thickened by perisplenitis and scars. On section, the splenic pulp is usually deep red with a grey or brown cast and the follicles are almost never visible. Fibrosis is at times indicated by resistance to cutting. In some cases infarcts are present and there may be dark red or brown spherical demarcated nodules of bulging soft tissue (fig. 9). The liver is also enlarged one and one-half to four times the usual weight. On section, the parenchyma is congested but as a rule does not appear otherwise abnormal. In particular, the fine grey pattern of leukemic infiltrates is not present. Application of the Prussian blue reaction will often demonstrate increased iron. Lymph nodes are not notably enlarged.

Bone marrow of long bones, skull, vertebrae, pelvis, ribs and sternum shows uniform change. All the marrow may be deep red, moist and succulent, displacing the usually intermingled yellow fat and appearing grossly hyperplastic. In other cases the bones may be uniformly dense, grey-white and hard with thickened cortices and without any well defined marrow spaces, or may show small scattered foci of red or yellow marrow. (figs. 1 and 2).

These findings taken together are rather infrequent. They are mimicked at autopsy most closely by those occasional cases of carcinoma of breast, prostate or other organs with a predilection for osteosclerotic metastases to marrow. Such cases of metastatic cancer are distinguishable by the macroscopic masses of tumor found in the liver, lungs, lymph nodes or other viscera. Infiltrates of myelogenous or lymphatic leukemia in the liver, lung, kidney, spleen and lymph nodes have a distinctive yellow-grey pattern and a focal increased consistency not part of the
hepatosplenomegaly under discussion. Hodgkin's disease in the spleen, liver and marrow produces marbled deposits of a varicolored tan, grey or yellow with prominent focal hemorrhages, softenings and scarring.

Microscopic appearances of the bone marrow are of the greatest importance for a final diagnosis. In the earliest stage observed in this series, marked hyperplasia of marrow cells is present, with partial or practically complete displacement of the normal fat (figs. 3, 4). Both myelopoietic and erythropoietic elements are increased. Usually groups of myeloblasts and myelocytes are recognizable and similar clumps of erythroblasts and normoblasts, with an increase in the number of component cells. Sometimes these groups of hematopoietic cells are so crowded to-
Fig. 3. (Upper left)—Case 1. Vertebral marrow. Marked reduction of fat cells, with hyperplasia of all types of mature hematopoietic cells. Hematoxylin and eosin stain. X 500.

Fig. 4. (Upper right)—Case 22. Vertebral marrow. Reticulum cells, megakaryocytes and normoblasts identifiable. Group pattern preserved. No replacement of bone by hyperplastic marrow found. Hematoxylin and eosin stain. X 500.

Fig. 5. (Lower left)—Case 23. Sternal marrow, biopsy. Megakaryocytes and mature elements present. Early myelosclerosis indicated by fusiform nuclei. Hematoxylin and eosin stain. X 500.

Fig. 6. (Lower right)—Case 28. Vertebral marrow. Myelosclerosis and irregular pattern of osteosclerosis with prominent cement lines. Marked reduction of marrow constituents. Vascular channels prominent. Hematoxylin and eosin stain. X 250.
marrow reticulum cells, not usually prominent in marrow preparations, are increased in size and number, forming linear and curved septations which give the histologic preparations a rather characteristic subdivided or compartmented appearance under low power magnification. The hyperplastic marrow abuts against and distorts the reticulum without breaking or destroying it (figs. 4 and 5). This feature will aid in distinguishing between the violent hyperplastic cases and frank leukemias. Sheets of neoplastic hematopoietic cells have not been found stretching from one bone trabecula to the next as in leukemia.

Later in the disease, marrow atrophy supervenes. Foci in the marrow become practically or completely devoid of hematopoietic cells. The reticulum and vascular endothelial cells remain viable and a few scattered, nondescript, small, rounded elements, possibly stem cells, represent the only surviving blood-forming tissue. Megakaryocytes also tend to remain longer in the aplastic areas. Fat cells are still few in number. The regions of atrophy are at first relatively small, localized and surrounded by masses of hyperplastic marrow (fig. 5). With time, however, most of the marrow is destroyed and a search is required to find persisting islands of active blood cell formation. The histologic appearance differs from hypoplastic or aplastic marrows usually seen, in that the whole soft tissue mass is altered in architecture. The structure is not that of a normal marrow from which the blood-forming cells have been erased. The marrow reticulum is equal to, or more prominent than before and its cells, with the vascular endothelium, now comprise the majority of the living components. The loose network of reticulum is filled in histologic preparations by a pink, finely granular or vacuolated material resembling coagulated protein-containing fluid. On the fixed and stained slide it often appears gelatinous, but is probably fluid in vivo. At other times the intercellular matrix is slightly laminated parallel to the axes of reticulum cells and around blood vessels, simulating collagen formation. Not infrequently, however, special stains, such as the Masson-Goldner trichrome, demonstrate little in the way of collagen. The term "myelofibrosis" for this condition is thus misleading and use of myelosclerosis is preferable in describing this sequel of completed chronic marrow failure. Presence of fibrin or hemorrhage in the myelosclerotic matrix is uncommon, although some macrophages laden with hemosiderin may be present.

Blood vessels and sinusoids of the marrow in the hyperplastic stage are generally of normal appearance except for some enlargement of their endothelial nuclei. Hematopoiesis is observed both outside and inside the sinusoids, and as areas of atrophy appear, continued formation of blood cells is noted longest within and immediately around vessels. The more prominent the reticulum network becomes in the sclerotic marrow, the more dilated are the blood vessels, possibly due to the pull of the long narrow cytoplasmic processes of the reticulum cells. The microscopic picture when these different changes are all well developed may be summarized as follows:

The marrow is relatively acellular, made up of scattered reticulum cells between which is a pink fibrillar or granular matrix and with numerous dilated empty vessels surrounded by small groups of bizarre megakaryocytes or nondescript small hematopoietic cells.
The end stage in a certain number of cases with myelosclerotic atrophy of marrow involves a distinct type of new bone formation, well described in the German literature, but which has elsewhere received less attention. In the earliest phase of this fretwork osteosclerosis focal granular deposits of calcium are found in the eosinophilic matrix where reticulum cell nuclei lie parallel and close to a trabecular surface. After the matrix is calcified, bone is deposited in a layer about part or all of the old trabecular surfaces.

Prominent cement lines permanently demarcate the margins of the original trabeculae. This process, at first focal, is often later generalized but irregular and the eventual trabecular pattern is quite tortuous with jutting rounded thickenings of spongy bone. There is no mosaic pattern as in Paget’s disease and practically no osteoblastic or osteoclastic activity. In more marked instances of this osteosclerosis, complete new bone trabeculae are also formed in the original marrow spaces by similar precipitation of calcium in the fluid or gelatinous reticular matrix, with an intermediate osteoid stage before ossification is complete. The new trabeculae are markedly irregular in thickness and direction, with free unattached ends. The fretwork pattern produced has thus an interesting and apparently characteristic histologic appearance (figs. 6 and 7). Reticulum cells are caught within some of the new-formed bone and remain as osteocytes, but are neither as regularly oriented nor spaced as in normal bone. The marrow cavity remains sclerotic with an amorphous or fibrillar non-collagenous reticulum.

The histopathology of the spleen reveals variable amounts of extramedullary hematopoiesis in the red pulp. Sinusoidal lining cells are enlarged, proliferating and desquamating into the lumens. These cells when free and rounded in shape are identical in appearance with hematopoietic stem cells and form the most primitive blood cell elements identified. Associated with these stem cells, inside and at times around the sinusoids, are groups of up to ten hematopoietic cells, among which are found many myeloblasts, myelocytes, erythroblasts, normoblasts and the occasional megakaryocyte (fig. 10). As in normal marrow, small clumps of the same lineage are characteristically massed together. The extramedullary hematopoiesis differs from that found in other pathologic conditions mainly in amount and degree of differentiation. In individuals with this bone marrow dystrophy varying amounts of hematopoiesis are found ranging from scattered small cell groups to inundation of the entire red pulp. The splenic follicles take no part in hematopoiesis; in the more extreme cases a few marrow elements mingle with the most peripheral lymphoid cells. In such cases, although the splenic reticulum is stretched and compressed by cellular proliferation, it is not broken up or destroyed as in malignant neoplasms, such as leukemia. The hematopoietic cells retain a semblance of grouping by relationships and include as a rule representatives of the three major marrow cell families. Regions of organized hemorrhage sometimes are the site of vigorous hematopoiesis with formation of the dark red nodules described grossly.

Other less striking splenic changes include some reticular proliferation, some fibrosis and deposits of iron pigment in macrophages. Phagocytosis and necrosis of hematopoietic elements are not seen except after local radiation.
Fig. 7. (Upper left) Case 13. Sternal marrow, autopsy. Characteristic picture of terminal osteosclerosis showing prominent fretwork bone pattern. Phosphotungstic acid-iron hematoxylin stain. X 50.

Fig. 8. (Upper right) Case 18. Liver. Intrasinusoidal hematopoiesis with various cell types. Megakaryocytes prominent. Hematoxylin and eosin stain. X 500.

Fig. 9. (Lower left) Case 14. Spleen, 735 Gm. Moderate enlargement with large demarcated hemorrhagic nodules, demonstrating hematopoiesis microscopically. About 1/4 life size.

Fig. 10. (Lower right) Case 18. Spleen. Focus of extramedullary hematopoiesis with prominent megakaryocytes and surrounding myeloblasts, myelocytes and erythroblasts. Hematoxylin and eosin stain. X 500.
In the liver, hematopoiesis is also observed (fig. 8). It is uniformly less marked than that found in the spleen, which is reflected in the proportionally smaller weight gain. Groups of granulopoietic and erythropoietic cells can be identified, lying in and dilating the sinusoids locally. Megakaryocytes are usually found singly. The liver architecture is rarely altered and there are no cellular infiltrates in portal areas or vessel walls, such as characterize the leukemias. Iron-containing pigment in variable amounts is present.

Hematopoiesis in spleen and liver, like the marrow, has a tendency with time to show an increasing proportion of more immature cells, especially stem cells.

If the disease progresses slowly enough, at autopsy there may be no differentiated tissue blood cell forms present except for occasional megakaryocytes. As the persisting stem cells continue to show the same localization, grouping and growth properties as other hematopoietic elements, no histologic evidence can be adduced that they are neoplastic. Conversely, if extramedullary hematopoiesis is regarded as compensatory in this condition, as in all others in which it is found, progressive lessening of its differentiation can be recognized as a qualitative failure of blood cell replacement similar to that which earlier affected the bone marrow.

Lymph nodes usually contain proportionally less hematopoiesis than liver or spleen, but it may be quite prominent (fig. 11). Like the sinusoidal endothelium of spleen and liver, cells lining the lymph node sinusoids become enlarged with
pale finely stippled nuclei. These may lie as a cellular desquamate in the lumens, where they are indistinguishable from hematopoietic stem cells. Small groups of myeloid and erythroid cells and scattered bizarre megakaryocytes are found in the sinusoids, dilating them but not often producing a clinically apparent lymphadenopathy. With time, proportionally more stem cells are seen, making a striking picture (fig. 12). Differentiation from Hodgkin's disease should not prove difficult in an isolated biopsy if one holds close to the accepted criteria for distinguishing between megakaryocytes and Reed-Sternberg cells. In addition, the lymphoid tissue shows minimal hyperplasia, and normal node architecture is preserved without necrosis or fibrosis.

Other sites of extramedullary hematopoiesis are less regularly present. Fat surrounding the renal pelvis will occasionally show intermingled hematopoiesis in proportions closely simulating normal bone marrow. Rarely the subserosal fat of the gastrointestinal tract will contain marrow foci. Small foci of blood cell formation also exist occasionally in sinusoids of the adrenal cortical and kidney parenchyma, particularly near the corticomedullary boundary. Qualitatively these foci resemble those already described.

With the presence of widespread blood cell formation in sinusoids of many organs beside bone marrow, it is easy to understand that immature forms may often be found in blood smears, including erythroblasts, normoblasts, myeloblasts, myelocytes, unidentifiable blast cells and rarely megakaryocytes. As the mechanism regulating the number of circulating blood cells is not yet understood, fluctuating levels of erythrocytes, granulocytes and platelets are difficult to analyze. It is, however, clear that leukocytosis and immature circulating leukocytes no longer can suffice alone for the diagnosis of leukemia.

Clinical Aspects

In the literature consulted, 129 adequately studied acceptable cases of this same morphologic entity were found, and there are numerous other less accessible reports. Sixty-one were men and 54 women. The age range was 17 months to 79 years, including three infants and one child. There were 7 patients aged 20-30 years, 10 aged 31-40 years, 27 at 41-50 years, 35 at 51-60 years, 19 at 61-70 years and 5 at 71-79 years. Bone marrow structure was described as normal in 2 cases, atrophic in 2, hyperplastic in 16, myelosclerotic in 32 and osteosclerotic in 48 cases. Nine writers considered the condition leukemic, 29 believed it to be reactive and not neoplastic, and 12 were undecided.

The present series of 30 cases included 18 men and 12 women, with an age range of 25 to 72 years. Twenty-two patients were 51-70 years old. The duration of the disease was from 12 months to about 20 years. Details are given in table 1.

Cases 1-4 had histories of rather severe and usually prolonged exposure to benzol. The first 2 patients were daughter and father. The latter, an enthusiastic amateur painter, used about five gallons of 60 per cent benzol paint remover yearly in his home for over six years, and his daughter was exposed to the fumes for eleven months. Both cases had recognized medicolegal status as benzol poisoning. Case 3 had been exposed to gasoline fumes for twenty-six years and paint remover fumes
### Table 1. — Summary of Clinical Data in Thirty Cases of Chronic Bone Marrow Failure, Myelosclerosis and Osteosclerosis (See footnotes for abbreviations.)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>R.B.C. (Million/cmm.)</th>
<th>W.B.C. (Thousands/cmm.)</th>
<th>Immature (per cent)</th>
<th>Bone Marrow</th>
<th>Spleen</th>
<th>Liver</th>
<th>Lymph Nodes</th>
<th>Remarks</th>
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<td>2.0-4.0</td>
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<td>—</td>
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<tr>
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<td>4.0-12.4</td>
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<td>—</td>
<td>—</td>
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<td>2.3-10.5</td>
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<td>Hyp.</td>
<td>—</td>
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<td>Hypo-plasia</td>
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<td>Ms.</td>
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<td>Hypo. &amp; Ms.</td>
<td>—</td>
<td>—</td>
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Footnotes:
- Hyp: Hypoplasia
- R-E: Reticulo-Endothelial System
- Enl: Enlarged
- My: Myeloid
- Met: Mononuclear
- Gm: Granulocyte
- Stem: Stem cells

Remarks:
- Fatal lobar pneumonia and agranulocytosis.
- Severe anemia and hemorrhages.
- Hematopoiesis also in omentum, adrenal and kidney.
- Progressively less mature hematopoiesis.
- Bronchopneumonia, hemorrhages.
- Terminal auricular fibrillation and ascites. Cirrhosis.
- Obesity, refractory anemia.
- Oral hemorrhage, petechiae.
- "Toxic" polymorphonuclear. Final course unknown.
- Macrocystosis. Fragility normal. Gout, liver dysfunction.
- Terminal miliary tuberculosis. Cirrhosis.
- Many transfusions. Liver hemosiderosis.
- Refractory anemia. Liver hemosiderosis.
- Portal cirrhosis and hemosiderosis. Urinary sepsis.


<table>
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<th>Case No.</th>
<th>Age (yrs.)</th>
<th>Sex</th>
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<th>W. R. C. (Thousands/mm³)</th>
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<th>Spleen</th>
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<td>1080</td>
<td>My. Met.</td>
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<td>57</td>
<td>F</td>
<td>3.3-3.6</td>
<td>2.0-5.1</td>
<td>2-16</td>
<td>11-20</td>
<td>1080</td>
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<td>28.*</td>
<td>63</td>
<td>M</td>
<td>2.0-3.8</td>
<td>11.44.0</td>
<td>1-4</td>
<td>13-4</td>
<td>1320</td>
<td>My. Met.</td>
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<td>29.*</td>
<td>36</td>
<td>F</td>
<td>2.8</td>
<td>11.12.6</td>
<td>+</td>
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<td>610</td>
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<td>30.</td>
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<td>15.7-17.5</td>
<td>2</td>
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for nine additional years. He showed leukemic infiltrations at autopsy, restricted
to the liver and possibly arising there. Case 4* employed benzol paint remover for
over seven years. Both experimentally23, 24 and clinically, 25–27 benzene is known
to produce necrosis of all types of hematopoietic cells, as well as neoplastic-like
or leukemic changes.21 It is also implicated in refractory anemia.3 It is notable
that of 10 cases first reported as "agnogenic myeloid metaplasia," 29 6 were later
found to have occupational exposures to related industrial solvents.30

In Cases 5 and 6, radiation therapy had been administered intermittently for
several years, in total doses of 12,000 and 7,500 r respectively. In Case 6, lymphoma
was suspected, but never proved morphologically, and in retrospect, postnecrotic
cirrhosis could be blamed for the symptoms. It is known that ionizing radiation
produces necrosis of all bone marrow elements.31 32 The exposure required for
development of chronic marrow failure apparently must be long continued and of
low or moderate amount. No cases have followed instantaneous heavy exposure,
as in atomic warfare.33 The most thoroughly studied human instances of chronic
radiation are the radium dial painters,34 and through the courtesy of Dr. Harrison
Martland it was possible to review some of his material for comparison with the
present cases. Histologically, the sequences of extreme marrow hyperplasia followed
by replacement sclerosis are identical in radium poisoning and chronic marrow
failure of diverse etiology. In Martland’s cases, however, local radiation led
further to marked anaplasia of marrow reticulum and osteogenic sarcomas.
Extra-medullary hematopoiesis was not found in liver and spleen, but the reticuloendo-
thelial cells contained brown pigment and it is probable that sufficient radium
was stored here to inhibit myeloid metaplasia.

Cases 7–11 had suggestive histories of occupational or therapeutic exposure to
extrinsic toxic chemicals, including weight-reducing pills, insecticide sprays,
pharmaceutic products and paints or paint removers. Unfortunately, searching in-
vestigations of the exact type and duration of exposure were not made. The chemi-
cals most often implicated include arsphenamine, acetanilide, phenacetine, amido-
pyrine, paraphenylene-diamine and dinitrophenol. Usually their toxicity is shown
by sudden onset of agranulocytosis or aplastic anemia,35, 36 but occasionally the
proper combination of dose, resistance and duration of effect ends with chronic
marrow failure.3 37

In Cases 12 and 13, liver abnormalities were demonstrable. The former had sub-
normal hippuric acid excretion and prothrombin tests. The latter had ten years
of occupational exposure to carbon tetrachloride and autopsy revealed a post-
necrotic cirrhosis. Several other patients had evidence of liver dysfunction which
was not extensively studied. It appears desirable to employ tests of certain hepatic
detoxification and conjugation processes more often in chronic marrow failure.3
These include measurement of excreted pyramidon, phenols, hippuric acid, bili-
rubin or porphyrin in urine. The vitamin K tolerance test also may be abnormal.38
The preference for these tests is explained in discussion of pathogenetic mecha-
nisms.

Marked hemosiderosis was an outstanding finding in Cases 14–16. They had

* See footnote to table 1.
received thirty-eight, thirty-eight, and one hundred and forty blood transfusions respectively, and could be considered examples of "exogenous hemochromatosis." Only Case 16 showed portal cirrhosis at autopsy. While transfusion hemoglobin doubtless contributed to the hemosiderosis, anemia was the primary difficulty. Identical cases never transfused have been reported,\textsuperscript{40} so that exogenous hemoglobin iron is not essential. An alternate explanation proposed is that a hepatic "biochemical lesion" is present associated with anemia, and that eventual visible tissue deposit of excess iron develops, with variable fibrosis. Biochemical studies have demonstrated high free erythrocyte protoporphyrin\textsuperscript{42} and high plasma iron\textsuperscript{43} in refractory anemias, indicating failure of efficient coupling and local excess\textsuperscript{44} of these hemoglobin precursors. Chronic marrow failure, pellagra,\textsuperscript{45} and hemochromatosis\textsuperscript{40},\textsuperscript{41} have histologic and biochemical abnormalities in common. Pellagra is often accompanied by extensive cytosiderosis, and occasionally by marrow hyperplasia and anemia.\textsuperscript{46} Bone marrow hyperplasia was encountered in nine of eighteen autopsied hemochromatosis cases reviewed, and three had extramedullary hematopoiesis. The peripheral blood is usually normal.\textsuperscript{47}

Endocrine abnormalities were found in Cases 17 and 18. The former developed severe anemia 10 years after removal of his one remaining testis and discovery of a leukoerythroblastic blood picture. Case 18 died of pulmonary edema and heart failure after 25 years of diabetes mellitus, with mild polycythemia followed by clinical myeloid metaplasia for the last three years of life. Cases 19-22 represented four examples of chronic marrow failure in women with polycythemia. Case 22 has been separately reported in detail.\textsuperscript{49} The bone marrow of these 4 patients varied in histology from early myelosclerosis to generalized osteosclerosis. In series of polycythemia vera patients followed sufficiently long, from 17 to 24 per cent have been reported to show leukemoid or leukoerythroblastic reactions identical with our patients.\textsuperscript{51} Such changes are attributed to the natural course of polycythemia, or more likely to eventual attrition of the hematopoietic system by the chemical or physical agents employed to reduce the erythrocyte count.

Blood loss or destruction appeared outstanding in Cases 23-27. Case 23 had repeated hematemesis from gastric and esophageal varices for fifteen years before death, and showed splenomegaly with focal pipe-stem calcification at necropsy. Two myelosclerosis cases recently encountered had marked dilatation of the splenic, gastric and esophageal veins without demonstrable portal hypertension. In "Banti's disease," splenic hematopoiesis is frequent,\textsuperscript{55} and myelosclerosis and osteosclerosis rare. Cases 24-27, which were accompanied by abnormal red cell fragility, are a type which is termed adult erythroblastosis in the European literature.\textsuperscript{54} Chronic hemolytic anemia can thus lead to marrow failure and myelosclerosis indistinguishable pathologically from the other cases. Similar findings have been reported in various acquired hemolytic anemias, including Marchiafava-Micheli disease,\textsuperscript{56} Cooley's anemia\textsuperscript{57} and drug sensitivity.\textsuperscript{58} Experiments employing the hemolysin saponin,\textsuperscript{59} indole fed to dogs with black-tongue,\textsuperscript{60} and horse serum sensitization of rabbits also have produced marrow damage and myeloid metaplasia.\textsuperscript{61} Extrinsic chemical agents such as mercury, nitric acid, aniline
dyes and nitrates are hemolytic, and Case 25 was exposed to them in a hat factory for nineteen years.

The illness in Case 27 was associated with severe diarrhea and pancreatitis. Blood cholesterol was subnormal. Pathologically myelosclerosis and osteosclerosis were widespread and there was marked proliferation of macrophages in the intestine, lymph nodes and elsewhere, with erythrophagocytosis. The mechanism of development of this case may be related to the anemia of idiopathic steatorrhea, Whipple's disease or Hand-Schuller-Christian disease. In the last condition, clinical leukoerythroblastic anemia with myelosclerosis may develop. In Cases 28-30, valvular heart disease, with mitral and aortic stenosis and regurgitation, was prominent. The relationship to myelosclerosis appears uncertain, although circulating normoblasts have been reported in congestive heart failure. Whether abnormal abdominal and bone marrow hemodynamics can be responsible for chronic marrow failure remains to be determined.

A few clinical features deserve emphasis. First, the natural life span in chronic marrow failure and myelosclerosis usually extends over many years, although the patient may not appear for examination until late in its course. Second, a searching history will uncover evidence of toxic exposure in many instances. Third, for a proper diagnostic assay, complete hematologic investigation including a bone marrow biopsy, not puncture, is indicated. The alternate possibility of myelosclerosis secondary to carcinoma metastases can then be evaluated. Fourth, application of methods useful in treatment of leukemia and hypersplenism is generally contraindicated. Splenectomy usually shortens the patient's life.

**Etiology and Pathogenesis**

The bone marrow has been compared in size with the liver, and pathologic analogies may be drawn between myelosclerosis and hepatic cirrhosis. Both are morphologic entities without etiologic unity. In both diseases, various toxic agents, deficiencies and injuries cause necrosis of parenchyma followed by reparative hyperplasia of surviving cells. Continuance of parenchymal damage leads to overgrowth of the tougher stromal cells, and clinical abnormalities develop because of inadequate organ function, progressing to organ failure and death.

In chronic marrow failure, five major etiologic groups have been identified: extrinsic toxic agents, liver dysfunction, endocrine disease, chronic hemorrhage or hemolysis and cardiovascular disease. Ten of the 30 cases reported above involved more than one of the above etiologies. Ten other patients suffered also from chronic inflammations including pyelonephritis, bronchitis and arthritis, interpreted as an additional burden upon an inadequate hematopoietic system. Both in the literature and the present series, terminal bronchopneumonia and generalized tuberculosis were common. It was surprising to find how closely the suspected etiologic factors corresponded with the 66 cases of refractory anemia reported by Bomford and Rhoads. Their cases formed a group predominantly of shorter duration but overlapping with chronic marrow failure both clinically and morphologically. Refractory anemia was considered by them to be a conditioned susceptibility to exogenous or en-
dogenous aromatic hydrocarbons associated with hepatic dysfunction, failure of
detoxification and circulating or marrow hemolysins.

The present investigations of etiology have been handicapped in that they have
consisted mainly in analysis of records of patients already dead. Some of these
cases antedated the newer tests of hepatic function, and several were not studied
more thoroughly once a diagnosis of leukemia was entertained. Whether the
etiologic factors discussed are important will require further investigation in living
cases before they are generally acceptable.

Those who find acceptable the morphologic sequences and etiologic agents de-
scribed above may be interested in a working hypothesis of the pathogenesis of
chronic marrow failure and myelosclerosis. Benzene and related aromatic com-
ounds are known to be metabolized by oxidation to phenol, catechol and hydro-
quinoone, which are normally rapidly conjugated in the liver to sulfates and glu-
curonates and excreted in urine.71-73 Adrenal cortical and estrogenic steroids, which
possess phenolic or quinone groups, are similarly conjugated and excreted by the
liver in bile and urine.74-78 Failure of efficient hepatic conjugation exposes tissues
to higher concentrations of these substances, which are toxic to the lipoid-con-
taining, partly mature hematopoietic cells.79 Their protein breakdown products
may then form trophic stimuli to hyperplasia of the surviving cells and extra-
medullary hematopoiesis.80,81

Studies of liver conjugation have shown that Coenzyme 1 is necessary for in-
activation of estrogenic phenolic compounds.82 In chronic marrow failure,
pellagra, hemochromatosis83 and copper poisoning,85 suspicion has been directed
toward deficient or inactivated Coenzyme 1 as a basic "biochemical lesion." In
its absence important glycolytic and hydrogen transport mechanisms become in-
operative. Dustin86 has implicated both hydroquinone and radiation as related
mitotic poisons which also inhibit other unidentified enzymes. Perhaps these
ideas may stimulate further investigation of the basis of chronic marrow failure,
a complex process many of whose factors remain unknown or poorly understood.

SUMMARY

Thirty cases, including 20 autopsied, of chronic bone marrow failure, myelo-
sclerosis and osteosclerosis have been presented and compared with similar reports
in the literature. The bone marrow histopathologic sequence observed involved
repeated necrobiosis of maturing hematopoietic cells, followed by overgrowth of
marrow reticulum and frequent ossification. Immature erythrocytes and leukocytes
were often found in the circulation, and extramedullary hematopoiesis was char-
acteristic. One case was complicated by leukemia. Etiologic factors implicated
included exogenous toxic chemicals, liver dysfunction, endocrine abnormalities,
blood loss or destruction and cardiovascular disease. Suspicion was directed toward
the pathogenetic importance of protracted bone marrow exposure to certain sub-
stances normally conjugated rapidly in the liver and excreted.

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CHRONIC MARROW FAILURE

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