MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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MYELOFIBROSIS

(Agnogenic Myeloid Metaplasia; Primary Myeloid Metaplasia; Myelosclerosis)

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I. Definition and Nomenclature:

Myelofibrosis can be defined as a syndrome characterized by symptoms referable to anemia and leukoerythroblastic hematologic changes, progressive splenomegaly, varying degrees of marrow fibrosis and evidence of extramedullary hematopoiesis.

The initial description of the clinical complex:

1.) Heuck, G.: Zwei Fälle von Leukämie mit Eigenthümlichen Blut-resp. Knockenmacksbefund. Virch. Arch. 78:475, 1879.

- presentation of 2 cases that had the clinical and laboratory features of chronic granulocytic leukemia, but his finding of ("peculiar") fibrosis of the marrow and hematopoietic islands in the spleen and liver suggested a separate disease.

Although the first case in the English literature was:

2.) Sippy, B. W.: Splenic Pseudoleukaemia (Anaemia, Splenica, Splenomegalie Primitive). Amer. J. Med. Sci. 118:428, 1899.

It was:

3.) Donhauser, J. L.: The Human Spleen as an Haematoplastic Organ, as Exemplified in a Case of Splenomegaly With Sclerosis of the Bone Marrow. J. Exp. Med. 10:559, 1908.

- case report that delineated the clinical and (most) laboratory findings that have been amplified only slightly by large collected series. In addition, his speculations on etiology covered all of the possibilities that currently can be supported.

The confusion in characterization of this disorder is well characterized by the profusion of terms used to describe cases or series:

Current Terms: Myelofibrosis (4); Agnogenic Myeloid Metaplasia (5); Primary Myeloid Metaplasia; Myelosclerosis.

Other Names: Aleukemic Myelosis; Chronic Non-leukemic Myelosis; Osteosclerosis; Myelosclerosis; Splenomegaly With Marrow Sclerosis; Megakaryocytic Myelosis; Atypical Myelosis; Osteopathic Condensans Disseminata.

II. Clinical Features:

The clinical features in the 675 patients described in references 4-16 are compared in Table I for those series presenting adequate delineation of the findings.

4.) Metlier, S. and G. Y. Rusk. Fibrosis of the Bone Marrow (Myelofibrosis) Associated With a Leukemoid Blood Picture. Report of Two Cases. Amer. J. Path. 13:377, 1937.

5.) Jackson, H. Jr., F. Parker, Jr. and H. M. Lemon. Agnogenic Myeloid Metaplasia of the Spleen. A Syndrome Simulating Other More Definite Hematologic Disorders. N. E. J. M. 222:985, 1940.

- see Table I. In addition, of their 10 patients, 3 had been splenectomized with death at 6 weeks for 2 and at 1 year for the third and they made a vocal case against "useless and harmful splenectomy".

6.) Korst, D. R., D. V. Clatnoff and R. F. Schilling. On Myelofibrosis. Arch. Int. Med. 97:169, 1956.

- the Wisconsin experience

7.) Linman, J. W. and F. H. Bethell. Agnogenic Myeloid Metaplasia. Its Natural History and Present Day Management. Amer. J. Med. 22:107, 1957.

- Michigan experience

8.) Leonard, B. J., M. C. G. Israels and J. F. Wilkinson. Myelosclerosis. Quart. J. Med. 26:131, 1957.

- Manchester study

In addition to their 28 cases (see chart), in serial evaluation of 197 cases of CGL and 90 polycythemia patients - only 2 conversions to myelofibrosis seen, in two polycythemia patients treated with x-ray.

9.) Bouroncle, B. and C. A. Doan. Myelofibrosis. Clinical, Hematologic and Pathologic Study of 110 Patients. Amer. J. Med. Sci. 243:697, 1962.

- in addition to their 110 cases (see chart), 300 patients with polycythemia have been followed in the Ohio State Clinic with 10 converting to myelofibrosis, all treated with ^{32}P serially.

10.) Pitcock, J. A., E. H. Reinhard, B. W. Justus and R. S. Mendelsohn. A Clinical and Pathological Study of Seventy Cases of Myelofibrosis. Ann. Int. Med. 57:73, 1962.

- the St. Louis experience

In addition, 2 patients had + Coombs test and 3 had coagulation abnormalities. In 18/60 who had bone surveys areas of sclerosis were seen.

11.) Nakai, G. S., C. G. Craddock and W. G. Figueroa. Agnogenic Myeloid Metaplasia. A Survey of Twenty-Nine Cases and a Review of the Literature. Ann. Int. Med. 57:419, 1962.

- UCLA experience

12.) Silverstein, M. N., M. R. Gomes, W. H. ReMine and L. R. Elveback. Agnogenic Myeloid Metaplasia. Natural History and Treatment. Arch. Int. Med.

- Mayo Clinic experience with 137 cases. Median survival was 50 months.

13.) Hickling, R. A. The Natural History of Chronic Non-Leukaemic Myelosis. Quart. J. Med. 37:267, 1968.

- Charing Cross experience of 68 patients. Sequential marrow studies in a series of patients followed up to 20 years demonstrating a gradual change from hyperplastic islands to complete obliteration of the marrow.

14.) Rosenthol, D. S. and William C. Maloney. Myeloid Metaplasia. A Study of 98 cases. Postgrad. Med. 45:136, 1969.

- Boston City Hospital experience. This unusual series had 26 cases of polycythemia with subsequent evidence of myeloid metaplasia with a 2½:1 ratio of women to men in that group!! Average survival was 2.3 years (range 2 weeks to 12.5 years).

15.) Ward, H. P. and M. H. Block. Myeloid Metaplasia: A Revolution. In Myeloproliferative Disorders of Animals and Man. Edit. W. J. Clarke, E. B. Howard and P. L. Hackett. U. S. AEC Symposium Series 19:609, 1970.

16.) Ward, H. P. and M. H. Block. The Natural History of Agnogenic Myeloid Metaplasia (AMM) and a Critical Evaluation of its Relationship With the Myeloproliferative Syndrome. Med. 50:357, 1971.

- The above 2 papers represent an extended follow-up of 45 patients at Colorado.

Table I

References ( ) as Recorded

	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(16)
Number of Cases	10	23	56	28	110	70	29	45
Age	30-70	21-73	37-80	38-72	35-80	32-78	3-79	av. 60
Sex	5M:5F	15:8	29:27	14:14	50:50	39:31	15:14	20:25
Malaise	100%	100%	49/56	20/28	64%	94%		64%
Weight Loss		30%	43/56	6/28	48%	50%		23%
Bleeding		30%		3/28		20%		16%
Splenic Pain		40%	42/56	12/28		18%		
Gout		2/23	1/56	1/28				16%
Renal Stones		1/23						23%
Diarrhea						3%		10%
Fever			12/56			15%		19%
Bone Pain		5/23	18/56	8/28	1%	10%		0
Splenomegaly	100%	100%	100%	100%	94%	97	28/29	100%
Hepatomegaly	3/10	23/23	50/56	10/28	71%	86	28/29	54%
Petechiae			9/56		7%	24	5/29	26%
Lymphadenopathy		30%	3/56		12%	8	1/29	10%
Peripheral Edema			15/56		11%	15%	7/29	
Deafness								9%
Gouty Arthritis	1/10							8%
Jaundice	5/10		3/56		1%	3%		8%
Ascites			2/56		1%	10%	3/26	2%
Anemia (or Hb)	100%	10/23	53/56	26/28	64/100	88%	24/29	Mean 10 gm
Nucleated RBC's	100%	21/23	41/56	100%	"most"		24/29	100%
WBC								
< 5,000	2/10	4/23	6/56	4/28		25%		13%
> 10,000	6/10	10/23	30/56	9/28	50/100	38%		56%
% Blasts		16/23	34/56	24/28		18%		15/45
		2%		1-15%				
Platelets								
Low		5/23	13/56	3/28	5/100	20%		22%
Normal			13/56	21/28		32%		49%
High		11/23	30/56	4/28	50/100	48%		29%
Marrow								
Normal	1/10		2/56	3/15			4/29	
Hyperplastic	1/10	4/23	2/56				3/29	
Fibrotic	5/10	23/23	56/56				14/29	
Sclerotic	1/10	11/23						
Duration of Survival	10 yrs.	≅ 5 yrs.	6 yrs.	+ 2 yrs.	+ 3 yrs.			

The University of Texas Southwestern Medical School series consists of 56 patients with clinical features that parallel data reported to date:

Classically the patient is in the age range of 45-75 years and the frequency by sex is approximately equal. The important features were:

1.) Over 90% of our patients presented with weakness and ease of fatigue that was beyond correlation with the physical findings or laboratory findings(primarily the degree of anemia).

2.) Weight loss in the absence of decreased appetite, but often with ease of satiety with small quantities of food, was seen in over 50% of the patients.

3.) Approximately 20% of the patients complained of discomfort, sense of fullness or an actual mass in the left upper quadrant. Five patients had episodes of left upper quadrant pain sometime in their clinical course with a pleuritic component that suggested splenic infarction and/or subcapsular bleeding.

4.) 20% of the patients complained of a bleeding diathesis usually characterized as superficial flat ecchymosis ("senile purpura") over the extremities that was a cosmetic problem or black tarry stools.

5.) Less than 10% of the patients complained of bone pain. When present it was characterized as long bone pain primarily in the lower extremities. Three patients had arthralgias, but no patient was seen with acceptable criteria of gouty arthritis.

Unlike other series, we did not have patients with fever (7, 10, 15, 16), diarrhea (10, 16) or deafness (16).

Physical findings have been:

1.) Splenomegaly was clearly the most common finding. All but two of our patients had evident and significant splenomegaly and one of these two had an enlarged spleen by scan. Ward and Block (16) have provided evidence that the duration of the disease correlates with splenic size with the rough rule of "1 cm/ year splenic extension downward". Our retrospective study provides such data in less than 20% of our cases.

2.) Hepatomegaly was seen in approximately 50% of the cases and did appear to correlate with the duration of the disease. Two patients who were splenectomized (see below) had an increase in liver size of over 5 cm over the subsequent 18 months and a third had little or no change over the next year.

3.) Superficial ecchymoses were seen in almost 30% of the patients, generally over the upper extremities.

4.) Lymphadenopathy was seen in only 3 patients. In one the initial diagnosis was made by lymph node biopsy which demonstrated extramedullary hematopoiesis.

Unlike Korst et al. (6), sternal tenderness and/or bony tenderness was never seen.

III. Laboratory Findings:

1. Blood:

a.) Red Cells: All but 3 patients had hemoglobin levels below 11 gms%. The red cell changes can be considered one of the hallmarks of the diagnosis. The red cells were generally normochromic with marked (++++) anisocytosis and poikilocytosis, with "tailed" poikilocytes. Polychromatophilia (reticulocytosis) and nucleated red cells were seen in over 90% of the patients, although not always on presentation.

b.) White Cells: The white counts were variable. Not unlike the other series approximately 20% of the patients had counts below 4500/mm^3, approximately 25% in the 4,500-10,000/mm^3 range and 55% above 10,000/mm^3. A shift to the left was seen in 80% of the patients but less than 10% had cells younger than myelocytes on presentation. A slight increase in circulating basophils and eosinophils was common and at least 5 patients had cells with mixed eosinophilic and basophilic granules.

c.) Platelets: Platelet counts were variable and paralleled the reported series, about 1/3 of the patients having thrombocytopenia and 1/6 thrombocytosis, the remainder having platelet counts in the normal range. A frequent dichotomy was noted between the enumerated platelet values (low) and the count assessed on the smear (high). Platelet clumping, making counting inaccurate, appears to be common in these patients. In addition, large and bizarre platelets (presumably young platelets and from extramedullary sources) were common.

2. Bone Marrow:

As has been well documented in every series and study to date the principle features are:

a.) An aspirate that provides scanty or no material.

b.) A biopsy (preferably Jamshidi) that demonstrates fibrosis and/or sclerosis. Usually hematopoietic islands are scanty, but hyperplastic foci may be seen, especially early in the disease (13). Platelet sheets and megakaryocytes enmeshed in reticulum fibers are common.

3. Other Tissues (Spleen, Liver, Nodes):

Evidence of extramedullary hematopoiesis strongly supports the diagnosis, especially when red and white cell precursors and megakaryocytes (i.e. trilinage representation) are seen (15, 16).

4. Ferrokinetic and Red Cell Survival Studies:

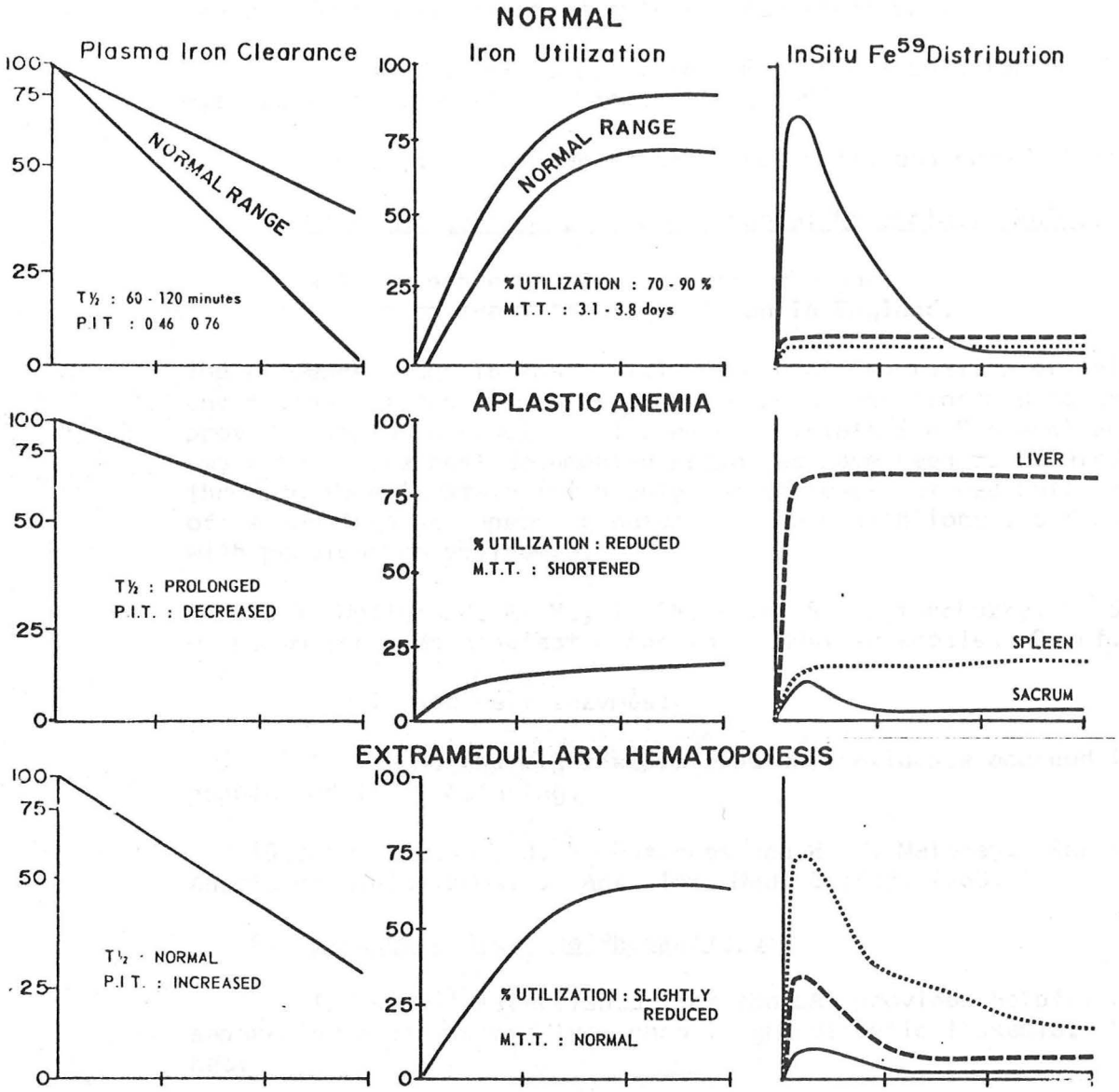
a.) Classical ferrokinetic studies should provide the best delineation of the sites and mechanisms of the altered erythron. Actually, as one might expect from the variable actual or residual marrow activity, considerable variation in ferrokinetic results have been found (6, 11, 17). Clearly the most careful study (17) has demonstrated:

1.) Increased Plasma Iron Turnover Rate - (since the PITR provides a reasonable assessment of the size of the erythron, this indicates increased erythroid mass [activity]).

2.) Decreased Utilization of the ^{59}Fe - (the measurement of the "effectiveness" of erythropoiesis). The combination of an expanded erythron with decreased utilization of the radioiron in the presence of reduced peripheral red cell values provides evidence that ineffective erythropoiesis is a major mechanism in the anemia.

3.) Marrow transit times are appropriate for the degree of anemia (the M.T.T. being an excellent correlate to the level of erythropoietin stimulation).

4.) Surface counting provides evidence of extramedullary hematopoiesis in spleen and/or liver.


NORMAL
Plasma Iron Clearance
Iron Utilization
InSitu Fe59Distribution
100
75
50
25
0
NORMAL RANGE
T½ : 60 - 120 minutes
P.I.T : 0.46 0.76
% UTILIZATION : 70 - 90 %
M.T.T. : 3.1 - 3.8 days
APLASTIC ANEMIA
T½ : PROLONGED
P.I.T. : DECREASED
% UTILIZATION : REDUCED
M.T.T. : SHORTENED
LIVER
SPLEEN
SACRUM
EXTRAMEDULLARY HEMATOPOIESIS
T½ : NORMAL
P.I.T. : INCREASED
% UTILIZATION : SLIGHTLY REDUCED
M.T.T. : NORMAL

b.) ^{51}Cr autologous red cell survival studies demonstrated a modest shortening of red cell survival $T\frac{1}{2}$ 12-21 days (normal 26-30 days) and in spite of significant splenomegaly the spleen to liver ratios were normal: 1:1 to 2:1. (Spleen to liver ratios in excess of 3:1, and probably as low as 2.4:1 or greater, can be considered selective splenic sequestration.)

17.) Szur, L. and M. D. Smith. Red Cell Production and Destruction in Myelosclerosis. Brit. J. Haem. 7:147, 1961.

- a masterful series of ferrokinetic and survival studies on 19 patients.

5. Other Mechanisms of the Peripheral Hematologic Values:

a.) Evidence of megaloblastic changes:
- an event far more common in England.

The evidence suggests that: 1.) Laboratory evaluation of folate deficiency (serum and tissue folates, FIGLU or urocanic acid excretion and folate clearance studies) provides variable results. Therapeutic trials (in England) are therefore essentially empirical. The best documented responses have been associated with repair of the thrombocytopenic state (with only modest repair of red cell values). The incidence of responsiveness appears greatest in those with long standing disease and in patients with previous polycythemia.

18.) Hoffbrand, A. V., I. Chanarin, S. Kremenchuzky, L. Szur, A. H. Waters and D. L. Mollen. Megaloblastic Anemia in Myelosclerosis. Quart. J. Med. 37:493, 1968.

b.) Red cell enzymes:

As one might expect the only evidence accrued is that a young red cell population is circulating.

19.) Bartos, H., J. F. Deforges and W. C. Maloney. Red Cell Enzymes in the Anemia of Myelofibrosis. Ann. Int. Med. 68:533, 1968.

6. Leukocyte Alkaline Phosphatase:

It is well established that the LAP provides helpful but not absolute data in separating myelofibrous from chronic granulocytic leukemia. Kaplow (20) in 154 cases had:

high values (> 100) in 62%
normal values (15-100) in 23%
low values (< 15) in 15%
↳ in CGL

Mitus et al. (21) in a series of 30 cases from Dameshek's laboratory had similar numbers and this has been the common experience of all above series.

20.) Kaplow, L. S. Leukocyte Alkaline Phosphatase Cytochemistry: Applications and Methods. Ann. N. Y. Acad. Sci. 155:911, 1968.

21.) Mitus, W. J. and K. A. Kiossoglou: Leukocyte Alkaline Phosphatase in Myeloproliferative Syndrome. Ann. N. Y. Acad. Sci. 155:976, 1968.

7. Chromosome Studies:

Although a variety of karyotypic abnormalities have been described, these have been variable and non-specific; usually Group C-trisomy (22). The critical marker of chronic granulocytic leukemia, the Philadelphia chromosome has been found in only one acceptable case (23): a patient from Brooke Army Hospital with documented marrow fibrosis of 8 years duration demonstrated the pH' chromosome.

22.) Nowell, P. C. and D. A. Hungerford. Chromosome Studies in Human Leukemia. IV. Myeloproliferative Syndrome and Other Atypical Myeloid Disorders. J. Nat. Canc. Inst. 29:911, 1962.

23.) Forrester, R. H. and J. M. Louro. Philadelphia Chromosome Abnormality In Agnogenic Myeloid Metaplasia. Ann. Int. Med. 64:622, 1966.

8. Other Laboratory Observations:

Support for a relationship to other diseases affecting the myeloid mass comes from:

a.) Granulocyte survival: Evidence of prolonged survival of labeled granulocytes in the peripheral circulation with a $T\frac{1}{2}$ of 30-50 hours, similar to that of chronic granulocytic leukemia (24).

b.) Leukocytic histidine decarboxylase: Increased levels of this enzyme have been seen in polycythemia vera, myelofibrous and chronic granulocytic leukemia. This has been related to the elevated levels of blood and urine histamine and has been correlated with pruritus in some patients (25).

c.) Hyperuricemia: Approximately $\frac{1}{2}$ of the patients with myelofibrosis will have hyperuricemia (7, 11, 16). (Gouty arthritis does occur in a small number of patients - Table I).

Other laboratory observations help provide distinction for myelofibrosis:

a.) Serum alkaline phosphatase: Elevated levels have been noted in approximately 50% of the patients (16). The elevated levels appear to be hepatic in origin and correlate best with the degree of extramedullary hematopoiesis in the sinusoidal spaces.

b.) Leukocyte periodic acid-Schiff reaction: Microspectrophotometric analysis of PMN's revealed increased PAS reactive material in myelofibrosis compared to normals (26). (In CGL it is markedly reduced.)

c.) Vitamin B12 and B12 binding protein: Both the serum vitamin B12 and B12 binding protein are markedly increased in patients with chronic granulocytic leukemia, the evidence being that B12 binding protein has its origin in the granulocyte. In fact, the binding protein can be used as an assessment of granulocyte turnover (27).

- In myelofibrous serum B12 measurements as well as B12 binding protein have been in the normal (albeit at times high normal) range.

d.) The "PNH-like defect": Evidence of a paroxysmal nocturnal hemoglobinuric defect has been seen in a significant number of patients with myelofibrosis (28).

This identifiable change in the red cell membrane (producing increased complement sensitive lysis) has been seen in as high as 50% of cases of primary myelofibrosis, but absent in secondary forms of extramedullary hematopoiesis with marrow fibrosis (29).

If the development of PNH-like change is a "somatic mutation" it correlates best with findings in hypoplasia and relates to selected cases of acute leukemia (see Grand Rounds discussion - 1972).

24.) Athens, J. W., O. P. Haab, S. O. Raab, D. R. Boggs, H. Ashenbrucher, G. E. Cartwright and M. M. Wintrobe. Leukokinetic Studies. XI. Blood Granulocyte Kinetics In Polycythemia Vera, Infection and Myelofibrosis. J. Clin. Invest. 44:778, 1965.

25.) Krauss, S., H. S. Gilbert and L. R. Wasserman. Leukocyte Histidine Decarboxylase: Properties and Activity In Myeloproliferative Disorders. Blood 31: 699, 1968.

26.) Gahrton, G.: The Periodic Acid-Schiff Reaction in Neutrophilic Leukocytes in Chronic Myeloproliferative Disorders. Scand. J. Haemat. 3:106, 1966.

27.) Herbert, V. Diagnostic and Prognostic Values of Measurements of Serum Vitamin B_{12}-Binding Proteins. Blood 32:305, 1968.

28.) Hansen, N. E. and S.-A. Killmann. Paroxysmal Nocturnal Hemoglobinuria. A Clinical Study. Acta Med. Scand. 184:525, 1968 and Blood 36:429, 1970.

29.) Kus, C., A. V. Voolen and A. N. Morrison. Primary and Secondary Myelofibrosis: Its Relationship to "PNH-like" Defect. Blood 40:875, 1972.

9. Radiologic Changes:

The incidence of radiographic changes is 30-50% in the various series. The radiographic features are:

a.) Involvement of medulla with an intact cortex.

b.) Characteristic disorganization of the trebecular pattern with deposition of bone (osteosclerosis) throughout the marrow providing a "ground glass" appearance of the bone matrix with loss of definition of the trebeculae.

c.) Any bone can be involved, except the skull.

d.) However, extensive skeletal studies are considered useless (8). The clue to radiologic study should be pain.

IV. ?Variants of Myelofibrosis:

1.) Familial Type:

- recently described in the Texas-Oklahoma area is a non-proliferative leukoerythroblastosis with extramedullary hematopoiesis seen in children.

30.) Randall, D. L., C. W. Reiguiam, J. H. Githens and A. Robinson. Familial Myeloproliferative Disease. Amer. J. Dis. Child. 110:479, 1965.

2.) Acute or Malignant Myelofibrosis:

- first elucidated by Lewis and Szur(31):

It is myelofibrosis, but with an acute onset with profound thrombocytopenia and anemia. All of the clinical and hematologic features are those of myelofibrosis. Although the clinical course is "acute" with a progressive downhill course and death in 3-12 months, these deaths are due to bleeding and/or infection. Clinically these patients mimic acute leukemia, except for the absence of a proliferative hematopoietic response. Diagnosis may be difficult because organomegaly may be slight or even absent and initial marrows may fail to reveal extensive fibrosis.

31.) Lewis, S. M. and L. Szur. Malignant Myelosclerosis. Brit. Med. J. 2: 472, 1963.

32.) Mitus, W. J., N. Coleman, K. A. Krossaglou. Abnormal (Marker) Chromosomes in Two Patients With Acute Myelofibrosis. Arch. Int. Med. 97:169, 1956.

33.) Bergsman, K. L. and E. J. Van Slyck. Acute Myelofibrosis. An Accelerated Variant of Agnogenic Myeloid Metaplasia. Ann. Int. Med. 74:232, 1971.

V. Aspects of Secondary Myelofibrosis:

Experimental fibrosis of the marrow and/or localized and generalized extramedullary hematopoiesis has long been known to be inducible by a wide variety of agents and circumstances:

34.) Werzberg, A. Neue Experimentelle beiträge Zur Frage Der Myeloiden Metaplasia. Virch. Arch. 204:272, 1911.

Well documented and extensive experience with secondary forms has been compiled (16):

TABLE II

Causes of Secondary Myelofibrosis

a.) Toxic - e.g. benzene, xray
b.) Infections - e.g. tuberculosis, syphilis
c.) Neoplastic - e.g. carcinoma, leukemia
d.) Reactive - e.g. hemolysis, pernicious anemia
e.) Replacement - osteopetrosis; Gaucher's
f.) (?) Polycythemia
g.) Misc. - Banti's

Of these, the primary current clinical causes are:

1. T.B.
2. Cancer - especially stomach, prostate and breast
3. Radiation

35.) Rawson, R., F. Parker, Jr. and H. Jackson, Jr. Industrial Solvents As Possible Etiologic Agents in Myeloid Metaplasia. Sci. 93:541, 1941.

36.) Andre, J., R. Schwartz and W. Dameshek. Tuberculosis and Myelosclerosis With Myeloid Metaplasia. J. A. M. A. 178:1169, 1961.

37.) Kiely, J. M. and M. N. Silverstein. Metastatic Carcinoma Simulating Agnogenic Myeloid Metaplasia and Myelofibrosis. Cancer 24:1041, 1969.

38.) Vaughan, J. Radiation and Myeloproliferative Disorders in Man. In Myeloproliferative Disorders of Animals and Man. U. S. AEC Symposium 19:489, 1970.

39.) Anderson, R. E. and T. Yamamato. Myeloproliferative Disorders in Atomic Bomb Survivors. Ibid 19:501, 1970.

40.) Anderson, R. E., T. Hoskins and T. Yamamoto. Myelofibrosis With Myeloid Metaplasia in Survivors of the Atomic Bomb in Hiroshima. Ann. Int. Med. 60:1, 1964.

One of the stimuli to interrelating myelofibrosis with chronic granulocytic leukemia and other clearly proliferative hematopoietic lesions has come from the radiation data since lesions such as CGL are classically radiation inducible.

In addition, it is now evident that marrow fibrosis of varying degrees may be a common event in chronic granulocytic leukemia:

41.) Krauss, S.: Chronic Myelocytic Leukemia With Features Simulating Myelofibrosis with Myeloid Metaplasia. Cancer 19:1321, 1966.

42.) Grolnick, H. R. and J. M. Bennett. Bone Marrow Histology in Chronic Granulocytic Leukemia: Observations on Myelofibrosis and the Accelerated Phase. In Myeloproliferative Disorders of Animals and Man. U. S. AEC Symp. 19:583, 1970.

VI. Natural History:

As noted in Table I, there is considerable variation in mean survival in the different series. Representative of our patients would be the Colorado series (16) with a median survival time of approximately 10 years from the onset of symptoms and 5 years from the time of diagnosis. Infection, heart failure and bleeding are the 3 most common causes of death. Two other rare problems do occur in this group:

Portal Hypertension and Ascites:

43.) Shaldon, S. and S. Sherlock. Portal Hypertension in the Myeloproliferative Syndrome and the Reticulosis. Amer. J. Med. 32:758, 1962.

44.) Rosenbaum, D. L., G. W. Murphy and S. N. Swisher. Hemodynamic Studies of the Portal Circulation in Myeloid Metaplasia. Amer. J. Med. 41:360, 1966.

Demyelinating Syndrome (Leukoencephalopathy):

45.) Thompson, R. A. and M. Jones. Remitting Demyelinating Disease Associated With Myeloproliferative Syndrome and Histiocytosis of the Spleen. Neurology 19: 885, 1969.

VII. Etiology and Pathophysiology:

Three major theories have been proposed:

I. Compensatory Concept:

First clearly enunciated in 1908 (3) this merely accepts multiple mechanisms for marrow injury with compensatory hematopoiesis in areas where hematopoietic mesenchyme was active during embryogenesis.

The arguments in favor of this non-neoplastic reactive concept have been:

a.) The multiple mechanisms capable of producing the lesion (3, 13, 46).

b.) The evidence in the natural history that this is a non-proliferative type lesion as we commonly require for the documentation of neoplasia. The fibrotic changes can be considered a kind of desmoidal reaction (13, 47).

c.) The sequential evidence of focal injury in serial biopsies (13, 47).

The strong dissenters state:

a.) The extramedullary hematopoiesis may occur prior to evident pancytopenia; ergo, no "compensatory" phenomena is physiologically required.

b.) Panhyperplasia (focal or generalized as in polycythemia) may be present and yet metaplasia may be seen.

However, recent evidence suggests that in marrow injury and in primary myelofibrosis (perhaps by mechanisms proposed by Peace) there is an increased number of circulating stem cells which provide the potential for seeding in compatible sites (? embryonic hematopoietic sites) and, in addition, the growth characteristics and colony patterns are different from those seen in true proliferative hematologic lesions (48).

46.) Wyatt, J. P. and S. C. Sommers. Chronic Marrow Failure, Myelosclerosis, and Extramedullary Hematopoiesis. Blood 5:329, 1950.

47.) Peace, R. J.: Myelonecrosis, Extramedullary Myelopoiesis, and Leuko-erythroblastosis. A Mesenchymal Reaction to Injury. Amer. J. Path. 29:1029, 1953.

48.) Cherveneck, P. A. Increased Numbers of Stem Cells in Blood of Patients With Myelofibrosis. Proceed. XV Amer. Soc. Heme. 15:43, 1972.

2. Myeloproliferative Concept:

Currently the most popular theory. Far from new (3, 49), it was popularized most vigorously by Dameshek (50):

"These various conditions (myelofibrosis, chronic granulocytic leukemia, polycythemia vera, primary thrombocythemia, and DiGuglielmo syndrome) - THE MYELOPROLIFERATIVE DISORDERS - are all somewhat variable manifestations of proliferative activity of the bone marrow cells, perhaps due to a hitherto undiscovered stimulus. This may affect the marrow cells diffusely or irregularly with the result that various syndromes, either clear-cut or transitional, result. As a group it is difficult to draw any clear-cut dividing lines, in fact so many "transition" forms exist that one may with equal reasonableness call a single condition by at least two different terms."

This thesis quickly became one of a "neoplastic"-type syndrome based upon:

a.) Difficulty in establishing an absolute diagnosis in some cases of leukoerythroblastosis

b.) Evidence of transitions in type - eg. conversion of polycythemia to myelofibrosis and/or leukemia, etc. (51).

c.) Evidence of panhyperplastic marrows in many of the patients with the above entities.

Evidence against this concept is:

a.) "Transitional" cases often are transitional only in the sense that the initial diagnosis may have been made on less than the most firm criteria. Some (15, 16) have felt, in fact, that transition relating to myelofibrosis is not seen (except in long standing polycythemia) when the extramedullary hematopoietic foci are shown to have the specificity of all 3 lines of precursors, unless the patient has been treated with potential inducing agents (xray, cytotoxic agents, etc.).

b.) Since secondary forms of myelofibrosis are mirrors of the primary type, one would have to consider these cases neoplastic as well.

c.) Evidence of proliferation, the hallmark of neoplasms, is absent.

d.) Absence of an abnormal myeloid precursor as is commonly seen in the pH' chromosome defect in CGL (a defect seen in red cell, granulocyte and megakaryocyte precursors) supporting an origin in an abnormal stem cell.

49.) Hutt, M. S. R., J. L. Penninger and G. Wetherley-Mein. The Myeloproliferative Disorders With Special Reference to Myelofibrosis. Blood 8:295, 1953.

50.) Dameshek, W.: Some Speculations on the Myeloproliferative Syndromes. Blood 6:372, 1951.

51.) Glasser, R. M. and R. I. Walker: Transitions Among the Myeloproliferative Disorders. Ann. Int. Med. 71:285, 1969.

3. "Myelostimulatory" Concept:

This proposes that myelofibrosis represents a normal response of a normal stem cell to an unidentified stimulus (52):

Supported by:

a.) Evidence of a stem cell common to both hematopoietic cells and fibroblasts (16).

b.) Secondary cases of myelofibrosis are clearly not neoplastic and are indistinguishable from primary cases.

c.) Extramedullary hematopoiesis is seen due to many causes. One, polycythemia, is associated with these changes even when patient is not anemic.

d.) Since the extramedullary hematopoiesis has the same location and appearance as that seen during embryogenesis, there is no evidence that the lesion is neoplastic (16).

e.) In tissue culture, serum from one patient with myelofibrosis induced fibroblastic differentiation of culture colony (53).

52.) Hickling, R. A. Chronic Non-leukemic Myelosis. Quart. J. Med. 6:253, 1937.

53.) Reisner, E. H., Jr. Tissue Culture of Bone Marrow. III. Myelostimulatory Factors in Serum of Patients With Myeloproliferative Diseases. Cancer 20:1679, 1967.

VIII. Therapy:

1. Supportive measures

2. Androgens

3. Adrenal cortical steroids

4. Splenectomy:

The older literature (5, 52) documented a high mortality rate from splenectomy and it became a contraindicated procedure. More recent evidence (54, 55) has documented that given selected indications the procedure is relatively safe (56) and of benefit.

The indications for splenectomy are:

a.) Significant transfusion requirements due to documented (hyper)hemolysis where one can provide evidence that selective splenic sequestration exists:

generally: ^{51}Cr survival time of < 15 days.
spleen to liver ratio of 2.4 to 1 or greater.

b.) Severe thrombocytopenia with evidence of splenic pooling:

^{51}Cr labeled platelet study with recovery fraction of less than 80%.

c.) Recurrent splenic infarcts.

54.) Green, T. W., C. L. Conley, L. L. Ashburn and H. R. Peters. Splenectomy for Myeloid Metaplasia of the Spleen. N. E. J. M. 248:211, 1953.

55.) Jensen, M. K. Splenectomy in Myelofibrosis. Acta Med. Scand. 175:533, 1964.

56.) Meilleur, P. A. and M. C. Meyers. Thrombocytosis: A Postsplenectomy Complication in Agnogenic Myeloid Metaplasia. Amer. J. Med. Sci. 241:68, 1961.

5. Cytotoxic agents; ^{32}P; radiation

Of very limited and questionable value. Where tried, patients appear very sensitive with a great deal of toxicity.

6. Marrow stimulation by mechanical disruption:

As discussed last year, medullary disruption by curettage provides the potential for re-enactment of the embryologic development of the marrow. In fact, the best results to date have been not in hypoplastic anemia but in myelofibrosis (57).

57.) Wimer, B.: Bone Marrow Curettage in the Treatment of Myelofibrosis. Exp. Hemat. 15:3, 1968.

IX. Case Summaries:

1. PRIMARY MYELOFIBROSIS WITH NO SPLENOMEGALY

[redacted] 57-year old WM who has had a documented mild weakness and ease of fatigue related to a known anemia of 3 years duration. Therapy with multiple hematinics has been without effect. Physical examination fails to reveal any abnormalities. His Hb is 11.6 gm% and hematocrit 36 vol% with evidence of a leukoerythroblastic response. Serial bone marrow biopsies have revealed classical myelofibrosis. No secondary etiology has been identified. Liver-spleen scans have been normal.

2. PRESENTATION AS LIVER DISEASE OF "UNKNOWN ETIOLOGY"

[redacted]. 65-year old NM who was noted to have hepatosplenomegaly on routine examinati[redacted]. Initial laboratory studies revealed a mild anemia (approx. 11 gms) and an elevated serum alkaline phosphatase. A diagnosis of early cirrhosis was made on clinical grounds and the patient followed for 18 months at which time he was referred for evaluation of his anemia. His peripheral hematologic values were unchanged but he had classical evidence of a leukoerythroblastic response. Bone marrow biopsy revealed myelofibrosis and liver biopsy revealed extramedullary hematopoiesis of all 3 cell lines. Of interest is little change in organ size during this 2-year period, although his hemoglobin has declined to the 10 gm range in recent months.

3. "SECONDARY MYELOFIBROSIS" IN SYSTEMIC MAST CELL DISEASE

[redacted]. 57-year old WM admitted to [redacted] with fever and a parenchymal infiltrate and anemia. During his work-up, bone xrays provided a diagnosis of "myelosclerosis". Evaluation revealed a leukoerythroblastic peripheral blood picture and evidence of fibrosis in the bone marrow biopsy. Nodules and clusters of cells provided a "hyperplastic" appearance to the marrow which on special stains proved to be mast cell tumors with the classically associated myelofibrosis and myelosclerosis. The patient's chest cleared and he is asymptomatic except for his modest anemia.

4. EXTRAMEDULLARY HEMATOPOIESIS IN LYMPH NODES AND AN UNUSUAL RESPONSE TO ANDROGENS

[redacted] This 72-year old woman was first seen at age 68 with the complaint of recent development of a mass in the neck and a history of weakness and fatigue progressive over the previous year. On examination she had a 3 cm node in the left supraclavicular area with a 0.5 cm node in the right lateral cervical chain. The spleen was palpable 6 cm beneath the left costal margin and her liver 2 cm beneath the right costal margin. Lymph node biopsy revealed extramedullary hematopoiesis with all 3 cell lines involved. Peripheral hematologic and marrow biopsy further corroborated the diagnosis of myelofibrosis.

Because of profound anemia she was begun on androgens with a repair of her hemoglobin levels from 8 gms to 12 gms%, but she developed increased hyperuricemia (in spite of Allopurinol) and severe generalized bone pain requiring discontinuation of therapy. The bone pain suggested an underlying hormonally responsive tumor, but over the next 4 years no neoplasm was found. During this same period she redeveloped her anemia and every trial with androgen or related drugs resulted in excruciating generalized bone pain, requiring their discontinuation. During her 71-72 year of life progressive increases in IgM were noted without any other structural changes. At age 72 she developed acute bacterial endocarditis and died.

5. SPLENECTOMY FOR SIGNIFICANT TRANSFUSION REQUIREMENTS

[redacted]. This 67-year old [redacted] woman was well until age 55 at which time she began to have recurrent leg pains described primarily in the anterior aspects of the thighs. She had several admissions for "thrombophlebitis" in the late '50's without clear clinical evidence of venous disease. At age 60 she noted an increase in the girth of her abdomen and clinical evaluation documented splenomegaly with

peripheral hematologic changes compatible with myelofibrosis. Bone marrow aspiration and biopsy demonstrated myelofibrosis. Over the next 3 years anemia became a symptomatic problem in spite of androgen therapy. Transfusions were required because of cardiopulmonary symptoms beginning at age 63. Over the next 3 years her requirements increased to 3-4 units per month. No evidence of isoimmunization was identified. ^{51}Cr studies revealed a $T_{\frac{1}{2}}$ of 13.5 days (normal 27-32 days) with evidence of selective splenic sequestration with a spleen to liver ratio of 3:1 (normal 1:1). Of interest is that over this 7-year period there was no measurable change in spleen or liver size! Because of the transfusion requirements, elective splenectomy was performed at age 67. The spleen (and liver biopsy) revealed red cell, white cell and megakaryocyte precursors. Subsequent to splenectomy her transfusion requirements disappeared. Liver size did slowly increase over the next 2 years.

6. MYELOFIBROSIS WITH AN IgA λ MONOCLONAL GAMMOPATHY

[redacted] 41-year old WM who presented in [redacted] '72 with a 6-month history of weakness, fatigue and pallor. Past history revealed symptomatic lead intoxication in 1963 while employed in [redacted]. Liver was felt 4 cm beneath RCM; spleen 12 cm beneath LCM. Hb 7 gms, WBC 14,800, platelets 20,000 with a leukoerythroblastosis. Marrow biopsies revealed myelofibrosis. Serum protein electrophoresis revealed monoclonal β-γ spike of 4.1 gm% which on immunoelectrophoresis was IgA λ type. Decreased IgG and absent IgM. Ferrikinetics compatible with extramedullary hematopoiesis. In summer of '72 he developed a pleural effusion following trauma. Pleural fluid electrophoresis revealed serum-like pattern.

7. PRIMARY MYELOFIBROSIS WITH PNH-LIKE DEFECT AND SEQUELAE ASSOCIATED WITH THE DEFECT

[redacted] 60-year old WM with the diagnosis of myelofibrosis made in [redacted] '69 with classical clinical and laboratory features. Treated with oxymethalone in 1971 because of progression of his anemia, but onset of mild cholestatic jaundice led to its discontinuation. In [redacted] '72 had classical episode of mesenteric thrombosis. Subsequent to this evidence of hemoglobinuria led to studies of erythrocyte sensitivity to complement lysis:positive sucrose hemolysis; negative Ham test.

8. MYELOFIBROSIS WITH TERMINAL RETICULUM CELL SARCOMA

[redacted] 40-year old WM first seen in '68 because of weakness, fatigue and documented splenomegaly by his family physician of 2 years duration. Evaluation revealed liver 1 cm below the right costal margin, spleen 4 cm below the LCM. Hemoglobin 13 gms%/hematocrit 43 vol%, WBC 7500 with shift to left (to myelocyte stage) and platelets of 245,000/mm^3. His morphologic studies revealed marked anisocytosis and poikilocytosis of red cells. Ferrikinetics were consistent with ineffective erythropoiesis, and extramedullary hematopoiesis in spleen. Bone marrow was hyperplastic with fibrosis.

Over the next 2 years his hemoglobin fell and his spleen size increased to 13 cm beneath LCM. He was placed on androgens in 1970. He did well until [redacted] '72 (except for an episode of gouty arthritis in 1971) when he developed severe leg pain, ankle edema and rapidly progressive generalized lymphadenopathy.

He had pancytopenia (Hb 7 gms; WBC 1000 and platelets 30,000) and marrow was hypercellular with increased reticulum cells. PNH-like defect was noted at this time. Perilymphatic masses developed in the lower extremities which on biopsy were read as reticulum cell sarcoma. He was treated with COP with transient symptomatic and lab improvement but died 3 months later with disseminated reticulum cell sarcoma.

9. ACUTE MYELOFIBROSIS

[redacted] 24-year old WF well until [redacted] '71 when she developed fever, weakness and progressive weight loss. First admission was [redacted] '71 with the only positive finding that of a palpable spleen tip. Hb 11.4/hct. 33, WBC 1250, platelets 50,000 with leukoerythroblastosis. Bone marrow was somewhat hyperplastic with minimal fibrosis. No evidence of malignancy.

Over the next two months she had recurrent infections managed with difficulty and serial hematologic studies demonstrated progressive marrow fibrosis until her death in [redacted] '71 with pseudomonas sepsis. Autopsy corroborated diagnosis of acute myelofibrosis; no evidence of malignancy or other etiologic mechanisms.