0025-7974/83/6206-0147$02.00/0
MEDICINE


Vol. 62, No. 6
Printed in U.S.A.

# The Syndrome of Idiopathic Myelofibrosis

## A Clinicopathologic Review with Emphasis on the Prognostic Variables Predicting Survival

AJIT VARKI, M.D., RICHARD LOTTENBERG, M.D.,[1] ROGERS GRIFFITH, M.D. AND EDWARD REINHARD, M.D., F.A.C.P.

### Introduction

Terms such as "agnogenic myeloid metaplasia," "myelosclerosis" and "idiopathic myelofibrosis" have long been used to describe a clinical syndrome that is characterized by unexplained fibrosis in the bone marrow, extramedullary hematopoiesis, splenomegaly, and a leukoerythroblastic peripheral blood smear. Several previous clinicopathologic reviews of this syndrome have been reported, including one in the pages of this journal, in 1971 (8, 26, 36, 39, 45, 48, 52, 53, 56). A similar syndrome of "secondary myelofibrosis" can result from infiltration of the marrow by diseases such as acute leukemia (37), carcinoma (29, 30, 33, 57) myeloma (16) or tuberculosis (2, 17), or can follow chronic myeloproliferative disorders such as polycythemia vera or chronic granulocytic leukemia (12, 14, 23, 32, 44, 54). Recently, chromosomal and enzyme marker studies in a few patients with the "primary" syndrome have shown evidence for a clonal disorder affecting the bone marrow stem cell but not the marrow fibroblast (1, 27). There is also independent evidence to suggest that the bone marrow fibroblast does not have its origin from the bone marrow stem cell (20). Thus, the concept is emerging that, as in the case of "secondary myelofibrosis," the so-called primary myelofibrosis actually may result from a disease of the bone marrow stem cell that causes a secondary "reactive" fibrosis. For these and other reasons, many authorities feel that this syndrome represents a distinct disease entity within the spectrum of the myeloproliferative disorders. However, there is marked variability and unpredictability both in the clinical severity and in the duration of survival following diagnosis (8, 36, 45, 48, 52, 53, 56). Therefore, it remains possible that this clinical syndrome includes a heterogenous group of disorders, only *some* of which are related to a primary disease of the bone marrow stem cell.

Previous clinicopathologic studies of this syndrome have usually preselected patients who fit a classic description, having marrow fibrosis, extramedullary hematopoiesis, splenomegaly, and a leukoerythroblastic peripheral blood smear. In these series it is not entirely clear whether any patients who did not fit all of these somewhat arbitrary criteria were excluded. In addition, some of these series have included patients with previous diagnoses of other myeloproliferative disorders such as polycythemia rubra vera. We have therefore chosen to carry out a detailed clinicopathologic review of a *consecutive* series of *all* patients who fulfilled a single criterion: that of having fibrosis in the bone marrow without any apparent cause. These patients are generically defined here as having "idiopathic myelofibrosis" (IM). Accurate and complete information regarding most parameters was available on all these patients. We therefore set out to define, using appropriate statistical methods, the prognostic variables at the time of diagnosis that could predict the survival of the individual patient. We believed that the results of such an analysis could not only provide information of practical value to the clinician caring for such patients, but might also provide clues toward a better understanding of the underlying unknown cause(s) of this syndrome.

### Patients and Methods

#### *Selection of patients*

A complete listing had been maintained of the initial diagnosis made on *all* patients seen and followed by a Hematology

From the Division of Hematology-Oncology, Department of Medicine, and the Division of Surgical Pathology, Washington University School of Medicine, and Barnes Hospital, St. Louis, Missouri.

[1] Current Address: Division of Hematology, University of Florida College of Medicine, Gainesville, Florida.

Supported by American Cancer Society Institutional Grant No. IN-36(43192V) and the Barnes Hospital Cancer Research Fund.

Address reprint request to: Ajit Varki, M.D., Division of Hematology-Oncology, Dept. of Medicine T-011, University of California at San Diego, La Jolla, California 92093.

Consulting Service at Barnes Hospital run by one of us (E.H.R.) during the period 1968–1980. From this list, it was possible to identify all patients in whom the diagnosis following the initial workup and marrow biopsy included unexplained marrow fibrosis. The charts of these 88 patients were then reviewed. Patients with a clearcut history of a previous diagnosis of polycythemia vera (9 cases) or essential thrombocytosis (3 cases) antedating the appearance of marrow fibrosis were excluded from further analysis. Eleven other patients were excluded because of the appearance of an underlying primary disease very shortly after the initial diagnosis (acute leukemia in 6 cases, metastatic carcinoma in 3 cases, and a malignant lymphoma in 2 cases). The remaining 65 patients thus fulfilled the criterion of having bone marrow fibrosis for which no cause could be found. Of these, four cases had to be excluded from further analysis because of inadequate pathological specimens and/or missing records. The bone marrow biopsy specimens of the remaining 61 cases were retrieved and subjected to a review by one of us (R.G.) who was without access to any of the clinical information. In five cases, the bone marrow biopsy findings were found to be consistent with the diagnosis of "leukemic reticuloendotheliosis" or "hairy cell leukemia" (7, 11, 18, 21, 42, 60). In these cases, which were from the early years of the series, this diagnosis had evidently not been considered in the original bone marrow biopsy evaluation. Two of these patients were still under active follow-up and examination of their peripheral blood smears showed the presence of "hairy cells" containing tartarate resistant acid phosphatase (TRAP)-positive granules. These five cases were excluded from further analysis. In the remaining 56 cases, review of the initial and/or subsequent bone marrow biopsies showed evidence for increased amounts of fibrous tissue (see Results section for further details). These patients were considered to have unexplained bone marrow fibrosis or "idiopathic myelofibrosis" (IM).

### *Patient records*

Very extensive and complete office and hospital records had been maintained on all the patients. All follow-up hematological laboratory values, blood transfusions, and drug therapy (including dosages and duration) had been recorded on a standard "hematologic and therapy sheet." All hematologic values had been determined by a special hematology laboratory attached directly to the clinic, throughout the period of the study. Other studies had been obtained through the Barnes Hospital Laboratories. Laboratory reports from outside sources were not accepted for this analysis, with the exception of hemoglobins, hematocrits and total white cell counts. Wherever necessary, the referring physicians were contacted for up-to-date follow-up information.

### *Pathology review*

Histopathologic findings in the bone marrow biopsies were evaluated in a semi-quantitative manner by one of us (R.G.) using hematoxylin and eosin (H&E) and Gomori reticulin stains. The degree of reticulin fibrosis on the Gomori stain was estimated on a scale of 1+ to 4+. The overall percentage of the marrow area occupied by hematopoietic cells, adipose cells, and fibrosis was estimated on the H&E stain. In addition, the presence or absence of collagen fibrosis, osteosclerosis, or both was recorded, as well as the pattern of cell distribution (patchy or diffuse); the presence of maturation abnormalities in the myeloid cells; and the numbers of megakaryocytes.

### *Statistical methods*

Specially developed computer sheets were filled out by two of us (A.V. and R.L.) by reviewing each record in detail. Bone marrow biopsies were independently reviewed by R.G., who was without access to the clinical information, and the findings entered on a separate sheet. The information on the sheets was then entered on an IBM 370 computer via a key punching system, and stored as an SAS data set; most analyses were carried out using SAS procedures (49). Survival curves were plotted by the Kaplan-Mier method (28). Univariate analyses for the identification of prognostic factors were carried out using two separate methods, Breslow's modification of the generalized Wilcoxon statistic (10) and the log-rank test of Mantel-Cox (38). Multivariate analysis of the significant factors identified in this manner was carried out using the Cox Proportional Hazards function method (25). For following trends in serially recorded data, the cumulative sums (cusum) plot method was used (59). Chi-square analyses were carried out using Fisher's exact test (19).

## Results

### *General patient characteristics*

Of the 56 patients, 34 were men and 22 were women. The mean age was 61.27 years (SD 14.1; range, 23.2–83.8 years). The age and sex distributions are summarized in Figure 1. Five of the twenty women were post-menopausal at the time of diagnosis. There appears to be a bimodal distribution in the age incidence curve for women. The number of women in the younger age peak was too small to allow separate analysis to determine if they had a disease with distinct characteristics. We are therefore uncertain of the meaning of this finding. At the time of closure of the study (June 1981) 32 patients were dead, 19 were alive, and the status of 5 was not definite. These five cases were included in the survival analysis up to the date of the last known follow-up.

### *Follow-up intervals*

*The date of initial diagnosis* was defined as that date upon which the initial bone marrow biopsy showing fibrosis had been performed. In several cases, there was evidence of earlier symptoms or signs that could reasonably be attributed to the same disease process. Therefore, in addition to the date of diagnosis, *a date of onset of first symptoms or signs* that could be directly related to the IM was also recorded. The mean interval from the date of diagnosis to the date of last follow-up or death was 3.64 years (S.D. 2.95; range, 0.06–9.39 years). The mean interval from the date of onset of first symptoms or signs to the last follow-up or death was 6.01 years (SD 5.18; range, 0.44–33.4 years). Table 1 compares the general characteristics of the group

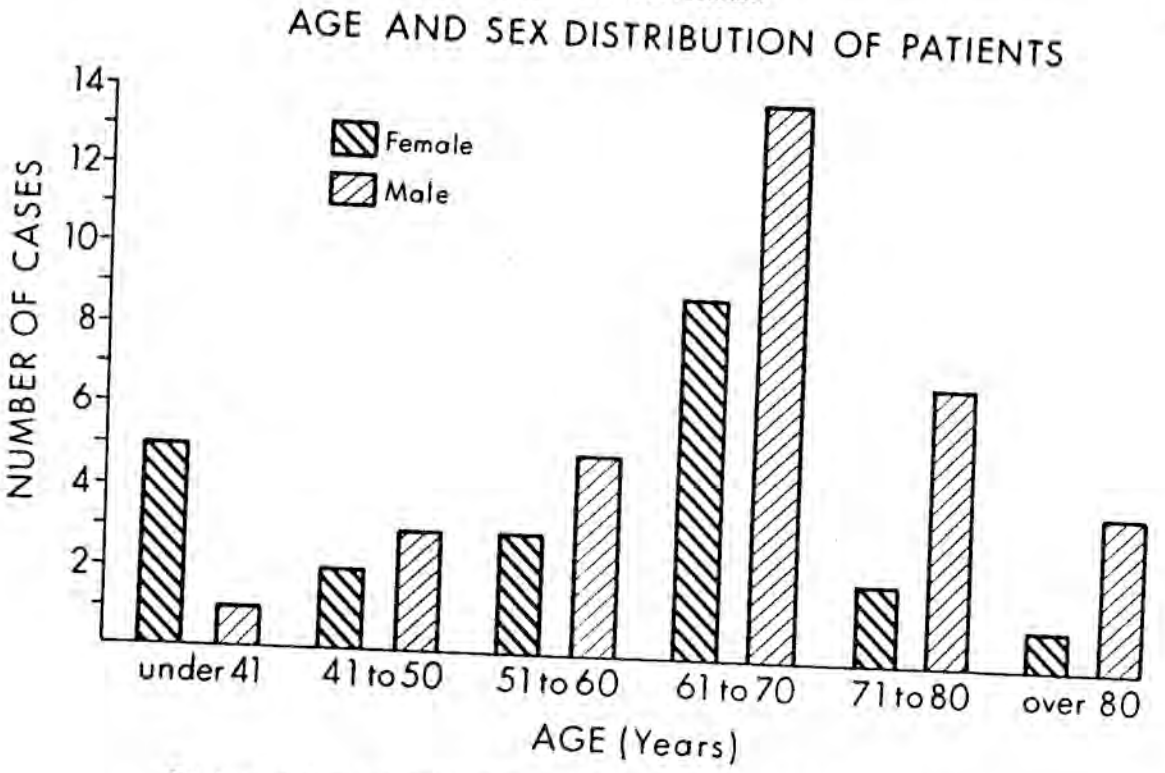


FIG. 1. Age and sex distribution of 56 patients with "idiopathic myelofibrosis" (IM)

**TABLE 1. General patient characteristics: Comparison with other series**

| Findings | This study (1982) | Linman and Bethell (36) (1957) | Pitcock et al (1962) | Bouroncle and Doan (8) (1962) | Silverstein et al (52) (1967) | Rosenthal and Moloney (48) (1969) | Ward and Block (56) (1970) |
|---|---|---|---|---|---|---|---|
| No. of cases | 56 | 56 | 70 | 110 | 137 | 98 | 45 |
| Time period covered | 1968–80 | 1942–55 | NM | 1952–62 | 1960–65 | 1954–68 | NM |
| Diagnostic criteria | BM. Bx. Fibrosis, no cause | Previous Dx of AMM | BM. Bx. Fibrosis, no cause | Previous Dx of AMM | Previous DX of AMM | Previous Dx of AMM | Previous Dx of AMM(?) |
| Bone marrow biopsy | All | 15/56 | All | 32/110 | All(?) | 71 | 39/45 |
| Consecutive series? | Yes | Yes | Yes | Yes | Yes | Yes | NM |
| Exclusions | 3-No path, 1-Lost | NM | None? | NM | NM | NM | NM |
| P. Vera include? | No | NM | Yes | Yes | Yes | Yes | NM |
| | | | | (10) | (24) | (26) | |
| Age at Dx(yrs): | | | | | | | |
| Median: | 61.3 | 62.5 | 61 | 60 | 58.4 | 63.8 | 60.5 |
| Range: | 23–84 | 37–80 | 32–78 | 15–80 | NM | 32–94 | NS |
| Male/Female | 34/22 | 29/27 | 39/31 | 55/55 | 61/76 | 50/48 | 25/20 |
| Number: | | | | | | | |
| Alive | 19/56 | 24/56 | NM | 30/110 | ?72/137 | 27/98 | NM |
| Dead | 32/56 | 17/56 | NM | 55/110 | 65/137 | 45/98 | NM |
| Lost to follow-up | 5/56 | 15/56 | 18/70 | 25/110 | ?None | 27/98 | NM |
| Survival from Dx(yrs.) | | | | | | | |
| Median | 5.0 | 1.5 | 1.5 | 2–3 | 5 | 1.4 | 5.2 |
| Range | 1–9+ | 1–5 | 1–10 | 1–10+ | NM | 1–12+ | 1–16+ |

NM = Not Mentioned, Dx = Diagnosis, Bx = Biopsy

of patients studied here with previous large series of similar patients reported in the literature.

*Symptoms*

The symptoms and other historical information elicited on the first evaluation are summarized in Table 2 and compared with the incidence reported in some other series. Twelve of the 56 patients were asymptomatic at presentation, and were discovered upon incidental physical examination (splenomegaly) or laboratory evaluation (abnormal peripheral smear). However, nine of these patients developed some significant symptoms during the course of the follow-up. Fatigue was the most frequent com-

**TABLE 2. Historical and physical findings: Comparison with previous series**

| Finding | % Incidence* | |
|---|---|---|
| | This series | Previous series† (Range) |
| History | | |
| Fatigue | 71 | 16–94 (6) |
| Asymptomatic | 21 | 0–69 (5) |
| Fever | 5 | 2–19 (4) |
| Symptoms of splenomegaly | 11 | 4–57 (6) |
| Symptoms of bleeding | 20 | 9–31 (6) |
| Symptoms of gout/renal stones | 13 | 6–23 (2) |
| Weight loss | 39 | 7–76 (6) |
| Night sweats | 21 | 10–40 (2) |
| Anorexia | 18 | 50 (1) |
| Hearing loss | 29 | — (0) |
| Dyspnea | 48 | 9–60 (5) |
| Physical examination | | |
| Wasting/emaciation | 13 | 37 (1) |
| Petechiae/ecchymoses | 20 | 7–26 (5) |
| Splenomegaly | 89 | 94–100 (6) |
| Hepatomegaly | 64 | 54–89 (6) |
| Decreased hearing | 19 | 9 (1) |
| Peripheral edema | 13 | 9–27 (4) |
| Evid portal hypertension | 2 | 1–4 (5) |
| Bone tenderness | 2 | 1–11 (3) |
| Adenopathy | 2 | 5–22 (5) |
| Jaundice | 0 | 0–8 (6) |

* Incidence = number with finding/number evaluable × 100.
† The % incidence of the findings reported in six major series (10, 36, 45, 48, 53, 56) of similar patients is reported as a range. The figure in parenthesis indicates the number of series in which the findings were mentioned.

plaint, occurring in 40 of the 46 patients who had any symptoms. Other relatively non-specific symptoms such as fever, night sweats, dyspnea, anorexia and weight loss also occurred. Appropriate studies for the origin of the fever had been carried out in each case. When laboratory findings, autopsy findings, or both failed to uncover a specific cause of persistent fever, the patient was entered as having "unexplained fever" and the date of onset noted. The degree of the weight loss had been quantitated (as a percentage of original weight) in the record in all but two cases. Other symptoms included excessive bleeding, symptoms of splenomegaly, hearing loss, pruritus, and a history of gout or renal stones (see Table 2).

*Other medical history*

Other medical problems included diabetes mellitus (3 cases), hypertension (1 case) and heart disease (4 cases). Two patients had had early-stage malignancies (cervical carcinoma, ovarian carcinoma) treated surgically more than 5 years previously, with no evidence of subsequent recurrence. There was no significant history of exposure to benzene, carbon tetrachloride, or any other known toxins.

*Physical examination*

The incidence of various physical signs noted during the initial evaluation is summarized in Table 2 and compared with other series. The spleen was palpable in most of the patients, but varied greatly in size. The liver was also palpable in the majority of cases, but again varied considerably in size. Several patients were reported to have ecchymoses and petechiae in the skin. Hearing loss was noted in several cases, but there was limited information about the type of hearing deficit.

*Laboratory findings*

The hematological findings at the time of diagnosis are summarized in Table 3. There was considerable variability in all the parameters. The peripheral blood smears showed nucleated red blood cells and immature white cells in all cases. Blast cells were seen on 24 smears (range, 1–13%) and the pseudo-Pelger–Huet anomaly was noted on 17 smears. The leuocyte alkaline phosphatase score was performed in 46 patients; 10 scores were low, 13 were high, and the remainder were normal. A sucrose hemolysis test was performed on 12 patients with suspected hemolysis; one was positive. In this patient, the acid hemolysis (Ham) test was also positive. This association has been previously reported (31, 35).

The other available laboratory data were difficult to evaluate for two reasons. First, most of the tests were not obtained on all the patients at or close to the time of diagnosis. Second, over the period of the study, the normal values of the Barnes Hospital laboratory changed when techniques of analysis were being modified or updated. Regardless, the following laboratory tests were abnormal at some time during the clinical course in the cases examined: LDH (31/33 high), bilirubin (16/41 high), uric acid (20/33 high), alkaline phosphatase (22/41 high), SGOT (20/40 high). All the other laboratory tests had been performed on fewer than 30 patients.

*Bone marrow review*

Bone marrow aspirates were attempted in all cases. Adequate aspirates were obtained only in six instances. Only sinusoidal blood was obtained in 21 other cases, while the tap was completely dry in 29. A bone marrow biopsy was obtained in all cases by either a surgical approach, or using a Jamshidi or Westerman-Jensen needle. In a few cases the initial biopsy was not available for the current review, and a subsequent biopsy specimen was used to allow

TABLE 3. Hematologic findings at the time of diagnosis

| | Mean | S.D. | Minimum | Maximum |
|---|---|---|---|---|
| 1. RBC count ($\times 10^{-6}$/mm$^3$ | 3.70 | 1.12 | 1.62 | 6.69 |
| 2. Hematocrit(%) | 32.1 | 9.0 | 16 | 53 |
| 3. Hemoglobin (g/dl) | 10.1 | 2.78 | 5.0 | 15.6 |
| 4. Platelet count ($10^3$/mm$^3$) | 346.0 | 260.9 | 7.0 | 980.0 |
| 5. Reticulocytes (%) | 4.1 | 3.7 | 0.4 | 19.4 |
| 6. WBC count ($\times 10^{-3}$/mm$^3$) | 16.6 | 28.3 | 2.1 | 185 |

TABLE 4. Bone marrow biopsy findings at diagnosis

| | This study | Ward and Block (56) |
|---|---|---|
| Number of biopsies | 48 | 39 |
| % Hematopoietic cells | | |
| 0–25% | 6% | |
| 26–50% | 10% | |
| 51–75% | 31% | |
| 76–100% | 52% | 26% |
| Pattern of cellularity: | | |
| Diffuse | 71% | 62% |
| Patchy | 29% | 38% |
| Megakaryocytes | | NC |
| Increased | 90% | |
| Decreased | 4% | |
| Normal | 6% | |
| Granulocytes | | NC |
| Increased | 70% | |
| Immaturity | 8% | |
| %Fibrosis/collagen (H&E) | | NC |
| 0–10% | 79% | |
| 11–25% | 15% | |
| 26–50% | 2% | |
| 51–100% | 4% | |
| Reticulin fibrosis (Gomori stain) (scale 1+ to 4+) | | NC |
| 1+ | 12% | |
| 2+ | 21% | |
| 3+ | 46% | |
| 4+ | 21% | |
| Osteosclerosis | 54% | 36% |

NC = not addressed in a manner suitable for comparative study.

inclusion in this series. Table 4 summarizes the findings in 48 biopsies that were performed at the time of diagnosis. As a general statement, the majority of the biopsies demonstrated hypercellular bone marrows, in which megakaryocytes were relatively increased. Evidence of fibrosis and osteosclerosis were seen on the H&E stain and the reticulin stain showed a marked increase in reticulin fibers (67%—3+ to 4+). These findings were compared with those described in previous similar series. Table 4 shows a comparison with some of the findings reported by Ward and Block (56). In the case of the other previous series, most of the parameters were not addressed in a manner suitable for a good comparative study with the present findings.

*Follow-up data*

Detailed follow-up data were available on most of the patients. However, only a brief summary will be presented here. There was marked variability in the severity of the clinical course of these patients following the diagnosis. This is exemplified by the finding that only 31 of the patients required hospitalization during the follow-up. Among the patients who were dead, the percentage of their lives spent in the hospital following diagnosis varied from 60% to 0.5% (detailed data not shown). The rate of growth of the spleen and liver was also quite variable. The raw data available for the serial measurements of spleen size were converted to cusum (cumulative sums) plots to allow clearer demonstration of trends (59), which are shown in Figure 2. It can be seen that the patients who eventually required splenectomy more commonly showed a rapid rate of growth. In a few patients, a decrease in spleen size clearly occurred. In these cases, this phenomenon could not be attributed to concomitant busulfan therapy, and remains unexplained.

A wide variety of complications and associated medical problems were seen during the follow-up period. These included infections (predominantly pneumonias and urinary tract infections), bleeding (in 15 cases, mostly not life-threatening), congestive heart failure (6 cases), cerebrovascular accidents (3 cases), and pulmonary embolism (3 cases). Clinically apparent extramedullary hematopoiesis in sites other than the spleen and liver occurred only in two patients. Hyperuricemia was noted in 20 cases, but only 2 patients suffered from renal stones. Portal hypertension and ascites were seen in three cases, but in all three instances, other possible etiologies for liver disease were present. Splenic pain occurred in eight cases, and in three of these there was definite evidence of infarction (new splenic rub). In two patients, an acute leukemic phase (characterized by high white blood cell counts and a predominance of blast forms) occurred (7 and 24 months after the initial diagnosis, respectively). In two other patients who had died of multiple complications, definite evidence of leukemic transformation with organ invasion was found at autopsy, although the peripheral blood smears had been unchanged at the time of death. No specific features at presentation appeared to predict the occurrence of acute leukemia. The exact causes of death could not be ascertained in some of the patients because they had returned to the care of their

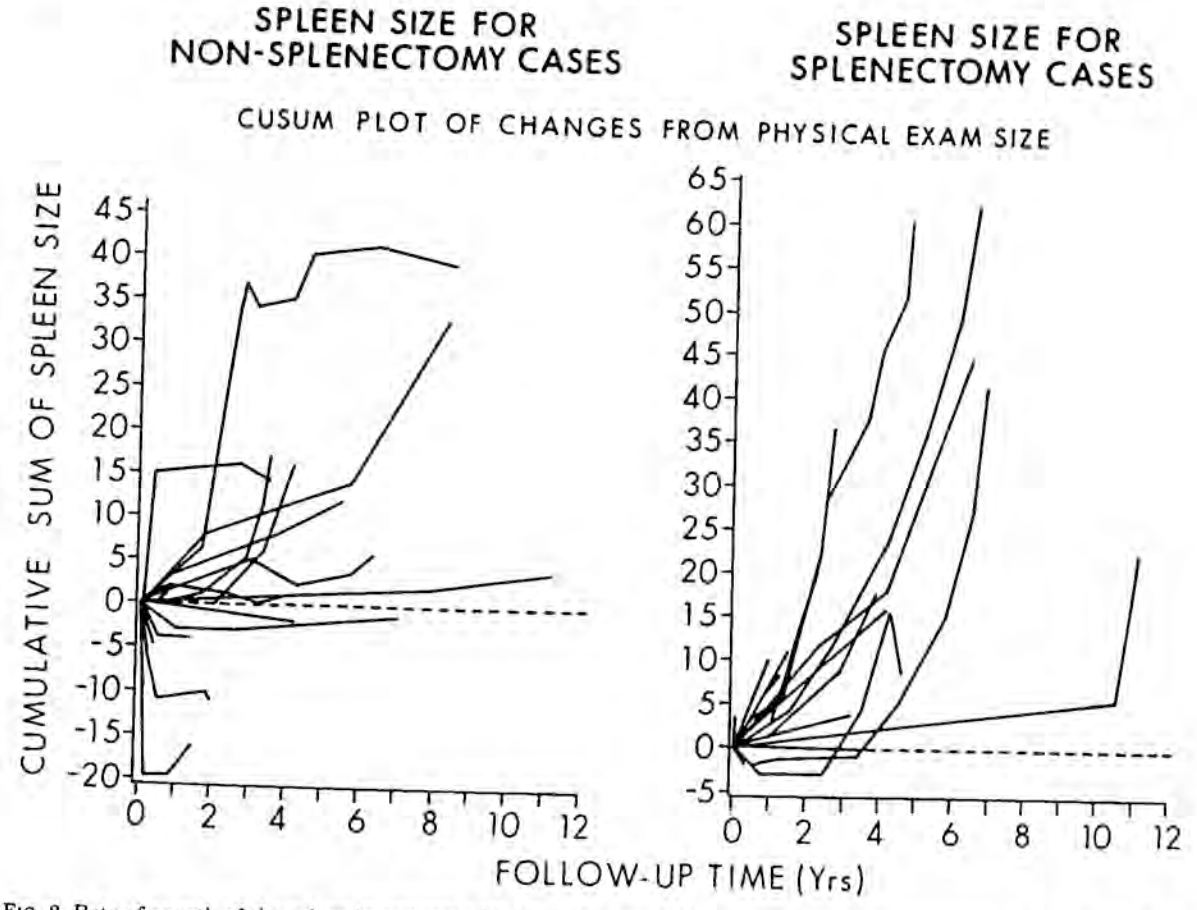


FIG. 2. Rate of growth of the spleen in patients with idiopathic myelofibrosis. The serial measurements of the size of the spleen (in cm below the left costal margin) were converted into cumulative sums (cusum) plots. The right panel represents patients who eventually required splenectomy during the course of their follow-up, and the left panel represents the remainder of the cases.

families before their demise. Among the known causes of death, infections, cerebrovascular accidents, cardiac failure, post-splenectomy complications, and acute leukemia predominated.

*Management and therapy*

Detailed information on all aspects of the management of most of these patients was available, and was subjected to a careful analysis. However, because of the retrospective and uncontrolled nature of the information, only a brief summary will be presented here. Several patients received androgens and/or busulfan; however, the clinical situations were sufficiently confusing that attempts to obtain reliable numerical data about responses were futile. An occasional patient appeared to have a striking response to androgen therapy. There was no clear-cut evidence that the arbitrary lowering of a high platelet count was of any clinical benefit. Some patients who received myleran for some duration developed severe thrombocytopenia, which persisted after the discontinuation of the drug. Transfusion therapy was the mainstay of treatment. However, only 39 of the 56 cases required red-cell transfusions during the course of the disease, and the transfusion requirements varied markedly. No patient received high doses of pryidoxine (46) or was subjected to marrow curettage (39).

Seventeen of the 56 patients had a splenectomy performed. All these procedures were done by the Surgical Service at Barnes Hospital. The indications were increased transfusion requirements (9 cases), thrombocytopenia (3 cases), splenic pain or abdominal fullness (10 patients) and following trauma (1 patient). Some patients had more than one indication for the procedure. The mean interval between the time of diagnosis and the time of splenectomy was 2.4 yrs. (SD 1.8 years; range, 0.2–7.2 years). Nine of the 17 patients had significant complications following the splenectomy. These included left lower lobe pneumonias and effusions (4 cases), other infections (3 cases), pulmonary em-

bolism (1 case) and hemorrhage (4 cases). Notably, none of the patients with hemorrhage had marked thrombocytopenia prior to the surgery. Three patients died as a direct result of complications following the procedure. Although the numbers were small, a chi-square analysis using Fisher's exact test demonstrated significant positive associations between the presence of pre-operative pain, massive splenomegaly, or both, and the outcomes of post-operative infection, left lower lobe problems and death (detailed data not shown). None of the other preoperative variables tested, including age at splenectomy, were significant for predicting the incidence of complications. The weights of the spleens examined pathologically varied from 600 to 4500 g, and all showed extramedullary hematopoiesis. In nine patients, excessive transfusion requirements were a major indication for the splenectomy. None of these patients had a positive direct Coombs' test, and no other definite cause for blood loss was found in any of them. In seven of the nine patients sufficient data were available to enable evaluation of the response. Figure 3 shows that only two of the seven patients had a clear-cut improvement in their requirement for red cell transfusions. Ferrokinetic studies were not performed prior to splenectomy in any of the cases. Survival studies of $^{51}$Cr-labelled RBC were done in only four of these seven cases before splenectomy. The numbers were too small to determine if the RBC survival studies were of value in predicting the response to splenectomy. Because of the retrospective nature of this study, it is also difficult to comment on the other subjective benefits of splenectomy in patients who survived the procedure, such as improvement in abdominal discomfort, pain and early satiety.

Three patients died as a direct consequence of complications following the operation. In the remaining patients in whom complete follow-up was available, the median survival after splenectomy was 25.6 months (range, 6.6–61.6 months). Symptomatic increase in liver size occurred in only four patients post-splenectomy, and was first noted at 4, 5, 14 and 60 months after the procedure. It should be noted that in the overall series of patients, 50% of those who died had not required splenectomy during their course.

## Analysis of Survival Data

### *Overall survival*

The overall survival in all 56 cases, plotted by the Kaplan-Mier method, is shown in Figure 4. When computed from the date of initial diagnosis (defined as the date of the first bone marrow biopsy that demonstrated fibrosis), the median survival was 5.1 years (range, 6 months–9+ years). Such a considerable variation in the survival has been noted in several previous reviews of similar patients. As mentioned earlier, the date was also noted of the first documented signs or symptoms that could be attributed to the disease process. When the survival data were plotted from this date, the median survival was considerably longer (8.1 years), with a range from 1 to 33 years (see Fig. 4.) However, it should be noted that the interval from the first evidence of disease to the date of diagnosis was also extremely variable.

### *Analysis for prognostic variables predicting survival*

As described, all of the patients had a complete history, physical examination, and hematologic evaluation done on or very close to the date of the first diagnostic bone marrow biopsy. From this initial data base, we studied each variable for which reliable information was available on at least 45 of the 56 patients. A list of these variables, with the number of evaluable cases for each variable is presented in Table 5. The variables from the bone marrow biopsy were based on the findings of the current review of specimens described above. In a few cases, the original diagnostic core biopsy specimen that had been reported to show fibrosis was not available for review, but a subsequent biopsy specimen was available for the confirmation of the diagnosis. In these cases the bone marrow biopsy review findings were not used for the survival analysis unless the available biopsy had been done less than 6 months from the initial date of the diagnosis.

A univariate analysis for the value of each of these variables in predicting survival from the date of diagnosis was then carried out. The survival curves of the various sub-groups indicated in Table 5 were plotted by the Kaplan-Mier method. In each case two independent tests for significant differences in survival were used. The Breslow modification of the generalized Wilcoxon method (10) gives greater weight to early observations, whereas the log-rank test of Mantel-Cox is more sensitive to late events that occur when few patients remain alive (38). The results of analysis of each variable using both tests of significance are summarized in Table 5.

### *Prognostic value of historical findings at diagnosis*

The most significant historical feature predicting poor survival was the presence of unexplained fever at diagnosis ($p < .0001$ with both tests of significance.) The age at diagnosis, the presence of weight loss and a history of night sweats were significant with one test, and borderline-significant with the

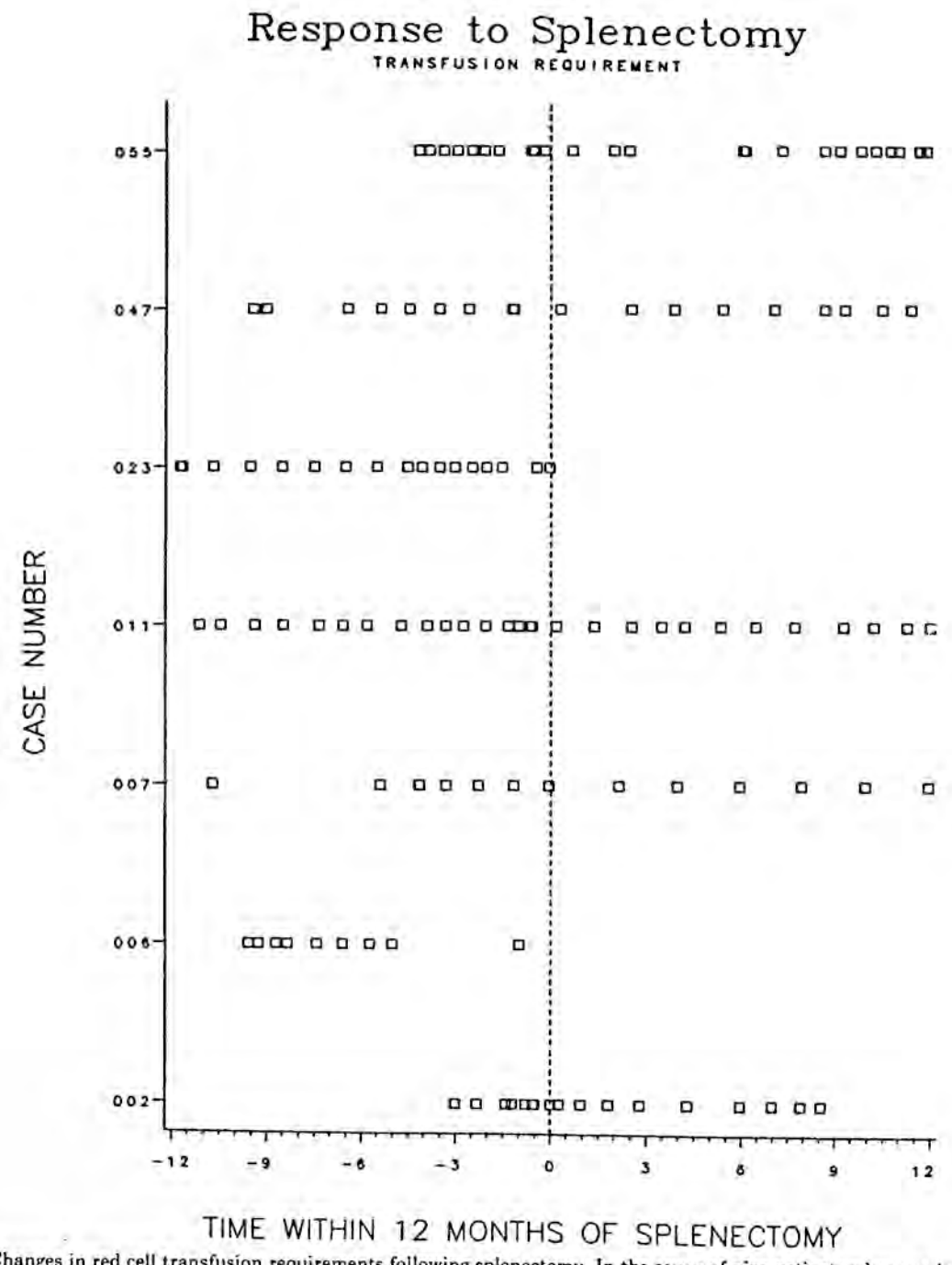


FIG. 3. Changes in red cell transfusion requirements following splenectomy. In the seven of nine patients whose major indication for splenectomy was an increasing red cell transfusion requirement, adequate follow-up data were available. Each box represents a transfusion of two units of packed red cells. The transfusions required during the 12 months preceding and following the date of the splenectomy are indicated.

other (see Table 5 and Fig. 5). The common symptom, fatigue, was also significant with one test. However, several patients also had congestive heart failure or other unrelated illnesses that could account for this symptom. As expected, a history of prior transfusions for the same illness was a prognostically significant variable. Notably, the sex, menopausal status, symptoms of splenomegaly, or symptoms of hearing loss were of no detectable significance (see Table 5.)

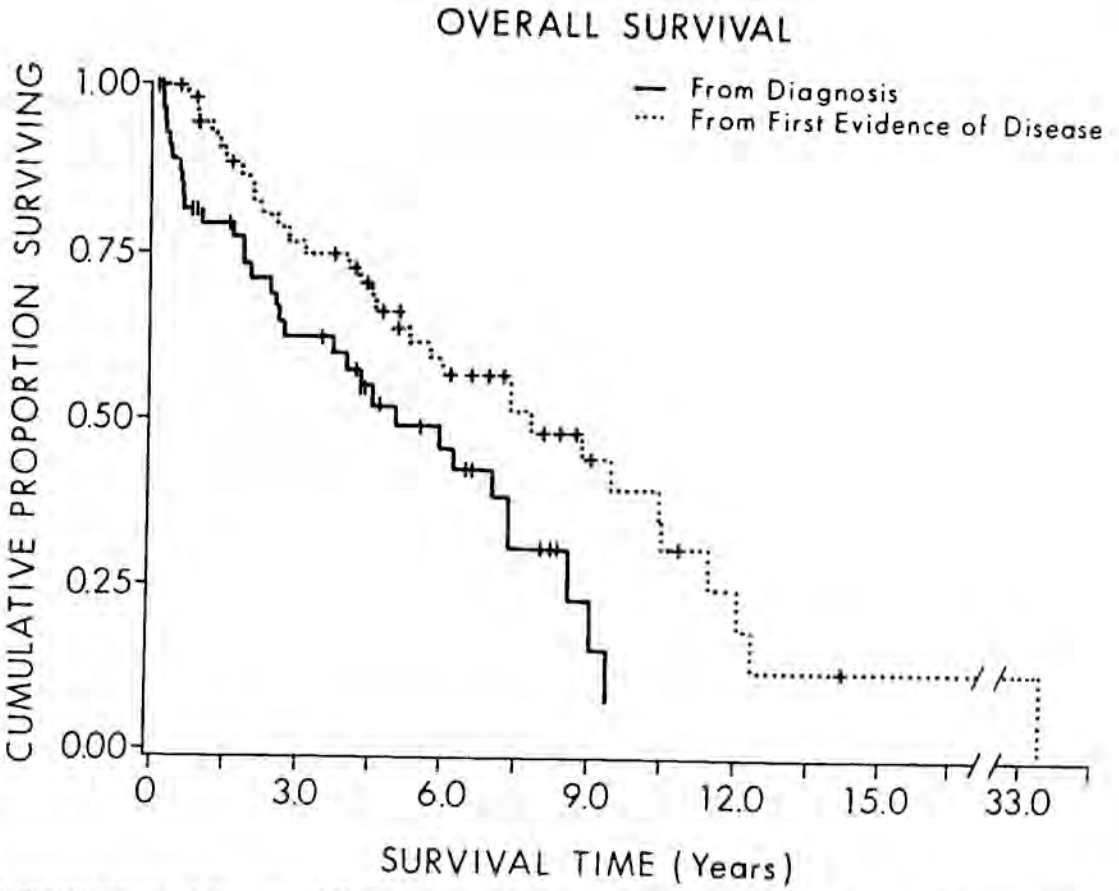


FIG. 4. Overall survival of the group of 56 patients with idiopathic myelofibrosis, from the date of the diagnostic bone marrow biopsy, and from the date of onset of first symptoms or signs of disease. The data are plotted by the Kaplan-Mier method.

*Prognostic value of physical findings at diagnosis*

The only finding of prognostic significance on the physical examination was the presence of petechiae and ecchymoses on the skin ($p = 0.0002$ and 0.0003 on the two tests). Notably, the size of the spleen or of the liver was of no prognostic significance whatsoever (see Table 5 and Fig. 6).

*Prognostic significance of laboratory values at diagnosis*

Of the hematological parameters that were evaluated, the presence of a low hematocrit, low hemoglobin or a low platelet count at diagnosis were found to be very significant predictors of a poor prognosis (see Table 5 and Fig. 7). The finding of ecchymoses and petechiae upon examination, and the presence of a history of bleeding (by site) were compared with the platelet count, as shown in Figure 8. It can be seen that all of the patients with ecchymoses and petechiae and/or a history of bleeding into the skin had lower than normal platelet counts. However, it is of interest that several of these patients had counts in the range higher than that usually associated with hemorrhage (i.e., > 10,000–20,000/mm$^3$). There was no evidence that a higher than normal platelet count was of poor prognostic significance (see Table 5). This remained true even when the small subgroup of patients with a platelet count greater than 900,000/mm$^3$ were separately compared with those who had a count in the normal range (data not shown). It was also of note that the total white blood cell count, the percentage of blasts or immature granulocytes seen on the peripheral smear, and the level of the leukocyte alkaline phosphatase were of no prognostic significance whatsoever (see Table 5).

*Prognostic value of bone marrow findings at diagnosis*

As shown in Table 5, the presence or absence of difficulty in obtaining an adequate marrow aspirate was of no prognostic significance. Furthermore, the overall cellularity of the marrow biopsy, the relative number of megakaryocytes, the degree of immatu-

**TABLE 5. Univariate analysis for effects upon survival (from date of diagnosis)**

| Parameter (at date of Dx.) | No. of cases evaluable | Groups compared | p value: Breslow (generalized Wilcoxon) | p value: Mantel-Cox (log-rank) | Comment |
|---|---|---|---|---|---|
| Initial history | | | | | |
| 1. Age(years) | 56 | <50/51-60/61-70/> 70 | 0.0920 | 0.0170 | S |
| 2. Fatigue | 56 | Yes/no | 0.0262 | 0.1650 | PS |
| 3. Unexplained fever | 56 | Yes/no | 0.0001 | 0.0001 | S |
| 4. Weight loss (% of body weight) | 52 | No/<10%/>10% | 0.0741 | 0.0415 | S |
| 5. Night sweats | 54 | Yes/no | 0.0471 | 0.1000 | PS |
| 6. Past history of transfusion | 56 | Yes/no | 0.0112 | 0.0432 | S |
| Initial physical examination | | | | | |
| 7. Nutrition | 54 | Normal/wasted obese/ | 0.0571 | 0.1514 | PS |
| 8. Ecchymoses/petechiae | 56 | Yes/no | 0.0002 | 0.0003 | S |
| 9. Liver size | 56 | 0/1-5/>5 cms. | 0.4932 | 0.5535 | NS |
| 10. Spleen size | 56 | 0/1-5/5-10/>10 cms. | 0.2712 | 0.1633 | NS |
| Initial laboratory data | | | | | |
| 11. Leukocyte alkaline phosphatase score | 45 | High/normal/low | 0.76 | 0.58 | NS |
| 12. Hemoglobin(dl) | 55 | <6/6-8/8-10/10-12/>12 | 0.0003 | 0.0001 | S |
| 13. WBC count ($\times 10^{-3}$/mm$^3$) | 55 | <4/4-10/10-20/>20 | 0.2206 | 0.3959 | NS |
| 14. Blasts(%) | 54 | 0/1-2/3-4/>4 | 0.0668 | 0.2125 | NS |
| 15. Platelet count ($\times 10^{-3}$/mm$^3$) | 54 | <25/25-150/151-400/>400 | 0.0024 | 0.0024 | S |
| 16. Absolute polymorph. count/mm$^3$ | 54 | <2000/>2000 (only 1 case <1000) | 0.2806 | 0.4915 | NS |
| Bone marrow biopsy: | | | | | |
| 17. Cellularity(%) | 48 | Normal(25-50%) vs. 51-75 vs. 76-100% | 0.9798 | 0.9852 | NS |
| 18. Reticulin | 48 | Scale 1$^+$-4$^+$ | 0.4076 | 0.2389 | NS |
| 19. % Fibrosis (H&E) | 48 | 5%/5-10%/>10% | 0.4500 | 0.4600 | NS |

Several different variables at the time of diagnosis were studied for their ability to predict subsequent survival. In each case, two independent tests for significant differences were performed, the Breslow (generalized Wilcoxon) and the Mantel-Cox (log rank) tests (see text for further details). The p values obtained reflect the probability that an observed difference in survival is real (S = significant, PS = possibly significant, NS = not significant). The variables that gave positive results are listed above, along with some significant negative variables. The following variables were also found to be not significant in predicting survival: sex, being asymptomatic at diagnosis, symptoms of splenomegaly, history of bleeding, history of gout or renal stones, dyspnea, hearing loss, pruritus, anorexia, level of alcohol consumption, cigarette smoking, menopausal status, % monocytes or % immature WBCs on the peripheral blood smear, the degree of difficulty in obtaining an adequate marrow aspirate, and the presence or absence of collagen on the H&E stain of the bone marrow biopsy specimen (detailed data not shown). As with the initial hemoglobin (see above), the initial hematocrit was highly significant (data not shown).

rity of the granulocytes, the degree of fibrosis and collagen formation (on the H & E stain), and degree of reticulin fibrosis (on the reticulin stain) were of no detectable significance (see also Fig. 9).

*Significance of appearance of bad prognostic variables on follow-up*

Since serial follow-up information was available on most of the patients, it was of interest to analyze the survival of the patients after the first time of appearance of a bad prognostic variable on follow-up. This was possible for two of these variables: unexplained fever and weight loss. In most patients, the follow-up record clearly indicated the date of appearance of fever. Among these, four patients could be identified in whom the fever could not be explained by any other known active process at the time. The survival of the four patients who developed unexplained fever was extremely poor from the time of the symptom's onset. Their median survival was 2 months from the onset of the symptom; all were dead within 39 months from the time of onset (survival curves not shown). A similar analysis was performed for the significance of weight loss appearing on follow-up. The weight of each patient (in lb) was recorded at the first visit and at every subsequent visit. With this information, it was possible to identify the time when each individual patient first developed weight loss that was greater than 10% of the original body weight. Seven such cases were identified. (As in the case of fever, this number is probably an underestimate, since the follow-up interval for some patients may have been inadequate to identify the onset of such weight loss.) Regardless, the survival of these seven patients from the time of onset of weight loss of greater than 10% of original body weight was also extremely poor. Their median survival was 19 months from the onset of the symptom, and all

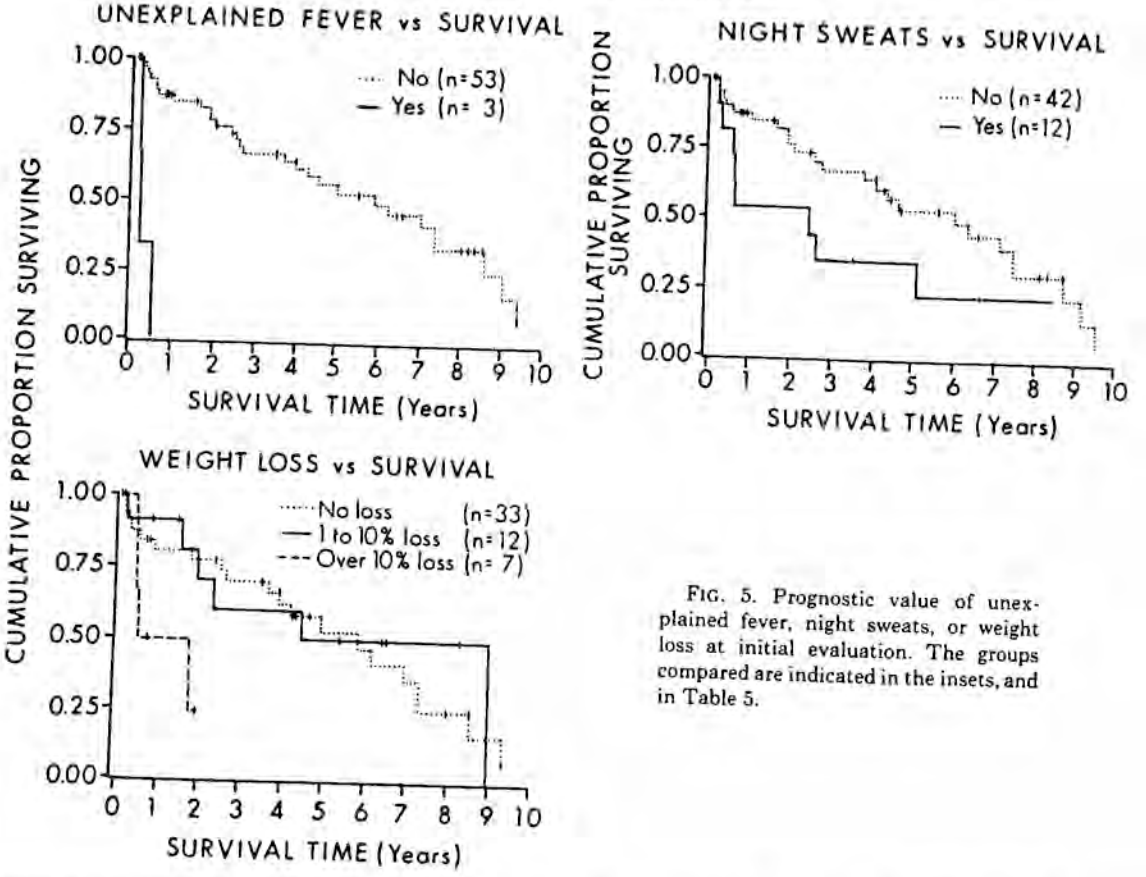


FIG. 5. Prognostic value of unexplained fever, night sweats, or weight loss at initial evaluation. The groups compared are indicated in the insets, and in Table 5.

were dead within 39 months. Similar analyses were not performed on the other prognostically significant variables viz. hemoglobin, hematocrit and platelet count, even though many follow-up values were available. The reason is that many of the therapeutic manipulations that were performed subsequent to the diagnosis (e.g. transfusions, busulfan therapy, splenectomy) could have had significant effects on these parameters, which therefore would not necessarily reflect the natural history of the disease.

*Multivariate analysis of prognostic factors*

The variables that were found to be of prognostic significance in the univariate analysis (fever, night sweats, weight loss, thrombocytopenia and anemia, and age) were also studied by a multivariate Cox analysis of proportional hazards of function and survival in order to determine which variables were independently most closely associated with predicting the survival time (25). Since the hemoglobin and hematocrit correlated very closely in all cases, the hemoglobin alone was used in this analysis. Likewise, since the presence of ecchymoses and petechiae correlated well with the platelet count (Fig. 6), the former variable was also excluded from the analysis. For this analysis the actual values of hemoglobin, platelet count and age were used, rather than the arbitrary intervals used in the univariate analysis. The other variables were entered as shown in Table 6. As shown in the table the platelet count, the age, and probably the presence of fever, remained significant in this analysis.

*Analysis of patient subgroups*

Separate chi-square analysis suggested that fever, weight loss and night sweats were associated symptoms, and that anemia and thrombocytopenia were correlated (data not shown). In order to confirm that the predicted prognostic variables would remain valid when reapplied to the same patient population, the cases were arbitrarily divided into four groups, as shown in Figure 10, based on the presence or absence of findings belonging to two complexes (fever/weight loss/nightsweats or anemia/thrombocytopenia). As shown in the figure, the group with findings in neither of the two complexes had the best survival (Group A). Those with

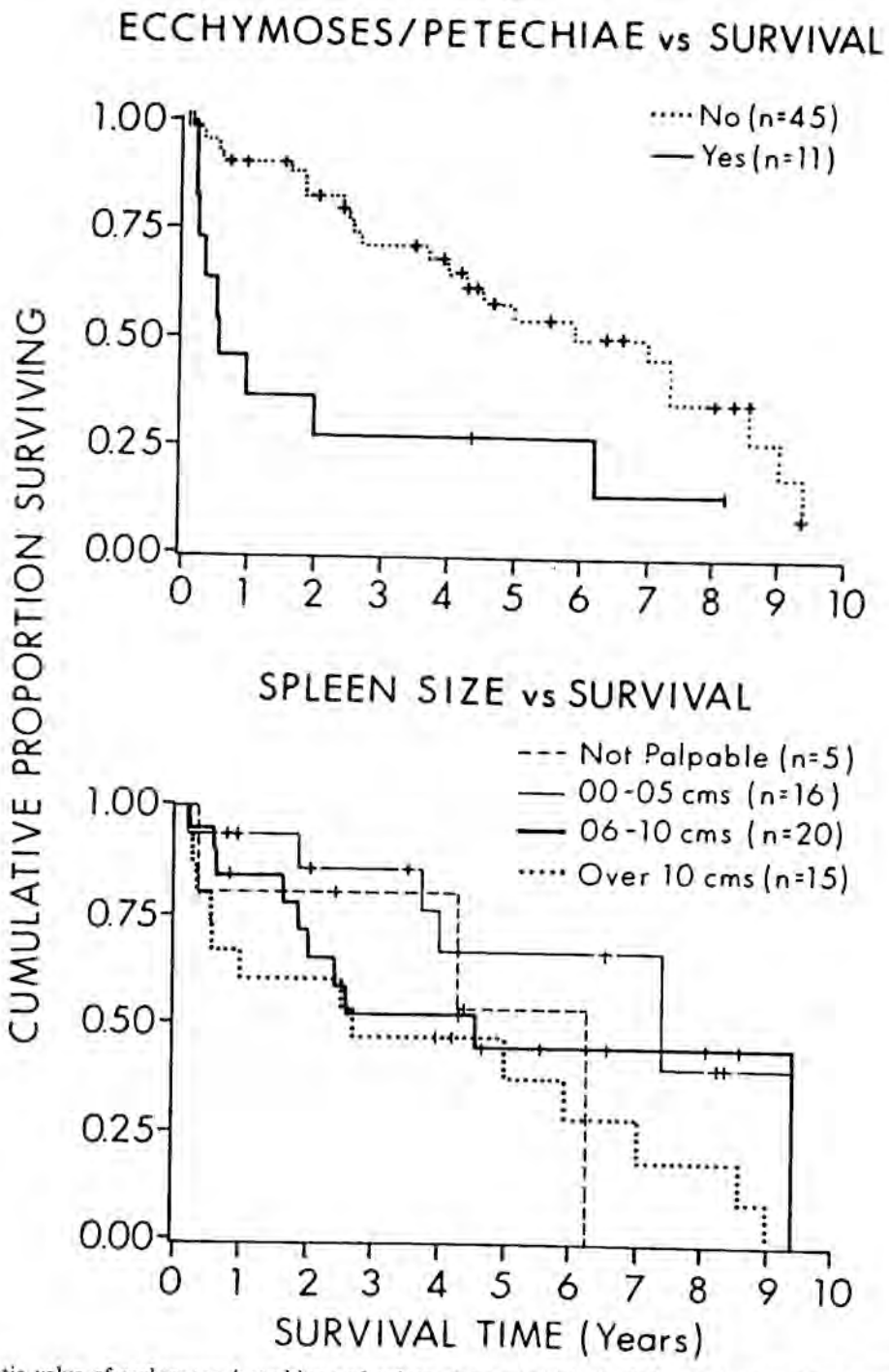


FIG. 6. Prognostic value of ecchymoses/petechiae and spleen size on initial physical examination. The groups compared are indicated in the insets, and in Table 5.

findings in either one of the two complexes had poorer, but similar survival (Groups B and C). Those that had at least one finding in each complex had much poorer survival than any of the other groups (Group D).

## Discussion

Several earlier studies have described groups of patients with clinical findings that are similar to those reported in the present series. (8, 26, 36, 43,

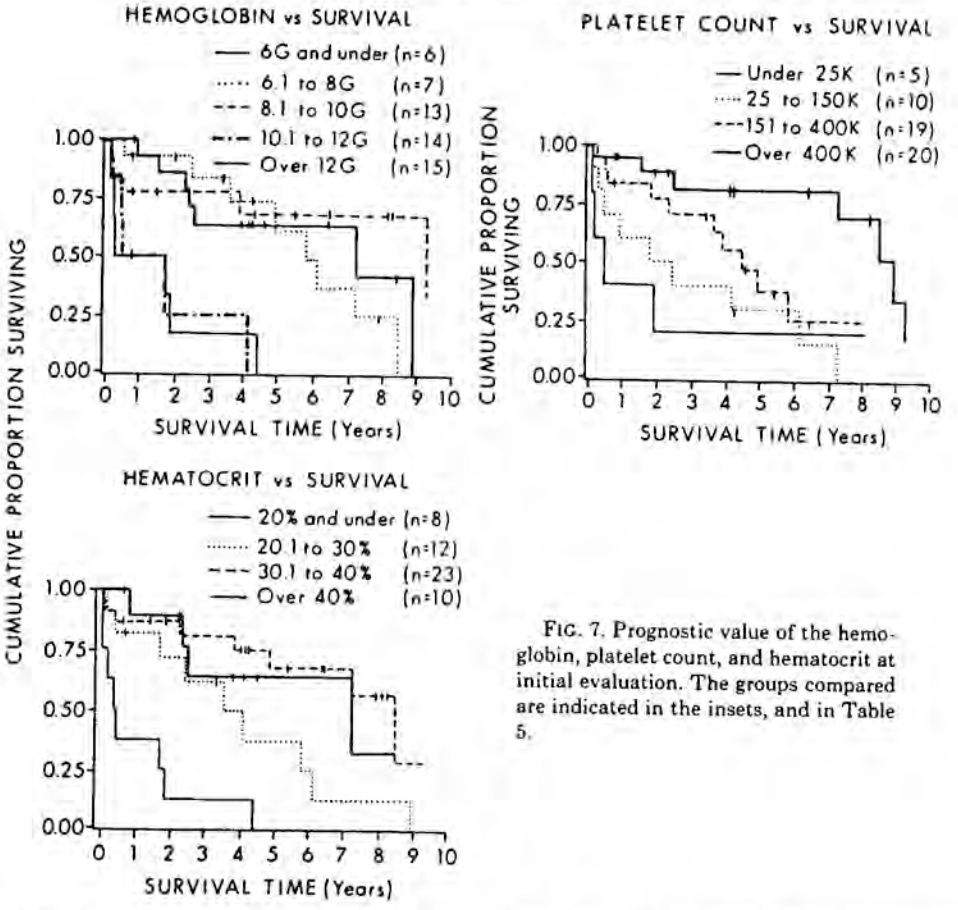


FIG. 7. Prognostic value of the hemoglobin, platelet count, and hematocrit at initial evaluation. The groups compared are indicated in the insets, and in Table 5.

45, 48, 52, 53, 56). The names used to described such syndromes have been myriad, including "agnogenic myeloid metaplasia," "myelofibrosis with myeloid metaplasia," "splenic myelosis," "megakaryocytic splenomegaly," "osteomyeloreticulosis," "chronic non-leukemic myelosis," and "primary myelofibrosis," causing Silverstein to call this the "syndrome of pseudonyms" (53). The lack of any absolutely uniform criteria by which to define the clinical syndrome makes comparison of these studies difficult. Furthermore, in most of these reports it is not clear if the series was consecutive and whether cases were excluded for any arbitrary clinical reasons. This is especially important because there is no conclusive evidence to indicate that all such patients have the same or similar underlying pathogenetic mechanisms accounting for their disease process. For these reasons, we have chosen in this study not to select patients by any arbitrary, pre-defined set of clinical criteria. Instead, we have reported on a series of unselected, consecutive patients with a single finding: unexplained fibrosis in the bone marrow ("idiopathic myelofibrosis"). We still cannot of course rule out other forms of selection bias, such as that which results from the fact that all of these patients were referred to a single consulting service at a tertiary care facility.

"Secondary" causes for the marrow fibrosis (acute leukemia, lymphomas, metastatic cancer) had become apparent very shortly after the diagnosis (less than 6 weeks for the leukemias, and less than 4 months for the malignancies). The pathologic review of the remaining cases revealed an unexpected finding: 5 of 61 patients who had originally been diagnosed as having idiopathic myelofibrosis in fact had the syndrome of "hairy cell leukemia" or "leukemic reticuloendotheliosis." These cases, which were from the earlier years of the series, had otherwise typical features of the syndrome of "agnogenic myeloid metaplasia" such as splenomegaly, marrow fibrosis, and a leukoerythroblastic peripheral smear. Furthermore, in most of these cases the infiltration of "hairy" cells in the bone marrow biopsy specimen was obvious only on careful re-examination. While the recent years have seen a better recognition and somewhat improved definition of "hairy cell leukemia" (7, 11, 18, 21, 42, 60) it seems likely that earlier series of patients

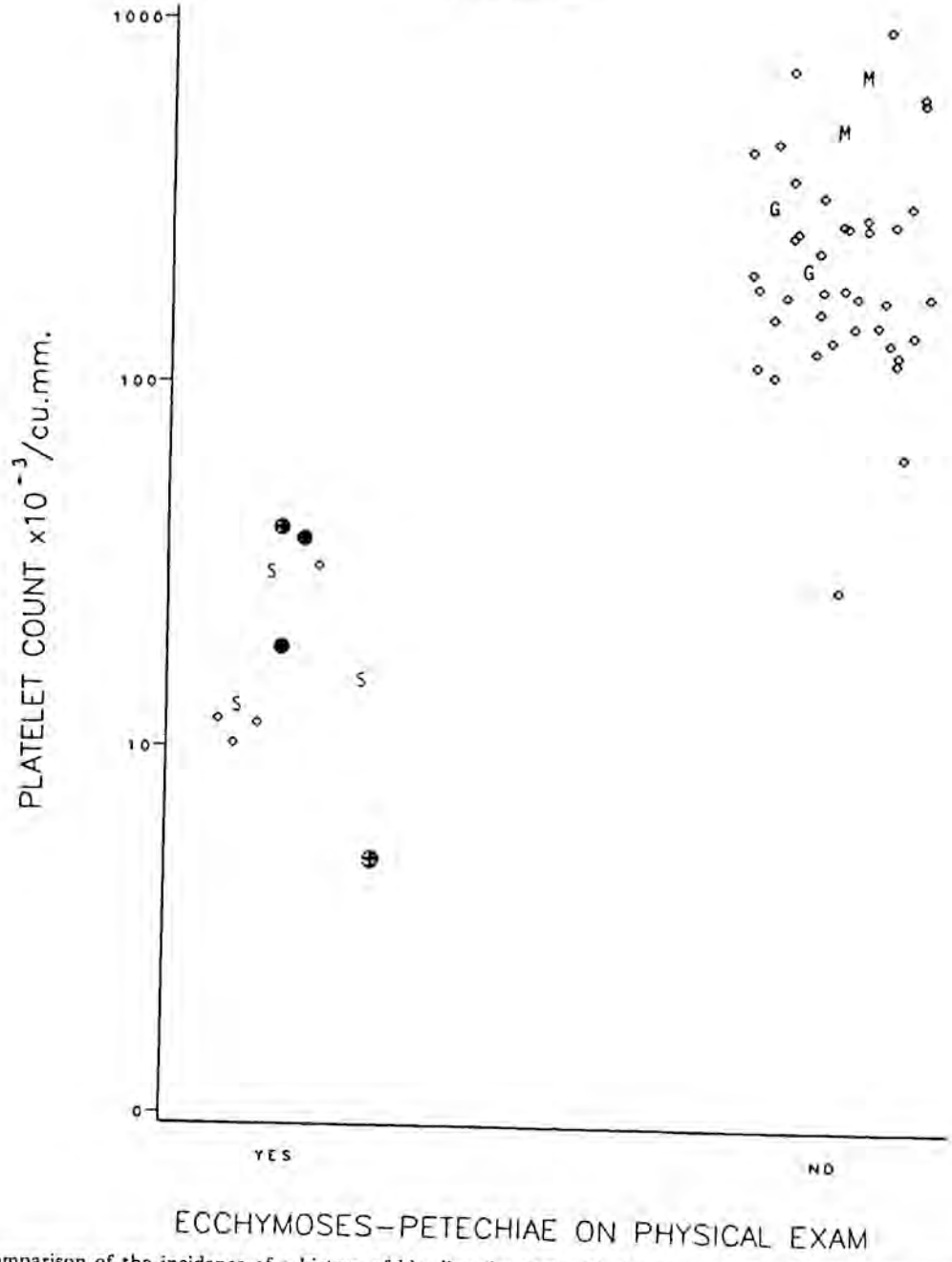


FIG. 8. Comparison of the incidence of a history of bleeding (by site) with the presence of ecchymoses/petechiae on physical examination and the platelet count (all at initial evaluation.) Patients without a history of bleeding are indicated by the symbol ○. Patients with a history of bleeding are indicated as follows (by sites of bleeding): S, skin; M, mucosal; G, gastrointestinal tract; ●, skin and mucosal; ⊕, gastrointestinal, skin, and other.

with "agnogenic myeloid metaplasia," "myelosclerosis" and "idiopathic myelofibrosis" may have inadvertently included many such cases. Perhaps most importantly, this finding emphasizes that more secondary causes of "idiopathic myelofibrosis" may well be uncovered as other new diseases of the hematopoietic system are recognized and defined.

In spite of the problems of patient selection just described, we felt it worthwhile to compare the general clinical and laboratory findings in this series with those reported in previous series of similar

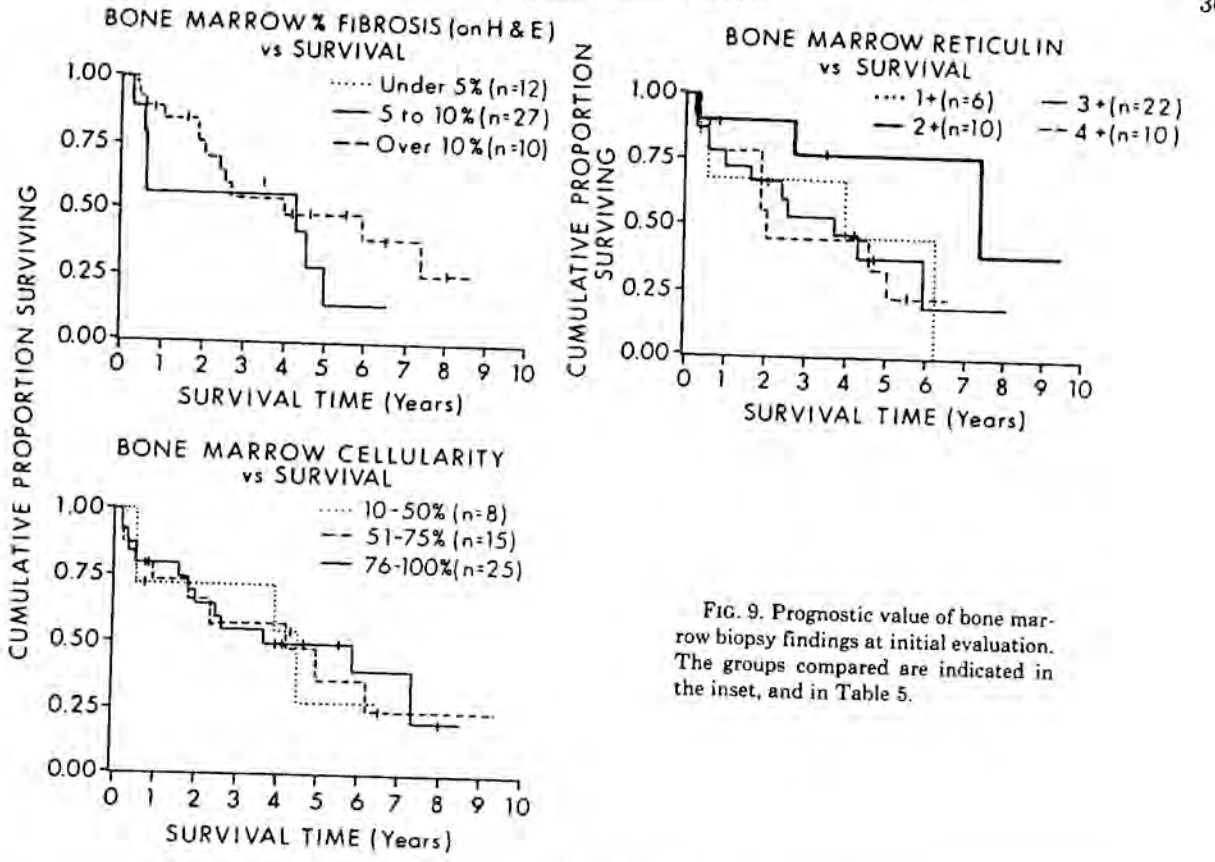


FIG. 9. Prognostic value of bone marrow biopsy findings at initial evaluation. The groups compared are indicated in the inset, and in Table 5.

**TABLE 6. Cox proportional hazards function: Survival analysis**

| Prognostic variable | How entered | p Value in the univariate analysis | | Final p Value | Final significance* |
|---|---|---|---|---|---|
| | | Breslow | Mantel-Cox | | |
| 1. Platelet count/mm³ | Actual value | .0024 | .0024 | .0030 | S |
| 2. Unexplained fever | Yes/no | .0001 | .0001 | .0817 | PS |
| 3. Age at Dx (years) | Actual | .0920 | .0170 | .0603 | PS |
| 4. Weight loss (% of body weight) | <10% vs. >10% | .0741 | .0415 | .4333 | NS |
| 5. Hemoglobin (g/dl) | Actual | .0003 | .0001 | .4484 | NS |
| 6. Night sweats | Yes/no | .0471 | .1000 | .2232 | NS |

* Significance in final Cox Analysis: S, significant; PS, possibly significant, NS; not significant.

patients. In general, the clinical and laboratory profiles were not very strikingly different (Tables 1 and 2). The findings can be categorized into several groups: those related to extramedullary hematopoiesis (splenomegaly, hepatomegaly, leukoerythroblastic blood smear), those arising from marrow failure and/or hypersplenism (anemia, thrombocytopenia, and their consequences), those related to hyperuricemia (gout, renal stones), and non-specific "hypermetabolic" symptoms suggesting a "systemic illness" (fever, weight loss, night sweats and anorexia). In addition, as in previous series, there was a high incidence (16/56) of unexplained hearing loss. It is of note that although the presence of ecchymoses and petechiae correlated with lower than normal platelet counts, bleeding (of various forms) occurred at platelet levels that are not usually clinically significant in other situations (viz., in the range of 25,000–100,000/mm³) (see Fig. 8). This may relate to the common occurrence of platelet function abnormalities in patients with myeloproliferative disease (13, 15, 41, 50). Interestingly, the presence of ecchymoses or petechiae was a very good predictor of a poorer prognosis, although obviously not independently of the actual platelet count. Recent reports have suggested an association between this syndrome and disorders of immune function (22, 47). The available information does not allow us to comment on the incidence of autoimmune phenomena in the patients in this series.

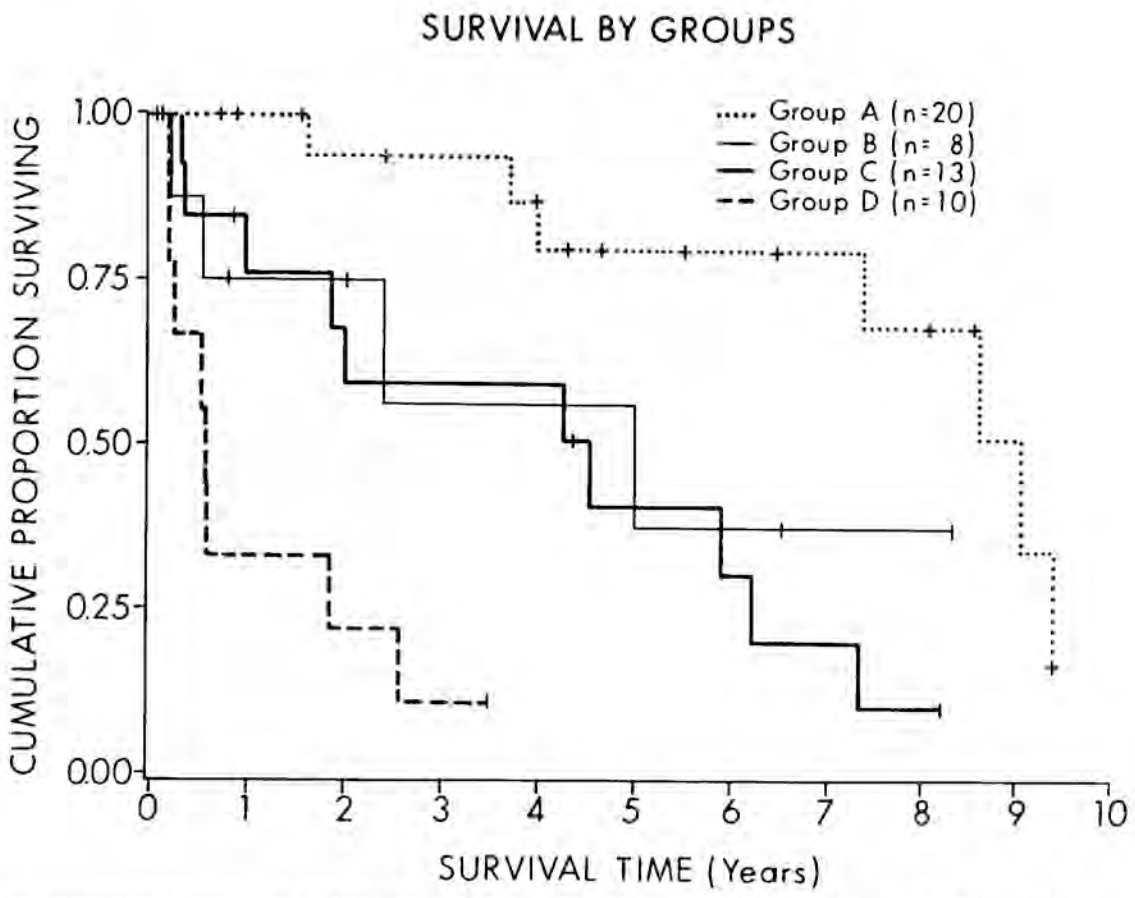


FIG. 10. Comparison of survival of selected groups of patients, based upon the presence or absence of bad prognostic variables at initial evaluation. Group B: Fever/night sweats/or weight loss (one or more); Group C: Anemia (hemoglobin less than 10 g/dl.) and/or thrombocytopenia (Platelet count less than 25,000); Group D, at least one finding from group B and group C; Group A, none of the above.

We have also summarized briefly the clinical course, complications and management of our series of patients. However because of the retrospective and uncontrolled nature of the data, we found it difficult to draw many reliable conclusions from this information, or to compare it with other literature concerning therapeutic modalities (4, 6, 9, 40, 51, 52). Contrary to some previous reports we found the rate of growth of the spleen to be quite variable. It should also be noted that in the overall series of patients, 50% of those who died had not required splenectomy during their course. Thus, while it appeared that surgery performed on a large, infarcted spleen carried a high risk of complications and mortality, it is difficult to recommend "prophylactic" splenectomy (40) when half the people may never require the procedure. Perhaps the rate of increase of the spleen size (Fig. 2) can predict the eventual requirement for splenectomy.

It is generally felt that it is the degree of marrow fibrosis and the extent of the extramedullary hematopoiesis (viz., spleen and liver size) that provide an indication of the severity of the disease process, and account for all of its manifestations. However, for the most part, the underlying cause(s) of these abnormalities remain obscure. More recently, clear-cut evidence has been presented to show that in a few cases there is an underlying primary clonal marrow stem cell disorder (1, 27). Furthermore, there is other independent evidence to show that the bone marrow fibroblast does not arise from the marrow stem cell (20). The hypothesis has been made that excessive production of platelet-derived growth factor by abnormal megakaryocytes could be the cause of the fibrosis (24). It remains possible however, that some cases could arise from other unknown forms of bone marrow injury, that *might not necessarily be progressive*. This distinction could well be of more than just nosological significance: it could perhaps be an explanation of one of the most perplexing aspects of this syndrome: the extreme unpredictability of the prognosis of a given

patient following the diagnosis. It is on this important aspect of this syndrome that we have concentrated in this study.

In this series, we found that the survival of patients could range from 6 months to 33 years. To some extent, it may be possible to explain this away by noting that the duration from the first onset of known symptoms and signs to the actual date of diagnosis was quite variable, and that several asymptomatic patients may well have gone unrecognized much longer if they had not been picked up serendipitously. However, it appears unlikely that this can be the sole explanation in the majority of the patients. We therefore analyzed our data to see if any of the presenting features could predict which patients had a poorer prognosis. We found that the nonspecific symptoms suggestive of a "systemic" disease (unexplained fever, weight loss and night sweats) and the signs of marrow failure or dysfunction (i.e., anemia, thrombocytopenia and poor platelet function) were very good predictors of a poor prognosis. On the other hand, the severity of the marrow fibrosis (in the bone marrow biopsy specimen) and the extent of extramedullary hematopoiesis (size of spleen and liver, immaturity of peripheral blood white cells) were of no detectable significance. We cannot rule out the possibility that the latter factors might not have had *some* significance if larger numbers of patients had been available. For example, there may have been too few patients with truly massive splenomegaly to allow us to determine if this was a bad prognostic sign. On the other hand, the findings on the many variables tested (see Table 5) were internally consistent: for example, the presence of ecchymoses and petechiae (related to platelet count) was significant, whereas a history of symptoms of splenomegaly (related to splenic size) was not. Furthermore, when unexplained fever or weight loss appeared during the follow-up period, the survival time from the onset of these symptoms was extremely short.

Most of the previous studies of similar patients have made only descriptive or anecdotal statements regarding the "natural history" and prognosis of this type of patient. Many series do point out that the patients who were asymptomatic at diagnosis had (not surprisingly) a better prognosis. Our findings are consistent with those reported in the monograph by Silverstein (53), in which he states that patients with anemia and thrombocytopenia had a poorer prognosis; however, we did not find that hepatomegaly was a poor prognostic sign. Some studies have also attempted to correlate the type of treatment given with the survival of various groups of patients. However, because of the retrospective, non-randomized, potentially biased nature of such information, we have not attempted to make such an analysis on the patients in our series.

In recent years, several authors have attempted to define a syndrome of "acute myelofibrosis," characterized by unexplained marrow fibrosis, minimal splenomegaly and leukoerythroblastosis, and short survival (3, 5, 37). However, there is no single cardinal feature that makes these cases distinctly different from those with a more indolent course. It is clear that a few patients with marrow fibrosis manifest an underlying acute leukemia very shortly after presentation (in our series, within 6 weeks), and that some of these reports must include such cases. In the cases in which the fibrosis remains unexplained, we find that severity of the clinical features and the duration of survival show a continuum in which any attempt to subclassify a group with more severe disease has to be arbitrary. We suggest that until the underlying pathogenetic mechanisms of these syndromes are better understood, it may be preferable to consolidate into one group all of these patients with unexplained marrow fibrosis.

Ultimately, the pathogenesis of "idiopathic myelofibrosis" must be explained on a molecular level. However, the achievement of this goal is not likely to be immediate. Meanwhile, this report represents an attempt to approach the problem with the available clinical information. While such a study has many well-known limitations, we feel we have obtained some useful data that not only bear on questions regarding the pathogenesis of this syndrome, but also provide information of practical value to the physician caring for such patients.

## Summary

We describe here a series of 88 consecutive patients with bone marrow fibrosis. Primary causes for the fibrosis were discovered in 26% of the cases shortly after the initial diagnosis. Pathology review of the remaining cases revealed an 8% incidence of "hairy cell leukemia" that had escaped detection orginally. The remaining cases, characterized as having "unexplained bone marrow fibrosis" or "idiopathic myelofibrosis," are the subject of this study. The clinical and laboratory findings are compared to those reported in previous series of selected cases with similar features in which patients were diagnosed as having "agnogenic myeloid metaplasia," "myelosclerosis," or "myelofibrosis." A brief summary of the treatment modalities used, and the clinical course and outcome of these patients are also presented.

There was a marked variability in the clinical severity of the disease and in the survival of these

patients. A detailed statistical analysis of 40 variables at the time of initial diagnosis showed that the factors that best predicted a poor survival were unexplained fever, weight loss, night sweats, anemia and thrombocytopenia. On the other hand, the size of the spleen or of the liver, the degree of immaturity of the peripheral blood white cells, and the degree of fibrosis or cellularity in the bone marrow biopsy were of no detectable prognostic significance.

These findings suggest that in patients with unexplained fibrosis of the bone marrow (the syndrome of idiopathic myelofibrosis) a poor prognosis is not a direct consequence of the marrow fibrosis or the associated extramedullary hematopoiesis, but rather is related to the presence and/or the severity of some unexplained primary marrow defect, which is also often associated with the nonspecific symptoms of a systemic illness.

## Acknowledgments

The authors would like to thank Dr. Philip Miller and Ms. Susanna Clarkson for their advice and help with the statistical analysis, and Dr. Elmer Brown for his encouragement and support.

## References

1. Adamson JW, and Fialkow PJ: The pathogenesis of myeloproliferative syndromes. Br J Haematol 38: 299, 1978.
2. Andre J, Schwartz R, Dameshek W. Tuberculosis and myelosclerosis with myeloid metaplasia. JAMA 1978: 1169, 1961.
3. Bearman RN, Pangalis S, Ligumski M: Acute ("malignant") myelosclerosis. Cancer 43: 279, 1979.
4. Benbassat J, Penchas S, Ligumski M: Splenectomy in patients with agnogenic myeloid metaplasia: an analysis of 321 published cases. Br J Haematol 42: 207, 1979.
5. Bergsman LL, Van Slyck EJ: Acute myelofibrosis. Ann Intern Med 74: 232, 1971.
6. Besa EC, Nowell PC, Geller NL, Gardner FH: Analysis of the androgen response of 23 patients with agnogenic myeloid metaplasia. Cancer 49: 308, 1982.
7. Bouroncle BA: Leukemic reticuloendotheliosis (Hairy cell leukemia). Blood 53: 412, 1979.
8. Bouroncle BA, Doan CA: Myelofibrosis, clinical hematologic and pathologic study of 110 patients. Am J Med Sci 243: 697, 1962.
9. Branda RF, Amsden TW, Jacob HS: Randomized study of nandrolone therapy for anemias due to bone marrow failure. Arch Intern Med 137: 65, 1977.
10. Breslow N: A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. Biometrika 57: 579, 1970.
11. Burke JS, Byrne GE, Rappaport H: Hairy cell leukemia (leukemic reticuloendotheliosis). Cancer 33: 1399, 1974.
12. Buyssens N, Bourgeois NH: Chronic myelocytic leukemia versus idiopathic myelofibrosis. Cancer 40: 1548, 1977.
13. Cardamone JM, Edson JR, McArthur JR, Jacob HS: Abnormalities of platelet function in the myeloproliferative disorders. JAMA 221: 270–273, 1972.
14. Clough V, Geary CG, Hashmi K, Davson J, T. Knowlson: Myelofibrosis in chronic granulocytic leukaemia. Br J Haematol 42: 515, 1979.
15. Cooper B, Schafer AI, Puchalsky D, Handin RI: Platelet resistance to prostaglandin D2 in patients with myeloproliferative disorders. Blood 52: 618–626, 1978.
16. Coughlin C, Greenwald ES, Schraft WC, Grossman S: Myelofibrosis associated with multiple myeloma. Arch Intern Med 138: 590, 1978.
17. Crail HW, Alt HL, Nadler WH: Myelofibrosis associated with tuberculosis—A report of four cases. Blood 3: 1426, 1948.
18. Debusscher L, Bernheim JL, Govaerts Collard-Ronge E, Govaerts A, Hooghe R, Lejeune FJ, Zeicher M, Styckmans PA: Hairy cell leukemia: functional, immunologic, kinetic, and ultrastructural characterization. Blood 46: 495, 1975.
19. Fisher RA: The use of multiple measurements in taxonomic problems. Annals Eugen 7: 179, 1936.
20. Golde DW, Hocking WG, Quan SG, Sparkes RS, Gale RP: Origin of human bone marrow fibroblasts. Br J Haematol 44: 183, 1980.
21. Golomb HM, Catovsky D, Bolde DW: Hairy cell leukemia: A clinical review based on 71 cases. Ann Intern Med 89: 677, 1978.
22. Gordon BR, Coleman M, Kohen P, Day NK: Immunologic abnormalities in myelofibrosis with activation of the complement system. Blood 58: 904, 1981.
23. Gralnick HR, Harbor J, Vogel C: Myelofibrosis in chronic granulocytic leukemia. Blood 37: 152, 1971.
24. Groopman JE: The pathogenesis of myelofibrosis in myeloproliferative disorders. Ann Intern Med 92: 857, 1980.
25. Gross A, Clark V: Survival distributions: reliability and applications in the biomedical sciences. New York: Wiley, 1975.
26. Hickling RA: The natural history of chronic non-leukemic myelosis. QJ Med 37: 267, 1968.
27. Jacobson RJ, Salo A, Fialkow PJ: Agnogenic myeloid metaplasia: a clonal proliferation of hematopoietic stem cells with secondary myelofibrosis. Blood 51: 189, 1978.
28. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Statist Assoc 53: 457, 1958.
29. Kiang DT, McKenna RW, Kennedy BJ: Reversal of myelofibrosis in advanced breast cancer. Am J Med 64: 173, 1978.
30. Kiely JM, Silverstein MN: Metastatic carcinoma simulating agnogenic myeloid metaplasia and myelofibrosis. Cancer 24: 1041, 1969.
31. Kuo CY, Van Voolen GA, Morrison AN: Primary and secondary myelofibrosis: its relationship to PNH-like defect. Blood 40: 875, 1972.
32. Laszlo J: Myeloproliferative disorders (MPD): Myelofibrosis, myelosclerosis, extramedullary hematopoiesis, undifferentiated MPD, and hemorrhagic thrombocythemia. Semin Hemat 12: 409, 1975.
33. Leland J, MacPherson B: Hematologic findings in cases of mammary cancer metastatic to bone marrow. Am J Clin Pathol 71: 31, 1979.
34. Lewis SM, Szur L: Malignant myelosclerosis. Br Med J 2: 472, 1963.
35. Lewis SM, Pettit JE, Tattersall MHN, Pepys MB: Myelosclerosis and paroxysmal nocturnal haemoglobinuria. Scand J Haematol 8: 451, 1971.
36. Linman JW, Bethell FH: Agnogenic myeloid metaplasia. Am J Med 22: 107, 1957.
37. Manoharan A, Pitney WR: Acute myeloblastic leukaemia with marrow fibrosis (malignant myelosclerosis): acute leukaemia or malignant myelosclerosis? Aust NZ J Med 7: 638, 1977.
38. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemo Rep 50: 163, 1966.
39. Matzner Y, Polliack A: Bone marrow curettage in myelodysplastic disorders. JAMA 246: 1926, 1981.
40. Mulder H, Steenbergen J, Haanen C: Clinical course and survival after elective splenectomy in 19 patients with primary myelofibrosis. Br J Haematol 35: 419, 1977.
41. Murphy S, Davis JL, Walsh PN, Gardner FH: Template bleeding time and clinical hemorrhage in myeloproliferative disease. Arch Intern Med 138: 1251–1253, 1978.
42. Naeim F, Gatti RA, Johnson CE, Gossett T, Walford RL: "Hairy Cell" leukemia: A heterogeneous chronic lymphoproliferative disorder. Am J Med 65: 479, 1978.
43. Nakai GS et al: Agnogenic myeloid metaplasia. A survey of 29 cases and a review of the literature. Ann Intern Med 57: 419, 1962.
44. Pettit JE et al: Polycythaemia vera—Transformation to myelofibrosis and subsequent reversal. Scand J Haematol 20: 63, 1978.
45. Pitcock JA, Reinhard EJ, Justus BW, Mendelsohn RS: A clinical and pathological study of 70 cases of myelofibrosis. Ann Intern Med 57: 73, 1962.
46. Rojer RA, Mulder NH, Nieweg HO: Response to pyridoxine hydrochloride in refractory anemia due to myelofibrosis. Am J Med 65: 655, 1978.
47. Rondeau E, Solal-Celigny P, Dhermy D, Vroclans M, Brousse N, Bernard JF, Boivin P: Immune disorders in agnogenic myeloid metaplasia: relations to myelofibrosis. Br J Haematol 53: 467–475, 1983.

48. Rosenthal DS, Moloney WC: Myeloid metaplasia: A study of 98 cases. Postgrad Med 45: 136, 1969.
49. Sall JP, Goodknight JH, Helwig J: SAS User's Guide. North Carolina: SAS Institute Inc., 1979.
50. Schafer AI: Deficiency of platelet lipoxygenase activity in myeloproliferative disorders. N Engl J Med 306: 381-386, 1982.
51. Silver RT, Jenkins DE Jr, Engle RL Jr: Use of testosterone and busulfan in the treatment of myelofibrosis with myeloid metaplasia. Blood 23: 341, 1964.
52. Silverstein MN, Gomes MR, ReMine WH, Elveback LR: Agnogenic myeloid metaplasia: Natural history and treatment. Arch Intern Med 120: 545, 1967.
53. Silverstein MN: Agnogenic myeloid metaplasia. Boston: Publishing Sciences Group Inc., 1975.
54. Silverstein MN: Evolution into and treatment of late stage polycythemia vera. Semin Hematol 13: 79, 1976.
55. Silverstein MN, Remin WH: Splenectomy in myeloid metaplasia. Blood 53: 515, 1979.
56. Ward HP, Block MH: The natural history of agnogenic myeloid metaplasia. Medicine 50: 357, 1971.
57. Weick JK et al: Leukoerythroblastosis: diagnostic and prognostic significance. Mayo Clin Proc 49: 110, 1974.
58. Weinberg SG, Lubin A, Wiener SN, Deoras MP, Ghose MK, Kopelman RC: Myelofibrosis and renal osteodystrophy. Am J Med 63: 755, 1977.
59. Wohl H: The cusum plot: its utility in the analysis of clinical data. N Engl J Med 296: 1044, 1977.
60. Yam LT, Li CY, Lam KW: Tartarate resistant acid phosphatase in leukemic reticuloendotheliosis. N Engl J Med 284: 357, 1971.