Melphalan Therapy of Polycythemia Vera

By GERALD L. LOGUE, JORDAN U. GUTTERMAN, THOMAS G. McGINN, JOHN LASZLO AND R. WAYNE RUNDLES

Twenty-seven patients with p. vera whose proliferative disease required the suppression of bone marrow function were treated with melphalan for periods of 20 to 72 months. The response was rated as good to excellent at three months in 24 of the 27 patients. At the end of one year 14 of the 27 patients had no evidence of disease. In eight of the remaining 13 the only persistent abnormality was a palpable spleen. Side reactions and adverse hematologic effects were infrequent. To date one patient has developed refractory anemia and evidence of myelofibrosis. Four patients have developed acute leukemia but none of these had been treated with melphalan alone. The results to date are sufficiently good to establish melphalan as one of the most effective agents in the control of p. vera.

POLYCYTHEMIA VERA (p. vera) is a chronic, relatively common type of myeloproliferative disease characterized by the overproduction of erythrocytic elements and usually some degree of excessive or abnormal granulocytic, megakaryocytic and fibroblastic proliferation.1 The relationship of the major clinical manifestations of p. vera to the variety of proliferative abnormalities which occur in this “panmyelopathy” is outlined in Table 1. Except for erythrocytic overproduction, the abnormalities which affect other cell strains of the bone marrow are comparable to those which occur in other myeloproliferative variants such as myeloid metaplasia, thrombocytopenia and myelofibrosis.

Polycythemia vera varies a great deal in severity from patient to patient, and in the degree to which different cell strains are involved. Each type of proliferative abnormality tends to produce unique clinical complications which affect the survival of patients. While some patients live in reasonably good health for many years without therapy,2 analysis of the complications and causes of death in a large group of patients admitted to hospitals in Denmark...
Table 1.—Clinical Features of Polycythemia Vera*

<table>
<thead>
<tr>
<th>Type of Abnormal Cellular Proliferation</th>
<th>Physical and Laboratory Abnormalities</th>
<th>Pathophysiology</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytic</td>
<td>Increased red cell count, and red cell mass</td>
<td>Increased blood viscosity, vascular distention, stasis</td>
<td>Plethora Arterial hypertension Peptic ulcer Blood loss Iron deficiency Proteinuria, Azotemia Pruritis Peptic ulcer Acute myelogenous leukemia</td>
</tr>
<tr>
<td></td>
<td>Decreased clot retraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytic</td>
<td>Neutrophilic leukocytosis with variable immaturity</td>
<td>Histamine release?</td>
<td>Acute or chronic gouty arthritis Renal urate stones Nephropathy</td>
</tr>
<tr>
<td></td>
<td>(No Ph1 chromosome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukocyte alkaline phosphatase increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High Serum B12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td>Uric acid overproduction</td>
<td>Acute or chronic gouty arthritis Renal urate stones Nephropathy</td>
</tr>
<tr>
<td></td>
<td>Hyperuricosuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extramedullary hematopoiesis, Splenomegaly, Hepatomegaly</td>
<td>Venous obstruction</td>
<td>Infarction, Hemolysis Thrombosis Gastrointestinal or postoperative hemorrhage</td>
</tr>
<tr>
<td>Megakaryocytic</td>
<td>Increased platelets, Megakaryocytosis in bone marrow</td>
<td>Hypercoagulability Defective platelet function</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Fibroblastic</td>
<td>Fibrosis of marrow and spleen</td>
<td>Myelofibrosis, Myelosclerosis</td>
<td>Acute myelogenous leukemia</td>
</tr>
</tbody>
</table>

* Adapted from Wasserman and Gilbert.11

showed that a surprising mortality of 50 per cent occurred during the first 18 months in patients with untreated disease.3 Venous and arterial thromboses were the principal causes of death. The median survival of patients from the same population treated with venesection was nearly four years. The incidence of thrombosis and hemorrhage remained high, though, approximately twice that of patients treated by measures to suppress bone marrow function.3 In contrast to chronic granulocytic leukemia in which acute exacerbation almost invariably occurs within a period of three to five years, the proliferative disease in p. vera tends to remain chronic. Ten to 15 per cent of patients with p. vera die with acute leukemia, but this is a late complication which usually develops a decade or more after the appearance of the disease and the use of irradiation therapy.3,8

Opinions regarding the optimal management of patients with p. vera are surprisingly diverse. A variety of agents and procedures have been recommended, repeated phlebotomy, suppression of bone marrow function by external irradiation,32P, chemotherapy using alkylating agents or antimetabolites, etc.9,13 Each of these may have a particular sphere of usefulness, but it seems likely that no one approach will provide optimal disease control in every patient.

The use of nitrogen mustard compounds in the treatment of myeloproliferative diseases has been of interest to us for many years.14-16 In 1960–1961 we began a comprehensive study of the therapeutic effects of L-phenylalanine mustard (melphalan, Alkeran, L-Sarcolysin, C. B. 3025) in patients with a variety of neoplastic diseases. Beneficial effects comparable and possibly superior to those of standard agents were observed in polycythemia vera, granulo-
### Table 2.—Patients with Polycythemia Vera Treated with Melphalan (Alkeran, CB 3025)

<table>
<thead>
<tr>
<th>Patient, Hospital No., Age, Sex, Race</th>
<th>Clinical Features</th>
<th>Previous Therapy, Beginning of Melphalan Therapy</th>
<th>Physical and Hematologic Features</th>
<th>Therapeutic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gm. %  Spleen Hgb. VPBC WBC Platelet Count</td>
<td>Overall Rating 3 Mos. 1 Yr. Later Status Effect on Disease Manifestations, Complications, Untoward Effects of Therapy</td>
</tr>
<tr>
<td>W.W.W., F4 4 231 56, M, W</td>
<td>1957–58. Back pain, fever, bruising, splenomegaly. WBC 40,000. Gout developed after busulfan therapy. VPBC rose to 66%.</td>
<td>1957 and 1961. Busulfan, Phlebotomies. 10 cm.</td>
<td>Spleen 1.7 cm. Hgb. 64.0* VPBC 24,390 WBC 280,000</td>
<td>Good Good Good at 72 mos. For 6 years after beginning melphalan his health was good. He then developed acute myelogenous leukemia and died in 1968.</td>
</tr>
<tr>
<td>H.N.S., F7 1 298 79, F, W</td>
<td>1962. Examination re &quot;sciatica&quot; led to discovery of splenomegaly and high blood counts.</td>
<td>5/10/62 None.</td>
<td>Spleen 2.5 cm. Hgb. 15.0 VPBC 47.0 WBC 21,500 Platelet Count 2.8 M. (Layer) 5 mm.</td>
<td>Good Good+ Good+ at 84 mos. Clinical status remained good, and performance status 100%. Spleen tip continued to be palpable. Evidence of myelofibrosis present after 90 months of therapy.</td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
<table>
<thead>
<tr>
<th>J.H.D., E1 4 585</th>
<th>1955</th>
<th>Prolonged bleeding following tooth extraction led to discovery of erythrocytosis (Hemat. 69%), leukocytosis, thrombocytosis, and splenomegaly. Phlebotomies, Palp. T.E.M. (1955)</th>
<th>18.8</th>
<th>58.0</th>
<th>8,130</th>
<th>200,000</th>
<th>Excellent Excellent at 66 mos. Melphalan and two other mustard compounds were about equally effective in controlling disease. Death from glioblastoma multiforme, March 1968.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.K.H., C8 0 831</td>
<td>1957, 1958, 1960</td>
<td>Melena.</td>
<td>11.6</td>
<td>42.0*</td>
<td>23,300</td>
<td>1.6 M. (4.5 mm.)</td>
<td>Excellent Excellent at 71 mos. Recurrent gastrointestinal bleeding stopped and health became good. Chronic headaches persisted.</td>
</tr>
<tr>
<td>O.H.B., A5 2 024</td>
<td>1963</td>
<td>Thrombocytosis. Subarachnoid hemorrhage, splenomegaly, high blood counts.</td>
<td>7/15/63</td>
<td>17.6</td>
<td>65.0</td>
<td>24,600</td>
<td>1.4 M. (2 mm.)</td>
</tr>
<tr>
<td>F.R.H., G2 3 345</td>
<td>1963–64</td>
<td>Headaches, weakness, elevated blood counts. Phlebotomies, 8 cm.</td>
<td>1963–64</td>
<td>16.4</td>
<td>56.5*</td>
<td>12,200</td>
<td>760.00</td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
<table>
<thead>
<tr>
<th>Patient, Hospital No., Age, Sex, Race</th>
<th>Clinical Features, Date of Onset, Manifestations, Associated or Complicating Diseases</th>
<th>Previous Therapy, Beginning of Melphalan Therapy</th>
<th>Physical and Hematologic Features</th>
<th>Therapeutic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gm. % (Layer)</td>
<td></td>
</tr>
<tr>
<td>J.H.O., F1 0352 76, M, W</td>
<td>Podagra, weakness. Spleenomegaly, high blood counts.</td>
<td>None.</td>
<td>13 cm. 18.5 63.0 16,550 688,000 (3 mm.)</td>
<td>Good Good at 24 mos. Blood counts became normal in 3 months and serum uric acid fell from 10.9 mg. % to 6.4 mg. %. Spleen became smaller but remained palpable. Death from prostatic carcinoma, 8/6/66.</td>
</tr>
<tr>
<td>E.L.C., G3 3975 73, F, W</td>
<td>Transient blurring of vision, dizziness, flushing of face, pruritus.</td>
<td>None.</td>
<td>Palp. 20.9 67.5 12,550 480,000</td>
<td>Fair Excellent Excellent at 26 mos. Physical and hematologic abnormalities subsided in 6 months. Mild cytopenia during first 3 months. Died January 1967, one week after resection of carcinoma of colon. (See Case Summary.) Circulatory symptoms subsided in 3 months, spleen not palpable after 6 months. Pruritus persisted for 10 months. Mild leukopenia at 2 months.</td>
</tr>
<tr>
<td>F.B.R., G3 8362 67, F, W</td>
<td>Ruddy face, flushing, pruritus, fatigue, weight loss, painful cyanotic feet, high blood counts.</td>
<td>1964. Phlebotomies, 4-5 cm. 15.8 57.0* 22,250 1.3 M. (2 mm.)</td>
<td>Excellent Good + at 57 mos.</td>
<td></td>
</tr>
<tr>
<td>L.W.W., G3 5422 59, M, W</td>
<td>Severe pruritus after bathing. Headaches and tinnitus. Hypertension and high blood counts.</td>
<td>None.</td>
<td>3 cm. 21.8 72.0 15,200 320,000 (2 mm.)</td>
<td>Good Excellent at 54 mos. Phlebotomies and melphalan given as initial therapy. Symptoms regressed in 2 months and spleen was no longer palpable. Pruritus persisted for 17 months, and then subsided.</td>
</tr>
<tr>
<td>E.C.C., G3 8385 79, M, W</td>
<td>Dizziness, blurred vision, elevated blood counts.</td>
<td>1964. Phlebotomies, 3-6 cm. 17.3 60.0 11,150 700,000 (1.5 mm.)</td>
<td>Excellent Excellent at 52 mos. Symptoms subsided and spleen not palpable at 6 months.</td>
<td></td>
</tr>
<tr>
<td>S.W.S., G4 7693 73, F, W</td>
<td>Abdominal pain, associated with splenomegaly.</td>
<td>1962-64. Phlebotomies. 5 cm. 15.8 56.0* 8,740 1.3 M. (2.5 mm.)</td>
<td>Good + Good + at 65 mos. Abdominal pain and pruritus subsided promptly but spleen continued to be palpable.</td>
<td></td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
<table>
<thead>
<tr>
<th>S.W.S., GA 7 693</th>
<th>1962.</th>
<th>Hospitalized with severe abdominal pain, pruritis, hgb. 19.5 Gm. %</th>
<th>4/23/65</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.L.B., G5 0 493</td>
<td>1945.</td>
<td>Hypertension.</td>
<td>None.</td>
</tr>
<tr>
<td>60, M, W</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.C.M., 15 909</td>
<td>1947.</td>
<td>Acute gout arthritis.</td>
<td>None.</td>
</tr>
<tr>
<td>78, M, N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V.E.S., G5 2 850</td>
<td>1963.</td>
<td>Recurrent visual disturbance, headaches, pruritis, thrombophlebitis of foot.</td>
<td>None.</td>
</tr>
<tr>
<td>56, F, W</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
Table 2.—Patients with Polycythemia Vera Treated with Melphalan (Alkeran, CB 3025) (Cont'd.)

<table>
<thead>
<tr>
<th>Patient, Hospital No., Age, Sex, Race</th>
<th>Clinical Features, Date of Onset, Manifestations, Associated or Complicating Diseases</th>
<th>Previous Therapy, Beginning of Melphalan Therapy</th>
<th>Physical and Hematologic Features</th>
<th>Therapeutic Results</th>
<th>Overall Rating</th>
<th>Effect on Disease Manifestations, Complications, Untoward Effects of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1959. ≠P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1962. Moderately severe gout, hyperuricemia and hyperuricosuria.</td>
<td></td>
<td></td>
<td></td>
<td>Fa r</td>
<td></td>
</tr>
<tr>
<td>W.R.B., G6 5 634 68, M, W</td>
<td>Ruddy face, pruritus, sweating, abdominal fullness, splenomegaly.</td>
<td>9/20/65 None.</td>
<td></td>
<td>Good</td>
<td>Excellent at 42</td>
<td>Excellent at 42 months. Symptoms became considerably less and spleen smaller during the first 3 months. Status after 6 months was excellent.</td>
</tr>
<tr>
<td></td>
<td>1962–64.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.W.S., G6 9 334 78, F, W</td>
<td>Pruritus after bathing.</td>
<td>12/15/65 5 cm.</td>
<td></td>
<td>Good+</td>
<td>Good+ at 35 weeks</td>
<td>Symptoms subsided after one month of melphalan. Moderate cytopenia at 3 months. Spleen continued to be palpable.</td>
</tr>
<tr>
<td></td>
<td>1956.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.G., E5 6 463 62, F, N</td>
<td>Headaches, tinnitus, nose bleeds, splenomegaly, high blood counts.</td>
<td>2/15/66 1 cm.</td>
<td></td>
<td>Good+</td>
<td>Good+ at 39 weeks</td>
<td>Moderate cytopenia at 3 months. Headaches persisted and spleen remained palpable.</td>
</tr>
<tr>
<td></td>
<td>1955.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1957–58. ≠P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1966. Recurrent headaches, tinnitus, dizziness.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/11/66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
L.M.F., G7 2 818
47, F, W
1957. Splenomegaly.
1958. High blood counts.

E.S., G8 0 152
78, F, W

R.H.P., D4 5 818
44, M, N
1957. Renal stone, hypertension, high blood counts, palpable spleen.

L.C.B., G9 5 657
76, F, W

M.H.H., H0 0 154
77, M, W
1957. Burning dysesthesia of feet.
1963-64. Flushed face, pruritus after bathing.
1967. Chest pain, high blood counts discovered.

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Symptoms</th>
<th>White Blood Cells</th>
<th>Hemoglobin</th>
<th>Platelets</th>
<th>Result</th>
<th>Follow-up</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.M.F.</td>
<td>4/7/66</td>
<td>Splenomegaly intermittently</td>
<td>1 cm.</td>
<td>21.6</td>
<td>14,250</td>
<td>530,000</td>
<td>Fair</td>
<td>Good+</td>
</tr>
<tr>
<td>E.S.</td>
<td>None</td>
<td>Not Palp.</td>
<td>7/8/66</td>
<td>15.5</td>
<td>43,200</td>
<td>665,000</td>
<td>Excellent Excellent at 35 mos.</td>
<td>Excellent Excellent at 55 mos.</td>
</tr>
<tr>
<td>R.H.P.</td>
<td>4 mc.</td>
<td>Not Palp.</td>
<td>20.4</td>
<td>65.0</td>
<td>18,800</td>
<td>765,000</td>
<td>Good</td>
<td>Excellent Excellent at 20 mos.</td>
</tr>
<tr>
<td>L.C.B.</td>
<td>None</td>
<td>2 cm.</td>
<td>16.5</td>
<td>52.0</td>
<td>14,900</td>
<td>1.1 M.</td>
<td>Good+</td>
<td>Excellent Excellent at 29 mos.</td>
</tr>
<tr>
<td>M.H.H.</td>
<td>2/16/67</td>
<td>Phlebotomy</td>
<td>4 cm.</td>
<td>14.5</td>
<td>51.0</td>
<td>10,600</td>
<td>Good</td>
<td>Excellent Excellent at 26 mos.</td>
</tr>
</tbody>
</table>

* Gastrointestinal bleeding or phlebotomies with iron deficiency.
cytic leukemia, hemorrhagic thrombocythemia and other myeloproliferative
diseases. The effects in p. vera were such that a larger series of representative
patients were recruited for long-term study. The present report concerns these
patients. Other studies included a long-term study of the effects of melphalan
and other agents in chronic granulocytic leukemia, and a randomized, double
blind comparison of the effects of melphalan with chlorambucil (chlorambucil,
C. B. 1345, Leukeran) in the lymphoproliferative diseases both of which will
be reported later.

METHODS

Melphalan therapy in the 27 patients presented here was begun between 1961 and
1966. Data relating to the individual patients are summarized in Table 2. Pretreatment
diagnostic studies and followup examination were carried out in the Hematology Laboratory,
Duke Hospital. All of the patients had evidence of panmyelopathy with symptoms, physical
and laboratory abnormalities sufficiently severe to require suppression of bone marrow
function. The only myelosuppressive agent used in these patients during the course of
the study was melphalan. In an occasional patient, usually early in the course of treatment,
phlebotomies were used to reduce excessive red cell mass quickly when this seemed ad-
visable (Table 2). The degree of therapeutic response at arbitrary periods of three months,
one year and on later followup was recorded. An “Excellent” response was defined as the
complete relief of symptoms with no physical or laboratory evidence of disease. A “Good”
response was defined as the relief of all major disabilities, and the reduction of blood
counts to the range of normal without clinically significant cytopenia, but with the per-
sistence of some pruritus, reduced performance status or splenomegaly. A “Fair” response
was used to indicate a significant degree of improvement in symptoms and gain in per-
formance status, but less than 50 per cent correction of abnormal blood counts and
splenomegaly. “Moderate” clinically insignificant cytopenias refer to a WBC of 2500–4000,
platelet counts reduced to 50,000–100,000, and volume of packed red cells (VPRC)
reduced to 35–38 per cent. A “Good +” status was used to indicate the complete relief
of symptoms and normal blood counts, but a persistently palpable spleen.

ILLUSTRATIVE CASE SUMMARIES

F.B.R., G35362
This 65-year-old business woman and housewife developed a ruddy complexion in 1962
and severe pruritus after bathing. Red face, red eyes, hot flashes and reduced exercise
tolerance a few months later led to the discovery of an enlarged spleen and elevated
blood counts. No treatment was advised. In the summer of 1964 her toes turned nearly
black and her feet became too painful for normal activity. Her hemoglobin concentration
was found to be 20.7 Gm. per cent, packed red cell volume 70.0 per cent and white cell
count 18,000/cu.mm. Six phlebotomies were performed following which she was given
Myleran for a period of two weeks. The pruritus and foot pain improved somewhat, but she
remained incapacitated.
She was first seen at Duke Hospital on October 30, 1964. On examination she appeared
fairly comfortable and not plethoric. Her blood pressure was 160/90. Her optic fundi
appeared normal. Her heart and lungs were normal to physical examination. The tip of
the spleen was palpable 3–4 cm. below the costal margin; the liver was not palpable. Good
good pedal pulses were present. When dependent her toes became cyanotic.

Review of her past medical history revealed that in her mid-thirties she was found to
have chronic proteinuria with no history of preceding renal disease. In later years she had
been troubled by recurrent episodes of diarrhea and abdominal pain, but diagnostic studies
on many occasions had disclosed no specific abnormality.

Her hemoglobin concentration, following phlebotomies and the busulfan chemotherapy,
was 15.8 per cent, hematocrit 57.0 per cent, white cell count 22,250/cu. mm. and platelet
count 1,280,000/cu. mm. In the stained blood films the leukocytes appeared normal, but
the erythrocytes were somewhat pale. Platelets were present in large clumps.

The urine protein excretion was 4.2 Gm./24 hours. Electrophoresis of the urine protein showed that 80 per cent was albumin and about five per cent a beta globulin component. Later, with control of the disease, the proteinuria fell to 0.6 Gm./24 hours.

Her clinical course after melphalan chemotherapy was begun is shown in Fig. 1. Ten mg. of the chemical were given daily for three days and 6 mg for four weeks. When the white cell count fell, the dose was further reduced and then suspended for two weeks when leukopenia developed. After eight weeks of treatment, her performance status was nearly normal, and the spleen no longer palpable. The pruritus became less troublesome and gradually diminished during the course of nine to 10 months until it became insignificant. Gastrointestinal complaints became minimal. With a melphalan dose of 2 mg. three times per week, her disease status was excellent after four-and-one-half years of therapy.

W.R.B., G65634

This 68-year-old retired farmer enjoyed good health despite having moderately severe arterial hypertension for many years until he developed chronic pruritus in 1962. This became so severe within a year or two that he was forced to take infrequent sponge baths wetting only a few square inches at a time. In early 1965 abdominal fullness developed, and in December of that year his family physician discovered a greatly enlarged spleen, a hemoglobin concentration of 22.4 Gm. per cent and leukocytosis. He was referred to Duke Hospital with a tentative diagnosis of chronic granulocytic leukemia.

On his first examination at Duke Hospital on December 15, 1965, he appeared thin, moderately uncomfortable and plethoric. His blood pressure was 200/105 mm. Hg. His conjunctivae were suffused but on funduscopic examination the retinal veins appeared to have normal caliber. The superficial lymph nodes were not enlarged. His lungs were clear to physical examination. His heart was not enlarged, but a soft systolic ejection murmur was present. The left half of his abdomen was almost completely filled with a large spleen which extended to within 1 cm. of the midline. His liver was not palpable. The remainder of the examination showed no definite abnormalities.

His hemoglobin concentration was 23.4 Gm. per cent and packed red cell volume 74.0 per cent. The white cell count was 15,750 and platelets 305,000/cu. mm. In the stained film the formed elements appeared normal. Bone marrow aspirated from the
sternum showed an increased number of myeloid and erythroid elements with a conspicuous increase in the number of megakaryocytes. The patient declined phlebotomies so therapy was initiated with melphalan. His clinical course is shown in Fig. 2. He was given 10 mg. of the chemical daily for five days and then the dose was reduced to 4 mg. daily and then finally to 2 mg. per day. Chemotherapy was suspended for three weeks in January 1965 when he developed a respiratory infection. After three months of therapy his performance status had improved and the spleen had become considerably smaller. His hemoglobin concentration was 15.6 mg. per cent, packed red cell volume 50.0 per cent and white cell count 9795/cu. mm. The pruritus gradually subsided and after six months' treatment he was able to bathe normally. His spleen was no longer palpable. With maintained melphalan therapy his status at one year after initiation of therapy was excellent, and the same at five years.

V.E.S., G52850

This 55-year-old school teacher, first seen at Duke Hospital on July 2, 1965, began to have spells of dizziness, headaches, and disturbed vision in 1962-63. Severe pruritus after bathing became a major complaint a year or two later and she began to have acute episodes of swelling with heat and pain about her left ankle. In June 1965 an enlarged spleen and abnormal blood counts were discovered, whereupon she was referred for hematologic studies. On examination she appeared thin, frail, and plethoric. Her blood pressure was 160/110 mm. Hg. Examination of her optic fundi showed only distended retinal veins. The superficial lymphnodes were not enlarged. The spleen tip was palpable 7 cm. below the left costal margin. The liver did not appear to be enlarged. Her left foot was hot, tender and slightly swollen. There were large varicose veins bilaterally.

Her hemoglobin concentration was 17.6 Gm. per cent, white cell count 39,000/cu. mm., packed red cell volume 56.0 per cent with 3 mm. of overlying white cells and platelets. The platelet count was 640,000/cu. mm. In the differential white cell count, there were 31 per cent segmented neutrophils, 2 per cent nonsegmented neutrophils and 67 per cent lymphocytes. The latter were characteristic of chronic lymphocytic leukemia, immature, had prominent nucleoli, etc. The red blood cells were somewhat pale. Platelets were increased in number and occurred in clumps. Bone marrow aspirated from the sternum was hypercellular and contained an increased number of erythrocytic precursors and
Megakaryocytes, but no abnormal lymphocytic infiltration. There was no stainable iron. Tests for occult blood in the stool were negative. Chest X-rays were normal.

Melphalan therapy was begun in a dose of 6 mg. daily and reduced to 4 mg. daily as her white blood count began to fall. She began to improve rapidly after three to four weeks of treatment. At the end of two months of therapy her hemoglobin concentration was 13.4 Gm. per cent, volume of packed red cells 45.0 per cent, white cell count 5990 and platelet count 65,000. Her spleen was just palpable, and some edema persisted at the left ankle. At five months her status was rated as “Good +.”

The maintenance dose of melphalan was decreased during the next one to two years to 2 mg. three times per week and finally to 2 mg. once a week. Evidence of relapse began to appear in June 1969, with return of malaise, loss of weight, reduced exercise tolerance, some pruritus and pain in the left upper abdomen. The spleen which had not been palpable in February 1969 became enlarged and tender. The hemoglobin concentration rose to 17.9 Gm. per cent, the white cell count to 34,500 and packed red cell volume to 50.0 per cent with 2 mm. of overlying platelets and white cells. Seventy per cent of the circulating leukocytes were lymphocytes and many of them appeared immature and contained nucleoli as before. Aspirated bone marrow was found to be hypercellular again, but there was no abnormal lymphocytic infiltration. With evidence that her p. vera had relapsed and in view of the abnormal lymphocyte proliferation, a trial of chlorambucil therapy was begun to compare its effect with that of melphalan.

After six weeks of treatment, she was comfortable and gaining strength. Her spleen was somewhat smaller. Her hemoglobin concentration was 13.8 Gm. per cent, packed red cell volume 42.0 per cent, white cell count 14,300 with 62 per cent lymphocytes and 34 per cent neutrophils. The platelet count was 205,000/cu. mm.

**Results**

The clinical and hematologic features of the 27 patients with p. vera treated with melphalan are summarized in Table 2. Their ages given as of July, 1969, or at the time of their death as noted in the table, ranged from 41-79 years. The total duration of disease ranged from two to 17 years and in over half of them p. vera had been present for more than 10 years. The period of melphalan therapy ranged from 20 to 72 months with an average of 44 months.

The major clinical abnormalities which occurred in these patients provide an index to the basic severity of the individual's disease, as well as the types of excessive cellular proliferation present. Pruritus, one of the most aggravating symptoms in p. vera, was a major complaint of 13 patients. Three had massive gastrointestinal hemorrhage, and three others had iron deficiency presumably due to occult blood loss. Six had gout. In two instances gouty arthritis had developed years before the p. vera and appeared to be “primary.”

Nine patients presented with neurologic symptoms, dizziness, blurred vision, tinnitus and mental confusion with loss of memory, all of which subsided with therapy. The diagnosis was made initially in one patient when he developed a subarachnoid hemorrhage. Occlusive vascular disease of the legs was the major problem in three patients and varicose veins in two.

In reference to previous therapy 11 of the 27 patients had been given no treatment for p. vera before melphalan. Six had had phlebotomies only. Ten had been treated with marrow suppressive agents, 32P, external irradiation, Daraprim, triethylene melamine, and Myleran with variable results (Table 2).

Evidence of panmyelopathy was present in every patient. Twenty-four of the 27 had enlarged spleens and the remaining three had a conspicuous leukocy-
tosis and thrombocytosis. Twenty-two patients had a leukocytosis of over 12,000/cu. mm. and 20 had thrombocytosis with platelet counts over 500,000 cu. mm. or a layer of packed platelets greater than 2 mm. Eight of the nine patients in whom the packed red cell volume was less than 56 per cent had had gastrointestinal bleeding, phlebotomies or a bone marrow with no stainable iron.

The initial dose of melphalan was 6–10 mg. taken in one dose before breakfast daily for five to seven days following which 2–4 mg. were given until disease control was achieved. To avoid undue depression of bone marrow function blood counts were checked at intervals of one to two weeks early in therapy and later, when disease control was stable, at intervals of one to two months. Therapy was suspended temporarily whenever the WBC fell below 4000/cu. mm. Maintenance therapy, necessary for most patients, ranged from 2–6 mg. per week.

The major signs and symptoms of disease in this group of patients usually began to improve within two to four weeks. At three months the status of 24 of the 27 patients was rated as “good” to “excellent.” With maintained therapy 14 of the 27 patients had no evidence of disease at the end of one year, and in eight of the remaining 13 the only abnormality was a palpable spleen. After one year of therapy, all 27 patients had normal blood counts, although in two individuals with chronic headaches and one with varicose veins and recurrent thrombophlebitis, an occasional phlebotomy was done for symptomatic purposes when the VPRC was below 50 per cent.

The time required to correct the various clinical and laboratory abnormalities, illustrated above for two representative individuals (Figs. 1 and 2), was relatively constant from patient to patient. Leukocytosis and thrombocytosis generally began to subside within one to two weeks while reduction of the packed red cell volume required one to two months. Circulatory symptoms began to subside and the performance status to increase with control of erythrocytosis and thrombocytosis. Maximal recovery in 18 patients with major circulatory symptoms required a period of two to six months. Splenomegaly and pruritus often regressed slowly. Twenty-three patients had enlarged spleens before melphalan therapy was begun. In two splenomegaly disappeared in less than three months and in nine others splenomegaly disappeared after between three and 18 months of therapy. In 12 patients the spleen became considerably smaller, but always remained palpable. An acute episode suggestive of splenic infarction occurred in one patient. Pruritus improved in all patients, but persisted to a minor degree for one to two years in four instances.

V.E.S. appeared to have both p. vera and chronic lymphocytic leukemia. The simultaneous occurrence of a myelo- and a lymphoproliferative disease is very rare.17 In this instance melphalan was effective in controlling both diseases.

Three patients suspended melphalan therapy, contrary to our plan, and relapsed after various intervals. R. G. took melphalan for only six weeks, quitting it when mild leukopenia developed. She remained well for two years, though, and for five to six years required only an occasional phlebotomy. Her spleen remained palpable. A full-blown relapse developed at eight years and melphalan therapy was resumed. F.R.H. quit taking melphalan after 36 months.
After 24 months without therapy he relapsed with fatigue, pruritus, splenomegaly, and pancytosis. Melphalan was resumed and he improved promptly. N.C.M. suspended therapy after 45 months but within four months had had a recurrence of pruritus. The hemoglobin concentration rose to 20.3 Gm. per cent, and the packed red cell volume to 66 per cent. Melphalan therapy was resumed.

Untoward reactions during melphalan therapy were infrequent. Moderate clinically insignificant leukopenia was produced in seven patients, usually during the first one to two months of therapy when the dose was being adjusted. Only one serious complication was encountered, severe leukopenia with pneumonia (L.M.F.). She recovered promptly and with maintained therapy has proved to be unusually sensitive to the effect of melphalan. Her disease has been satisfactorily controlled with as little as 1 mg. of the chemical per week. Moderate anemia was produced in two patients and transient thrombocytopenia in seven with platelet counts falling as low as 50,000–100,000. These evidences of depressed marrow function regressed promptly, within two to four weeks, with suspension of therapy in all instances.

In five of the six patients who had gouty arthritis, concomitant allopurinol therapy seemed advisable. The exception, J.H.O., had developed podagra two years before abnormal blood counts were discovered. Before melphalan therapy was begun, while he was taking probenecid and colchicine, his serum uric acid concentration was 10.9 mg. per cent. With control of the p. vera the serum uric acid level fell to 6.4 mg. per cent. Another patient, W.L.B., with persistent asymptomatic hyperuricemia was given allopurinol for prophylactic purposes.

Seven patients in this series have died, but the cause of death in four was not related to p. vera. B.T.R., after having three well-documented myocardial infarctions before he developed p. vera, died suddenly during an episode of chest pain. J.H.B. died of a brain tumor and J.H.O. of disseminated prostatic carcinoma. E.L.C. died one week following the resection of a carcinoma of the colon. Examination one month earlier had indicated that the p. vera was under “Excellent” control.

Four patients in this series developed acute leukemia, but none had been treated with melphalan alone. W.W.W. died of acute myelogenous leukemia after having had p. vera for 11 years. Early in the course of his illness he had been treated with busulfan. O.H.B. died of acute myelogenous leukemia 16 years after the onset of p. vera. He had been treated earlier with triethylene melamine. Neither of these two patients had received irradiation therapy. R.H.P. died of acute leukemia 11 years after the onset of p. vera and ten years after he had been given 4 mCi. P.L.A.C. developed acute myelogenous leukemia 17 years after the onset of p. vera. During the first years of his disease he was given spray irradiation.

Only one of the 27 patients treated with melphalan has developed refractory anemia, misshapen erythrocytes, and granulocytic immaturity indicative of myelofibrosis or the “burned-out” stage of p. vera.

**DISCUSSION**

Rational therapy for patients with polycythemia vera should be planned in reference to (1) the type and importance of specific proliferative abnormalities.
present in a given individual and (2) the hematologic effects of therapeutic agents or procedures hopefully chosen to normalize or compensate for abnormal marrow function.

Venesecion is a classic procedure which can effectively reduce red cell mass, plethora and the occasionally associated hypertension. The long-term effect is to produce iron deficiency and erythrocytes with low hemoglobin content. Blood letting has no beneficial effect on splenomegaly, pruritus, leukocytosis, thrombocytosis, the overproduction of uric acid, secondary gout, etc. The use of orthovoltage irradiation, or \(^{32}\)P to suppress bone marrow function affects erythrocytic, granulocytic and megakaryocytic cell strains more or less nonspecifically. In the course of time irradiation may promote bone marrow fibrosis, the development of refractory anemia or acute leukemia. Therapeutic failures may occur, too, for example when thrombocytosis persists in the presence of leukopenia and/or anemia. Intravenous nitrogen mustard is probably the most effective agent available to suppress marrow function quickly in emergencies such as thrombocytosis with incipient gangrene or infarction. Side reactions to nitrogen mustard, however, the necessity for intravenous injections, and the need to repeat therapy at intervals of two weeks or so make long-term therapy with this agent impractical. Triethylene melamine has been an effective agent in the treatment of p. vera, too, but the instability of the compound in the presence of gastric acidity, and the considerable variation in dose from patient to patient limit its usefulness. Busulfan, chlorambucil and cyclophosphamide have demonstrable therapeutic activity in p. vera. The hematologic and antileukemic effects of busulfan and chlorambucil are significantly different. Busulfan suppresses the growth of granulocytes and platelets primarily, when used with maximum therapeutic selectivity, while chlorambucil suppresses the growth of mature lymphocytes. Cyclophosphamide suppresses the growth of granulocytes while sparing platelets. These properties apply to the management of p. vera.

The use of busulfan is limited by its tendency to produce excessive and prolonged cytopenia in many patients, occasionally marrow aplasia, and late complications such as skin pigmentation and pulmonary fibrosis. Chlorambucil is particularly useful in patients with p. vera who have erythrocytosis with normal or low platelet and white counts. Cyclophosphamide spares platelets and is useful in similar circumstances, but the incidence of side reactions is greater. In a comparison of the three agents in one clinic the overall effects of chlorambucil seemed to be superior to those of busulfan and cyclophosphamide. In their patients the disease appeared to be relatively mild, however, since only 23 per cent had platelet counts above 500,000 and only 52 per cent WBC counts above 12,000. Their results of therapy are difficult to compare with other series. Data regarding the extent to which marrow suppressive agents control excessive uric acid production, secondary gout, and nephropathy in p. vera and other myeloproliferative diseases are not available.

L-phenylalanine mustard was first synthesized by Bergel and Stock in
1953.\textsuperscript{26} It was active against a number of animal tumors, but clinical studies lagged when early trials showed that it depressed bone marrow function more than chlorambucil.\textsuperscript{19,27} Following the report by Blokhin and colleagues of therapeutic activity in multiple myeloma,\textsuperscript{28} a multitude of studies confirmed its efficacy in this disease. The need for more comprehensive study of the effects of the compound in the myeloproliferative as well as the lymphoproliferative diseases led to the initiation of our studies in 1960-61.

The observations summarized above show that melphalan is an effective agent that can be used safely and conveniently over a period of years to suppress bone marrow function in patients with p. vera. As would be expected the compound is useful, too, in the treatment of other myeloproliferative diseases, chronic granulocytic leukemia,\textsuperscript{29} and hemorrhagic thrombocytopenia.\textsuperscript{30} In the lymphoproliferative diseases its effect is generally inferior to that of chlorambucil or cyclophosphamide, but in the patient whose case history was summarized above who had p. vera and chronic lymphocytic leukemia, both were adequately controlled by melphalan.

Cumulative toxicity with melphalan therapy has not developed in patients treated for as long as 72 months, and only one patient has developed complications of the type frequently associated with the use of other agents in this disease, refractory anemia, “spent” or “burned out” marrow, or myelofibrosis.

The incidence of leukemia in patients with p. vera treated with alkylating agents is reported to be less than those treated with irradiation.\textsuperscript{5,22} One of our patients who was first treated with busulfan and later melphalan has died of acute leukemia. Two of our other patients not included in this series, one treated with busulfan alone and another treated with triethylene melamine alone, died of acute leukemia five to six years after the onset of their disease and beginning of treatment. While none of our patients treated with melphalan alone have developed acute leukemia, we have no reason to think that this will not occur as time goes on.

The extent to which continuous melphalan therapy can prevent the development of marrow fibrosis and refractory anemia in patients with p. vera may not be clear for another decade or so. The maintenance of normal marrow function so far is encouraging.

Patients who have hyperuricemia or hyperuricosuria that persists despite the optimal control of their p. vera are liable to develop gout or gouty nephropathy. In them, the prophylactic use of allopurinol seems wise.

The diversity of opinion regarding the treatment of p. vera seems to be fairly intractable.\textsuperscript{12} A large-scale prospective comparison of the therapeutic effects of phlebotomy, chlorambucil and \textsuperscript{32}P and a subsidiary comparison of melphalan with other agents is now being undertaken by the P. Vera Study Group.

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Melphalan Therapy of Polycythemia Vera

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