POLYCYTHEMIA VERA is by no means a rare disease; in hematologic practice it represents a commonly recurrent problem, not only in diagnosis but in therapy. The excessively high blood volume, the greatly increased blood viscosity, the very high platelet level—these are all conducive to the development of serious thrombotic manifestations. Therapy may thus become a rather urgent matter in some cases. In the past, phenylhydrazine hydrochloride was used to reduce the blood volume through its hemolytic effect; it was a difficult drug to control and the retained products of hemolysis were undoubtedly a further means for causing marrow stimulation. Fortunately, it has been almost completely discarded. In the last two decades, two methods of therapy have gradually assumed preeminence: systematic venesection to induce an iron deficiency state, and radioactive phosphorus to reduce the marrow hyperactivity. Venesections done irregularly may be more stimulatory than beneficial, but systematic venesections in a fresh case, at intervals of twice a week for two to four weeks, induce an iron deficiency state. Although red cell production may continue unimpaired, there is insufficient iron for hemoglobin formation, and the mature red cells are microcytic and hypochromic. The hematocrit may then remain at normal levels for months to a year, with only occasional venesections being required thereafter. Maintenance of the iron deficiency state may be continued by the use of an iron low diet. However, the platelet level, often extremely high, will not be affected by this regimen. With the use of radioactive phosphorus, one has a potent method for quickly reducing the activity of all the elements of the marrow. However, the red cell mass does not become reduced straightaway, since the circulating red cells are unaffected by the radioactive material. For this reason, preliminary venesections followed shortly by radioactive phosphorus accomplish the dual purpose of reducing blood volume quickly and diminishing leukocyte and platelet levels. Which of these two methods (venesection alone vs. venesection plus P³²) is best both for initial therapy and for the ultimate life-span of the patient has by no means been settled.

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Multiple venesections plus a diet low in iron require a certain amount of technical equipment and care on the part of both the physician and the patient. Radioactive phosphorus requires a "set-up" for the administration and use of radioactive material. Because the therapeutic regimen of polycythemia vera differs somewhat from clinic to clinic, a panel of experts in the therapy of the disease was asked the following question:

**What is your regular therapeutic procedure in a fresh case of well-defined polycythemia vera? Do you recommend the use of an iron deficient diet for maintenance?**

**Dr. Lawrence:**

We cannot give a precise answer as to what our regular therapeutic procedure is in cases of well-defined polycythemia vera, since we do not follow a routine procedure. Each patient is individualized. The vast bulk of the patients received only P₃². However, in some patients who because of age, an elevated white count, or a history of thrombotic episodes may be considered candidates for a major vascular occlusion, we are inclined to phlebotomize the patient, removing between 1000 and 2000 cc. of blood. However, in each case, the patient is seen several times before the therapeutic procedure is initiated. Following this, the patient is seen at approximately weekly intervals whenever possible and the red count, hemoglobin and hematocrit followed. In some instances, phlebotomies are performed later, but generally when a phlebotomy is carried out it is done early in the course of therapy and in less than 50 per cent of the cases.

We do not recommend the use of an iron deficient diet for maintenance.

In summary, we do not believe that one should generalize with regard to the therapy in this disease and that each patient should receive therapy based upon our evaluation at the time seen here. We do not believe that one can follow a rigidly outlined procedure.

**Dr. Rosenthal:**

Perhaps the best way to answer the question concerning our mode of therapy in polycythemia vera is to present in summary form an outline of our results with the use of the several therapeutic methods we have personally used in fresh cases of the disease. These data are based on the first form of therapy used in the management of 189 ambulatory cases of the disease. The dose of P₃² used in these cases was 5–6 millicuries.

<table>
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<tr>
<th>Form of Treatment</th>
<th>No. of Cases</th>
<th>Remission more than one year</th>
<th>Remission less than one year</th>
<th>No improvement</th>
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<tr>
<td>P₃² alone</td>
<td>131</td>
<td>77</td>
<td>27</td>
<td>27</td>
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<tr>
<td>P₃² plus Phlebotomies</td>
<td>26</td>
<td>15</td>
<td>6</td>
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<tr>
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<td>4</td>
<td>.13</td>
<td></td>
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<tr>
<td>Triethylene Melamine</td>
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<td>3</td>
</tr>
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<td>3</td>
<td>1</td>
<td>2</td>
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</tr>
<tr>
<td>No treatment</td>
<td>4</td>
<td></td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>
As for the second question, we have impressed upon the patient that in addition to the basic form of therapy, a so-called iron deficiency diet is essential. For this purpose, the patient is urged to refrain from red meats, shellfish, and spinach.

DR. STICKNEY:

Previously untreated patients are first subjected to phlebotomy to reduce the percentage volume of packed red cells to approximately 55 per cent. This is done for immediate symptomatic relief and to reduce the possibility of vascular complications.

The patient then receives radioactive phosphorus. Patients without significant leukocytosis or myeloid immaturity are given an initial dose of 4.0 millicuries; those who have leukocytosis (counts of more than 15,000) or myeloid immaturity receive 5.0 millicuries. The intravenous route is preferred. In rare instances, when the latter route is not feasible, the radioactive phosphorus is given orally, which necessitates an increase in dose of about 30 per cent.

Patients are instructed to have determinations of the hematocrit, hemoglobin, erythrocytes, leukocytes and platelets repeated in 8 weeks; a second dose of radioactive phosphorus is then given if a well-defined remission has not taken place.

These blood studies are repeated at intervals of 8 to 12 weeks thereafter, and further treatment is instituted when indicated by hematocrit values of more than 55 per cent.

We have not made extensive use of low-iron diets in the management of polycythemia vera. However, some patients have been on a regimen of phlebotomy and low-iron diet prior to our examination. In other instances when patients were refractory to radioactive phosphorus, we have advised iron-poor diets. In no instance have we been impressed that the low-iron diet was an effective variable in the management of these patients. Some patients without either leukocytosis or a pronounced increase in the absolute erythrocytic volume do well when only phlebotomy is used.

DR. WASSERMAN:

A careful appraisal of the course of polycythemia vera with its inevitable progression through a myriad of complex interrelated syndromes and an understanding of the pathophysiology of the disease should allow for more intelligent management of these cases. Each stage of the disease may require treatment different from that used in the preceding phase. The following discussion will concern only the management of the initial erythrocythemic stage of erythremia.

Polycythemia vera is a chronic disease of unknown etiology with signs, symptoms, complications, and frequently even mode of death all due directly to the associated panmyelosis, hypervolemia and increased blood viscosity. Since the hematocytic marrow cells respond as a unit to the stimulus of the disease, granulocytosis and thrombocytosis are also present in addition to the erythrocytosis. Fibroblastic and osteoblastic hyperactivity of varying degree accompanying this hematic cell proliferation may eventually produce diverse pathologic pictures that may completely obscure the initial features of erythremia.
Until the specific cause of the disease has been ascertained, therapy, to be satisfactory, must in some way produce symptomatic relief as well as prevent the frequent complications incident to the total marrow hyperplasia and the expanded red cell mass. This can best be accomplished at present by the combination of initial venesection plus the subsequent use of a marrow-suppressive agent.

Were we concerned with only the increased red cell volume and blood viscosity, satisfactory control might be established by repeated venesections or the use of hemolytic agents such as phenylhydrazine. The latter form of therapy has been discontinued because of its uncertain effect, variable dosage necessary, and secondary stimulation of the bone marrow with a more marked leukocytosis and thrombocytosis perhaps due to retention of stromal substances. Venesections, if utilized as the sole therapeutic measure, or in combination with iron poor diets throughout the long course of erythremia, will produce an iron deficiency state with microcytic hypochromic polycythemia. Although a normal red cell mass may be attained by removal of blood, the marrow hyperactivity is further stimulated with more marked leukocytosis, thrombocytosis, and immature cellular elements in the peripheral blood despite the occasional reduced erythrogenetic activity. Iron is probably the most essential trace element involved in cellular activity, being intimately concerned in all vital processes, particularly those of oxygen transport. Its reduction much below the normal physiologic levels for a prolonged period of time will produce all the clinical signs and symptoms of severe iron deficiency, e.g., Plummer-Vinson syndrome.

Iron poor diets have occasionally been used to supplement treatment with phlebotomies. There is little to recommend such drastic dietary measures for the management of this chronic disease. Since less than 1 mg. of endogenous iron is excreted per day, a similar amount absorbed per day would be necessary to maintain an adult male in iron balance. The normal daily diet contains about 20 mg. iron with absorption from the gastro-intestinal tract of only 5–10 per cent. It is obvious that severe restrictions of the food intake are necessary to reduce the dietary iron content significantly below 10 mg. per day. The elimination of such iron-containing foods as muscle and glandular meats, eggs, cereals, bread, green leafy vegetables and fresh fruits from the diet is not conducive to a satisfying existence and good patient-physician relationship. And when one realizes that a venesection of 500 cc. removes about 250 mg. iron in a matter of minutes, it hardly seems worthwhile to undergo the dietary torments necessary to achieve a goal which can be so easily gained by another method.

Patients with erythremia treated by repeated venesections so as to induce iron deficiency become severely incapacitated and “polycythemic cripples,” of little use to themselves or their families. The administration of iron in therapeutic doses to such patients may produce dramatic improvement in their physical state with the polycythemia subsequently controlled by myelosuppressive therapy.

The fundamental disturbance in polycythemia vera is the marrow panmyelosis due perhaps to neoplastic stimulation of the primitive reticulum cell. The symptoms and complications of the disease are due, however, to the resultant erythrocytosis, thrombocytosis and granulocytosis. Since hemorrhage and thrombosis occur in about 50 per cent of untreated or poorly treated polycythemia vera
patients, it is necessary to expedite the correction of the abnormal erythremic state by initial rapid reduction of the blood volume by venesections until normal or almost normal red cell levels are attained.

Various agents have been utilized to reduce bone marrow activity, e.g., x-irradiation to spleen and long bones, total body irradiation, administration of radioactive isotopes including phosphorus, sodium, gold, zirconium and yttrium in ionic or colloidal form, and the chemotherapeutic agents nitrogen mustard, triethylene melamine and the antifols including darpim.

Despite the multiplicity of therapeutic measures available for myelosuppressive use, only two can be recommended: (1) radioactive phosphorus and (2) spray irradiation, with the former preferred because of its ease of administration and absence of any symptoms associated with its use.

Tri-ethylene melamine has been used successfully but its effect is unpredictable. Remissions are short-lived; about 50 per cent of the patients cannot tolerate it because of nausea and vomiting; and too long a period of time is required to establish a minimal effective therapeutic dose.

Nitrogen mustard not only produces severe reactions but remissions are too short and responses too variable to be particularly desirable.

Recently darpim, of weak antifolic activity, has been recommended for the treatment of polycythemia vera. Of all the agents mentioned, it is by far the least desirable. Its action is slow and unpredictable and nausea and vomiting occur in about 50 per cent of patients. When effective (in not more than 20 per cent of the cases), it produces a megaloblastic marrow, often with associated leukopenia and thrombocytopenia. Marrow aplasia may appear despite careful hematologic control; petechiae, mouth ulcerations and gastro-intestinal hemorrhages also have been noted despite no apparent change in the blood or marrow. Darpim is a treacherous drug to use in polycythemia vera and since it is rarely effective, its further use should be discontinued.

Radiophosphorus remains the treatment of choice in erythremia. When P³² is not available, spray irradiation may be utilized as a satisfactory substitute. Radioactive phosphorus may be given orally or intravenously, with the latter the preferred method of administration. Approximately 75 per cent of the patients with erythremia respond to small doses of 3–7 millicuries P³² and remissions may last from 6 months to over 5 years. Where remissions are not obtained within 6 months, the radioactive phosphorus may be administered again in the same dosage. If P³² proves ineffective in those exceptional cases of polycythemia vera, it may still be utilized together with venesection to control the thrombocytosis, granulocytosis and panmyelosis.

The excellent physical condition of the polycythemic vera patients so treated should certainly recommend the above as the approved method of therapy.

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**AGENTS USED FOR TREATMENT OF ERYTHREMA**

(In order of preference)

1) P³²:
   Treatment of choice; used intravenously.

2) Spray irradiation:
   When P³² not available; produces radiation sickness.
THE TREATMENT OF POLYCYTHEMIA VERA

3) Venesection:
   Used for initial rapid reduction of blood volume to normal; only in emergency thereafter.
4) Tri-ethylene melamine (TEM):
   Response slow and unpredictable; short remissions usually; (toxic symptoms frequent.

AGENTS NOT TO BE USED OR INEFFECTIVE

1) Daraprim:
   Treacherous; produces ulcerations, hemorrhages, marrow aplasia. Remissions few and temporary.
2) Nitrogen mustard:
   Severe reactions, variable response, short remissions.
3) Phenylhydrazine:
   Hemolytic agent, unpredictable; marrow stimulated.
4) Fowler's solution:
   Gastro-intestinal symptoms frequent; relatively ineffective.

PRINCIPLES OF MANAGEMENT OF POLYCYTHEMIA VERA

1) Normalization of red cell mass by 300-500 cc. venesection every 1-2 days followed by
2) Myelosuppressive agent: P₃² or spray irradiation.
3) Individualized therapy:
   P₃² no more than 3-7 mc. every 6 months; or
   Spray irradiation in minimal doses.
4) Venesections in resistant cases, with P₃² or x-irradiation to control thrombocytosis.
5) Periodic blood examinations.
6) Elective surgery permissible only after long (2 months or more) control. Emergency surgery only after rapid control by venesection.

Moderator's Comment

The panel is practically unanimous in advocating P₃² as by far the best method of therapy of the disease. Dr. Rosenthal's results are particularly impressive, especially when compared with the other less effective methods. Dr. Wasserman's emphatic comments regarding the induction of an iron deficiency state are refreshingly frank, although we ourselves have found no cause for alarm in treating polycythemic individuals by means of venesections and a low iron diet. Patients thus treated seem to carry on their various activities without perceptible difficulty; I think they would resent being called "polycythemic cripples." As for the low iron diet, most patients seem to react favorably to it. I find that many patients, polycythemic or otherwise, are anxious to have some
sort of diet for their condition. Patients given a low iron diet usually think this is a sensible arrangement; after awhile, they seem to become habituated to their restrictions and appear to suffer no ill effects. On the other hand, for those patients who have an unusually active marrow, a very high platelet level, a tendency to thrombosis, and a persistence of such symptoms as intense itching of the skin, etc., radioactive phosphorus is definitely indicated. Perhaps all patients with polycythemia vera should receive this material, although of this one is by no means sure. Treatment is certainly made simple and the remissions are often (not always) prolonged and complete. However, I for one still hesitate to expose an essentially normal person to the possibly delayed effects of radioactivity, even though the half-life of radioactive phosphorus is small. The various statistics on the incidence of acute leukemia in P32-treated polycythemias agree in showing a small but significant rate although this is perhaps no greater than might occur spontaneously. Further long-term comparative studies on these and other points are certainly desirable.—W. D.
Panels in Therapy: III. The Treatment of Polycythemia Vera

JOHN H. LAWRENCE, NATHAN ROSENTHAL, MINOTT STICKNEY and LOUIS R. WASSERMAN