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THE CONTROL OF POLYCYTHEMIA BY MARROW INHIBITION*

A Ten Year Study on 172 Patients

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Polycythemia vera, first described by Vaquez in 1892 (1) and later by Osler (2), has been considered a fatal disease with a relatively short duration of life after onset, although an unusually long duration has been observed in some cases. Lee states, "The prognosis is inevitably fatal, but it must be remembered that this is a chronic disease, the duration of which varies from several months to many years." In the true form of polycythemia, the usual duration even after diagnosis, which is usually not established for over a year, is a number of years (3). Symptomatic relief and control of the hematologic picture have been possible in many patients by means of venesections, phenylhydrazine given orally or roentgen irradiation, but there has been reported no large series of patients treated and observed for a long period in which evidence has been presented that there has been satisfactory control of the disease and marked lengthening of life.

Richardson and Robbins (4) treated, since 1932, 28 patients with total body roentgen irradiation, and they concluded that their results show that their method of therapy is superior to venesection or phenylhydrazine therapy. In the 12 patients who died, the causes of death were: pulmonary disease not related to the polycythemia (2), carcinoma of the breast (1), uremia due to prostatic obstruction (1), arterial thromboses (6; 3 coronary, 2 cerebral and 1 cerebral, aortic and subclavicular), the primary disease (1) and pulmonary embolism (1). In a series

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reported by Tinney and his co-workers (5) there was definite evidence that 36 out of 163 patients survived more than five years after onset. Common causes of death have been thromboses (6) in various arteries or veins, hemorrhage, the development of leukemia or anemia and infectious, neoplastic or other intercurrent disease.

In the absence of methods for preventing the disease, one is forced to look for methods of keeping the number of red blood cells normal or near normal. If this can be done, these patients are usually sympton free, and they may be less susceptible to thrombotic complications. In 1938, after extensive animal and clinical studies with radioactive phosphorus, it was found possible to give nonlethal doses of sodium radiophosphate to animals and cause inhibition of cell production in the marrow (7). The phosphate containing P^{32} (half-life approximately 2 weeks) localized to a marked degree in bone, bone marrow and rapidly growing tissue such as leukemic tissue (8), and it therefore seemed possible that one might have here a simple method for the inhibition of red cell production in polycythemia vera. Consequently we administered the material to 2 patients with polycythemia vera; their hematologic course since that time is shown in Figure 1 and 2. These patients were reported in the original article (9). The doses given were calculated and extrapolated after extensive experience with the effect of P^{32} on the hematopoietic tissues of animals and human beings (10). It is seen that in both of these patients the number of red blood cells has been kept at normal or near normal levels with the infrequent use of P^{32} and the symptoms and signs of the disease have likewise been controlled during this period.

Since the treatment of these first 2 patients we have treated in similar fashion 119 more patients suffering from polycythemia vera and have complete follow-up records on 116 of these patients. Figures 3, 4 and 5 are charts showing the hematologic courses in other representative patients. Other investigators have confirmed our original observations that the symptoms and signs of the disease can

be kept under control with P^{32}, (11), but the present paper is the first attempt to evaluate this new form of therapy with reference to life expectancy or prolongation of life. In the evaluation of any new therapeutic measure, relief of symptoms and signs and prolongation of life are the important criteria.

Since the beginning of this study of polycythemia, we have had the opportunity of carrying out numerous clinical and physiologic studies on 172 patients suffering from polycythemia from various causes; 134 of them had the clinical and laboratory picture of polycythemia vera; 26 of them had mild polycythemia of unknown etiology, and 12 had secondary polycythemia, usually associated with cardiac or pulmonary disease. There is no cleancut line between primary polycythemia and secondary polycythemia, although most patients with primary polycythemia do have the classic picture and most patients with seconday polycythemia have an obvious cause for the elevated red count, but there is a group of patients which seems to fall in between in which the question of anoxia arises, and one wonders whether an anoxic stimulus may not be a factor in all cases of polycythemia, whether they be of classic primary polycythemia vera or secondary cases such as those seen with heart and pulmonary disease. In this laboratory we have completed and have in progress numerous physiologic investigations directed toward the answer to this and other questions, which will be reported elsewhere.

The patients with polycythemia vera varied in ages from 19 to 75 years at the time of onset, with an average of 50.7 years (Fig. 6). Of these, 56.5 percent were male and 43.5 percent female. In the entire group 85.6 percent had received treatment previously with conventional methods, such as venesections, phenylhydrazine, and/or x-ray. Palpably enlarged spleens were present in 65 percent. After therapy the enlarged spleens became smaller or impalpable. Elevated white blood cell counts, above 10,000, were noted in 68 percent, when first seen by us, and of those having an elevated white blood cell count, 38 percent had myelocytes or immature white blood

cells. This is of interest in view of the known relationship between polycythemia vera and leukemia and the frequent occurence of leukemia as a complication of polycythemia vera (15). Of those having immature white blood cells, 69 percent had received previous therapy (phenylhydrazine, roentgen rays, phlebotomy). After therapy with P^{32}, immature white blood cells were found in only 27 percent of those originally having immature cells. Five patients out of 121 or 4 percent of the total series (5 percent of the group showing initial elevated white blood cell counts) showed myelocytes in the peripheral blood after P^{32} therapy but not before. In no patient with a normal total white cell count when seen here initially were there myelocytes in the peripheral blood after P^{32} therapy but not before. Thirty-three percent had an elevated blood pressure, and 35 percent of these had a fall of their elevated blood pressure after P^{32} therapy. This is interesting in view of the possible relationship of the probably slowed renal blood flow and consequent renal hypoxia (12). There was a peptic ulcer or a history of it in 11.5 percent; 14.8 percent had a thrombotic history.

The diagnosis of polycythemia vera was made from the history, physical examination and the laboratory findings, including sternal marrow examination (table) before and after therapy (13). In connection with the marrow findings, it is interesting that there was an increased nucleated red cell count which returned to near normal or normal after therapy.

Average Differential Count of Sternal Marrow in 94 Cases of Polycythemia Vera (Pretreatment) and 20 Normal Subjects

	Polycythemia Vera (Percentage)	Normal (Percentage)
Myeloblasts	0.86	2.2
Neutrophil myelocytes	24.0	20.8
Eosinophil myelocytes	0.8	1.6
Basophil myelocytes	0.03	0.04
Nonsegmented polymorphonuclear cells	18.9	24.3
Segmented polymorphonuclear cells	24.7	19.6
Eosinophils	1.0	0.8
Basophils	0.2	0.02
Lymphocytes	3.1	8.9
Monocytes	0.2	0.4
Reticulum	0.3	1.6
Hematogones	1.1	2.8
Megaloblasts	0.3	0.2
Erythroblasts	2.0	1.7
Normoblasts	22.5	15.0

When necessary, arterial blood oxygen saturation was done to rule out secondary polycythemia (14), as were special pulmonary and cardiac studies if indicated. The degree of unexplained polycythemia had to be 7,000,000 or above before the diagnosis was made, unless there were cleancut evidence of the diagnosis in the past or an enlarged spleen with a definitely elevated red blood cell count. In borderline cases, the red cell mass as determined by P^{32} labelled cells and the measurement of red cell production with Fe^{59} were often helpful in diagnosis.

During 1939, 1940, 1941 and 1942, 30 patients were treated. Since that time this group of patients has received one course (usually two injections of 3 to 6 millicuries) on the average of every three years. In this series of 121 patients treated, 47.8 percent received only one course of therapy, and, in the first group of 30 treated, 17 percent had remained normal, at the time of reporting, for over three years after the single course of therapy. In the group treated during the first five years, 28 percent have had only one course of therapy, some of them

not needing retreatment after four, five, six, seven and eight years.

There have been 21 deaths. The causes of death have been as follows: generalized arteriosclerosis (5), leukemia (5), neoplastic disease (3), coronary occlusion (3), cardiac failure (2), portal thrombosis (1), anemia and leukopenia (1) and cerebral thrombosis (1). Excluding the patient with portal thrombosis which had developed prior to our seeing or treating the patient, the average age of death in this series was 67.*

It is to be noted that there were 5 deaths associated with leukemia, or about 4 percent of the treated group. The high incidence of leukemia as a complication of polycythemia vera is well known (15). As pointed out by Moschowitz (15), the transition of polycythemia vera into leukemia has been reported by many authors. Minot and Buckman (15), for example, report a series of 15 patients with polycythemia vera, three of whom developed this complication. Likewise, Rosenthal (15) reports such a case where no therapy had been given prior to the development of leukemia.**

*Since the writing of this paper, there have been 3 more deaths, 1 from circulatory failure following widespread thromboses which had developed prior to P^{32}, and 2 from causes unkown, but none from leukemia or the disease itself.

**Since this article was written, Dr. N. Rosenthal (personal communication to the author) has observed 8 more patients suffering from polycythemia vera, untreated by any form of radiation, who developed a marked leukemoid reaction or a leukemia as a complication. Two of these patients had a blood picture indistinguishable from chronic myelogenous leukemia. The following are the white cell counts and abnormal white cells in these patients:

Patient	White Cell Count	Abnormal White Cells
1	18,100	--
2	189,000	25% myelocytes
3	53,600	1% myelocytes and 90% polymorphonuclears
4	46,000	94% polymorphonuclears
5	40,300	91% polymorphonuclears
6	8,500	9% myelocytes
7	60,000	2% myelocytes
8	182,000	25% myelocytes

In our own series of 172 patients, we also have three living patients with polycythemia complicated by a blood and marrow picture indistinguishable from chronic myelogenous leukemia (2 cases) and erythro-leukemia (1 case). Two of these patients had received no previous x-ray and none had received P^{32}.

Klumpp and Hertig (15) report 5 cases in which myelogenous leukemia occurred as a complication of polycythemia vera. In 3 of these there had been no previous therapy with x-ray or any other form of radiation. Hansen-Pruss and Goodman (15) report 2 cases of polycythemia vera under treatment with x-ray who died with the picture of acute leukemia. Kraus and Schiller (15) report a complicating leukemia in a patient polycythemia vera. The patient had never received any form of radiation. Schoen (15) reports leukemia developing in polycythemia vera apparently before any radiation therapy was given. Tinney et al. (15) report in a series of 163 patients suffering from polycythemia vera that 17 percent of them had a leukemic or leukemoid picture in their blood smears. Since these patients were under observation for a relatively short period of time and since the entire course of the disease was not completely followed, this figure would undoubtedly be higher if all of the patients could have been studied over a period of many years for the development of this complication. During a relatively short period of observation of 14 patients with polycythemia vera by Tischendorf and Herzog (15), 3 developed the complicating picture of myelogenous leukemia. Two of these patients apparently had received previous x-ray treatment. Stealy and Sumerlin (15) report a patient, untreated by x-ray or any other form of radiation, but receiving prolonged treatment with phenylhydrazine, who developed a terminal leukemoid reaction suggestive of leukemia. Hunter (15) reports a patient with polycythemia vera who, ten years after spray irradiation therapy, died of an acute, myeloblastic leukemia. Reifenstein (15) reports a case of polycythemia treated with Fowler's solution terminating in subleukemic myelosis. In a series reported by Graham (15) 24 percent of the patients developed a leukemic picture. Two cases of polycythemia vera untreated by radiation, with transition to acute myeloblastic leukemia are reported by Herxheimer (15) and Jung (15). Hall (11) reported 4 deaths from acute leukemia in a series of 124 patients treated with radioactive phosphorus but no deaths from acute leukemia during the past three years in their increasingly large series of patients treated with P^{32} (personal communication).

Although there is no evidence of an increase in the complication in our series,

this new form of treatment has not caused this serious complication to disappear. A brief analysis of the course of the five patients who died with leukemia follows.

Patient F. M. died at age 63 after a 10 year history of polycythemia. He was first seen by us 5 years after the onset of his disease. Prior to the beginning of P^{32} therapy, he had been treated by venesections, and on one occasion, 2 years after the onset of polycythemia, he had a white count of 12,300, the differential showing a few immature forms. When he was first seen by us, the red cells numbered 8,970,000, white cells 27,950, platelets 807,300, and there were 1 percent myelocytes in the blood smear. The first course of radioactive phosphorus (6 doses totaling 20.3 mc) was given over a period of three months. The patient's red cell count returned to normal and no immature forms were seen in the blood smear during the ensuing year. Then, occasional myelocytes were again observed. During the following 4 years the patient did well, but during the last two years of his life, there was a definite and marked increase in the number of immature white cells. Two years prior to his death 6 doses of P^{32} totaling 24.4 mc. were administered. Nine months prior to his death, 3 doses of P^{32} totaling 2 mc. were given the patient. A blood count taken just before the patient's death showed 2,740,000 red cells, 68,000 white cells with 8 percent myelocytes and 80 percent myeloblasts.

Patient C. H. died at the age of 78 after a 15-year history of polycythemia. Previous treatment included x-ray, phenylhydrazine, Fowler's solution, and venesections. His blood picture when first seen by us showed 10,730,000 red blood cells, 17.7 grams hemoglobin, 480,000 platelets, and 11,000 white blood cells but no abnormal cells. He was given 4.87 mc. of radioactive phosphorus over a period of 3 weeks. The red blood cell count, hemoglobin and white blood cell count gradually fell, and no abnormal white cells were found in the blood smear. Approximately 18 months later, an occasional myelocyte was noted in the blood smear, and the red cell count had begun to rise. Six months later the patient was given 2 doses of 3 mc. each of

P^{32}. Immediately following this therapy the red blood count, hemoglobin, platelet count, and white blood count gradually fell. A few weeks before the patient's death the blood picture showed 3.45 million red cells, 55 percent (8.0 grams) hemoglobin, 110,000 platelets and 4,000 white blood cells. Two days before his death, the peripheral blood smear showed 2 million red blood cells, 42 percent hemoglobin and 6,000 white blood cells with 25 percent blast cells. The patient died with a terminal picture of sub acute myelogenous leukemia. A post mortem examination revealed numerous erythroblasts, myeloblasts, and megakaryocytes in the bone marrow, and zones of hemopoietic activity in the sinusoids of the liver. The pathologist's interpretation was myelogenous leukemoid reaction.

Patient L.W. died at age 68 of chronic myelogenous leukemia after a history of polycythemia for 12 years. Shortly after the onset of her disease she was treated by x-ray and phenylhydrazine. Eight years later her white blood cell count was around 10,000 and on one occasion 2 percent myelocytes were noted. Therapy with P^{32} was started 9 years after the onset of polycythemia, and during the period of a year 3 doses were administered totaling 19 mc. At one time during this period 3 percent myelocytes were noted in the blood smear. Six months after the completion of P^{32} therapy, 5 percent metamyelocytes and 38 percent myelocytes appeared in the blood smear, but the white cell count at this time was not elevated. The patient's course from this time until her death a little over a year later was steadily downhill with a rapidly developing anemia. Many myelocytes and blast cells terminally were found in the peripheral blood.

Patient M.M. was a man who died at age 62 after an 8-year history of polycythemia never controlled by venesections. One year after onset, when he was first seen by us, his blood picture was: red blood cells 9,600,000, hemoglobin 24.8 grams, platelets 1,190,000, white blood cells 13,050. He was given 7 mc. of P^{32} followed 3 weeks later by a second dose of 5 mc. and a nice remission resulted.

Two and one-half years later 1.18 mc. of P^{32} were administered in the presence of a rising red cell count and hemoglobin. A fourth dose of P^{32} (5.35 mc.) was given 6 months later when his red cell count rose to over 8 million with 12,000 white cells. At this time, occasional metamyelocytes appeared in the peripheral blood smear. The patient remained in excellent remission for three more years. At the end of that time anemia and leukopenia developed. The blood picture a month before the patient's death was as follows: red cells 2.3 million, hemoglobin 37 percent (5.92 grams), white blood cells 102,400 with many myelocytes and some myeloblasts. The platelets were markedly reduced and the patient had grown progressively weaker. He died with a terminal sub-acute myelogenous leukemia and the bone marrow at autopsy showed marked cellularity with complete replacement by leukemic cells.

Patient C. G. died at age 67, four years after treatment with P^{32} and 15 years after the onset of polycythemia vera. Previous treaments had included venesections, x-ray, and phenylhydrazine. When we first saw her, the red blood cells numbered over 10,000,000, but after a course of P^{32} therapy, these were reduced to normal levels, and the patient remained in remission until 2 years later when she again developed an elevated red cell count (8,000,000) with approximately 20,000 white cells. No immature white cells were noted in the blood smear. Three doses of radioactive phosphorus totaling 9.98 mc. were administered, but the red cell count remained around 8,000,000 and the white count around 20,000. One year later the red cell count was over 8,000,000 and the white cell count had risen to 44,000. The patient had 2 venesections at this time. Rare myelocytes and metamyelocytes began to appear in the blood smear for the first time. The red cells decreased to around 6,000,000. No further P^{32} was given, but the white cell count continued to rise and continued to show rare myelocytes and a high percentage of polymorphonuclear cells until the time of the patient's death.

Thus, in summary, all 5 of these patients had typical polycythemia vera of relatively long duration. Four of them when first seen by us seemed to be

candidates for the complication of leukemia because of evidence of a very hyperactive marrow, as shown by the presence of young forms in the blood smear, and/or a high white count and high platelet count. In the case of the fifth patient (C.G.) the records of the original white cell counts were lost.

Thus it seems that there is no significant increase in the incidence of leukemia after P^{32} therapy. Also, the common leukemoid reaction seen at the outset of therapy disappeared in over 70 percent of the cases after therapy with P^{32}. There is no evidence of the consistent occurrence of other complications which might be related to the treatment. For example, there is no evidence that neoplasms are being induced by this therapy, the three we observed occurring soon after the beginning of therapy and probably related to the normal probability of the development of neoplastic disease (carcinoma of head of pancreas, carcinoma of prostate and carcinoma of kidney) in patients in this age group.

Also of interest are the few thromboses observed so far in this series (4.2 percent). Hall (11) found in a series of 124 patients with polycythemia that there was a history of thrombosis in 27 percent of them, whereas after P^{32} the incidence of thrombosis was only 2.4 percent. This is probably related to the fact that the red cell mass, platelets, and blood viscosity have been kept normal. With the present methods for the control of polycythemia and high incidence of serious thromboses in the past (16), it can not be emphasized too strongly that the numbers of the red cells and platelets of these patients should always be kept within normal limits in order to avoid damage to the vascular system. Such control of the red cell mass (as measured by accurate blood volume determinations) can be achieved only by adequate follow-up and frequent observation of all patients after they are treated. This applies particularly to patients in the older age group with high thrombocyte counts. Radiation is especially effective in controlling both of these formed elements of the blood. In this connection, it is of interest to observe that many of the patients treated with P^{32} were previously uncontrolled

by venesections. Approximately 60 percent had a high platelet count, and 25 percent had a history of one or more thromboses. Some patients treated only by venesections have shown a continued high red cell mass or a continued high red cell count with an abnormally low hemoglobin after this form of therapy. In young patients with a normal platelet count and no tendency toward thromboses, a trial series of venesections is often performed, and a few of them can be controlled for longer or shorter period of time in this way. During the early part of our work, we did not combine venesections with P^{32}, but during recent years, we sometimes carry out a series of venesections prior to P^{32} and in some patients immediately after P^{32} when we are reluctant to wait several weeks for the P^{32} to take effect. Also, in some instances, where several years after the first course of P^{32} there has been a rise in the number of red cells, infrequent venesections have controlled a previously uncontrollable polycythemia. We have grouped our patients with polycythemia vera according to the method of treatment, as follows:

66 patients treated with P^{32} only

32 patients treated with P^{32} followed within 4 months time by venesections

21 patients treated with P^{32} followed more than 4 months later by venesections

6 patients treated exclusively by venesections

9 patients treated and followed elsewhere.

Finally, since patients with polycythemia vera are usually not in the child-bearing age group and since the doses of radiation are extremely small (17), the possible genetic effects of irradiation on subsequent generations need not be considered.

Although this series must be extended in number and then followed for many more years, certain comments seem in order. First, the average age of onset of the patients is 50.7 years, and the average age of those patients who died was 67

years. This is nearly a normal life expectancy for persons in this age group (18). It is interesting to compare leukemia, diabetes mellitus and pernicious anemia with polycythemia vera with respect to average age at onset and duration. In a study of diabetes Joslin found that the duration was 14.1 years, with an average age at onset of 50.4 years and an average age at death of 64.5 years (19). This latter age is in excellent agreement with the average age at death from diabetes computed from mortality statistics for the nation for the years 1940-1945 (20). Hardgrove and his co-workers (21) summarized the data for 80 patients with pernicious anemia who were living in 1944. The average age of onset of this group was 57 years, although this assumes certain average tendencies for age distribution, which is not specifically stated in their data in that the ages of onset are given in ten years intervals ranging from 25 through 79 years. Isaacs (22) in 580 cases found the peak of the age distribution for onset of symptoms to be 55 years. The average age at death of persons having pernicious anemia throughout the years 1940-1945 was 67.1 years as computed from vital statistics data (20). Combining this with Hardgrove's data, one obtains an approximate average duration for pernicious anemia of ten years. The mortality of leukemia is on the rise (23). The average age at death from all forms of leukemia for the years 1940-1945 is computed to be 44 years from vital statistics data (19) and the average duration of life of chronic leukemia is about five years (24).

It can be seen that at the present time patients with polycythemia vera properly treated have as favorable an outlook as do patients with diabetes mellitus treated with insulin or those with pernicious anemia treated with liver.

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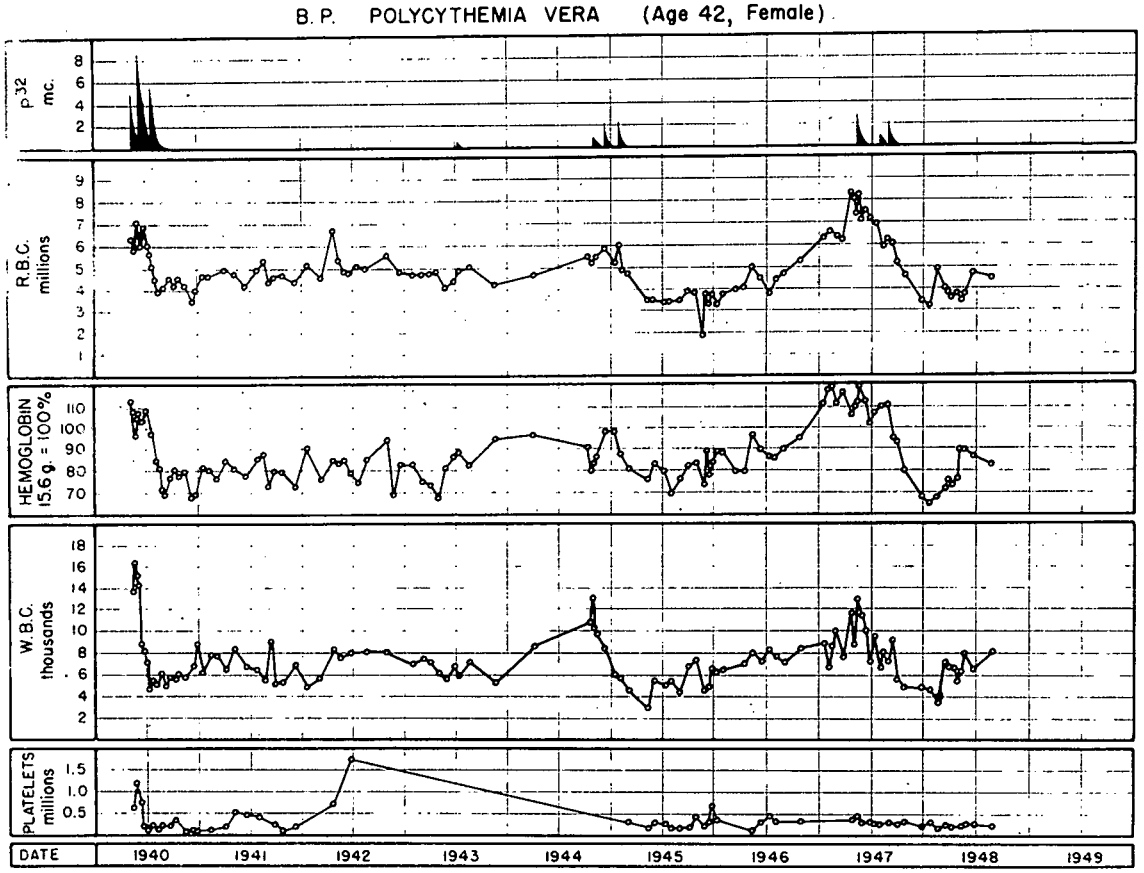
Fig. 1. Hematologic course in a 42 year old woman with polycythemia vera treated with P^{32}. The blood picture has been controlled by the infrequent administration of radioactive phosphorus.

Fig. 2. Hematologic course in a 57 year old woman with polycythemia vera treated with P^{32}. Figures 1 and 2 refer to the first two patients with polycythemia treated by this method.

B.P. POLYCYTHEMIA VERA (Age 42, Female)



M.L. POLYCYTHEMIA VERA (Female, Age 57)

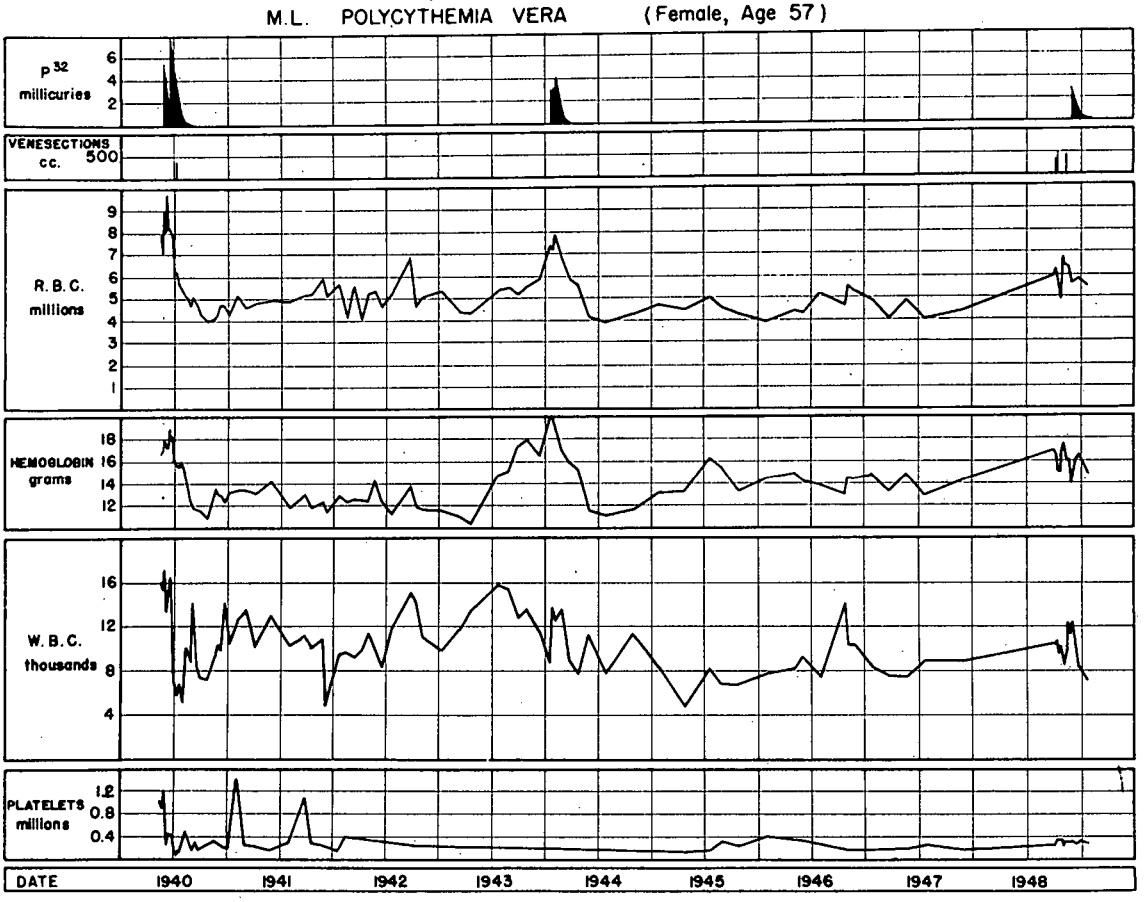
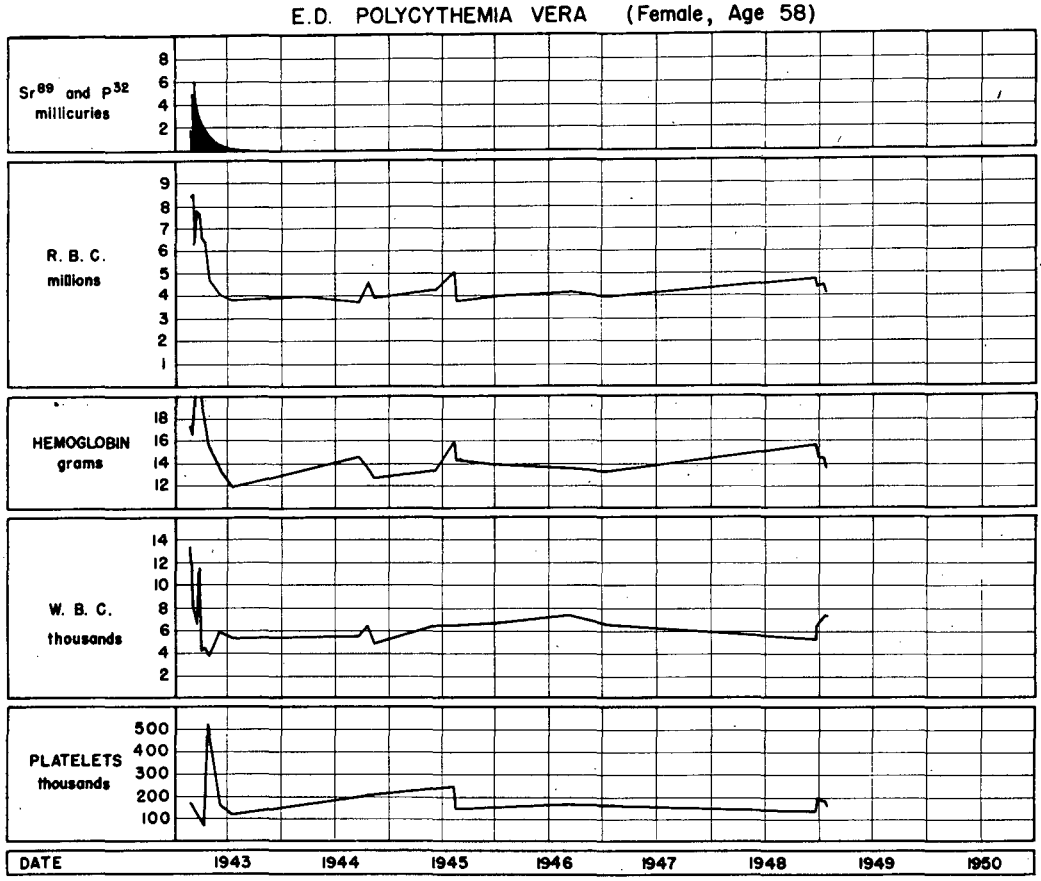


Fig. 3. Hematologic course in a 58 year old woman with polycythemia vera treated with P^{32}. A single course of 3 doses of P^{32} in 1943 has controlled the disease to the present (June, 1949).

Fig. 4. Hematologic course in a 47 year old man with polycythemia vera treated with P^{32}. Y^{90} indicates the administration of radioactive yttrium colloid which localizes in the bone marrow, spleen and liver and provides beta irradiation with a half-life of about 3 days.

E.D. POLYCYTHEMIA VERA (Female, Age 58)



J.G. POLYCYTHEMIA VERA (Age 47, Male)

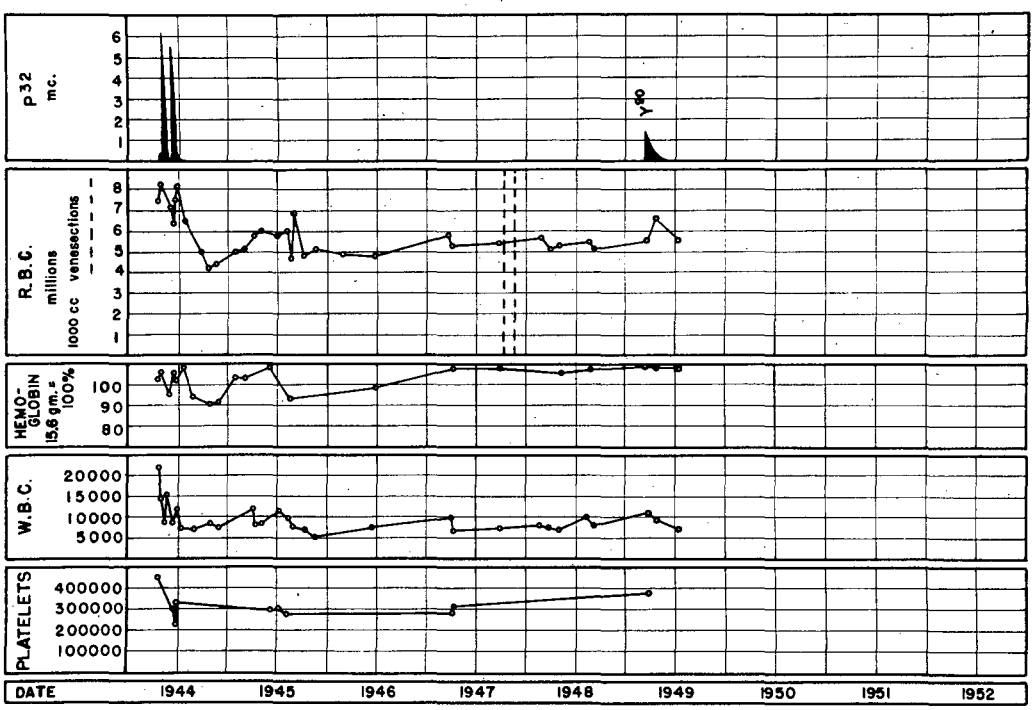


Fig. 5. Hematologic course in a 53 year old man with polycythemia vera treated with P^{32}. No further P^{32} has been needed since the first course in 1942.

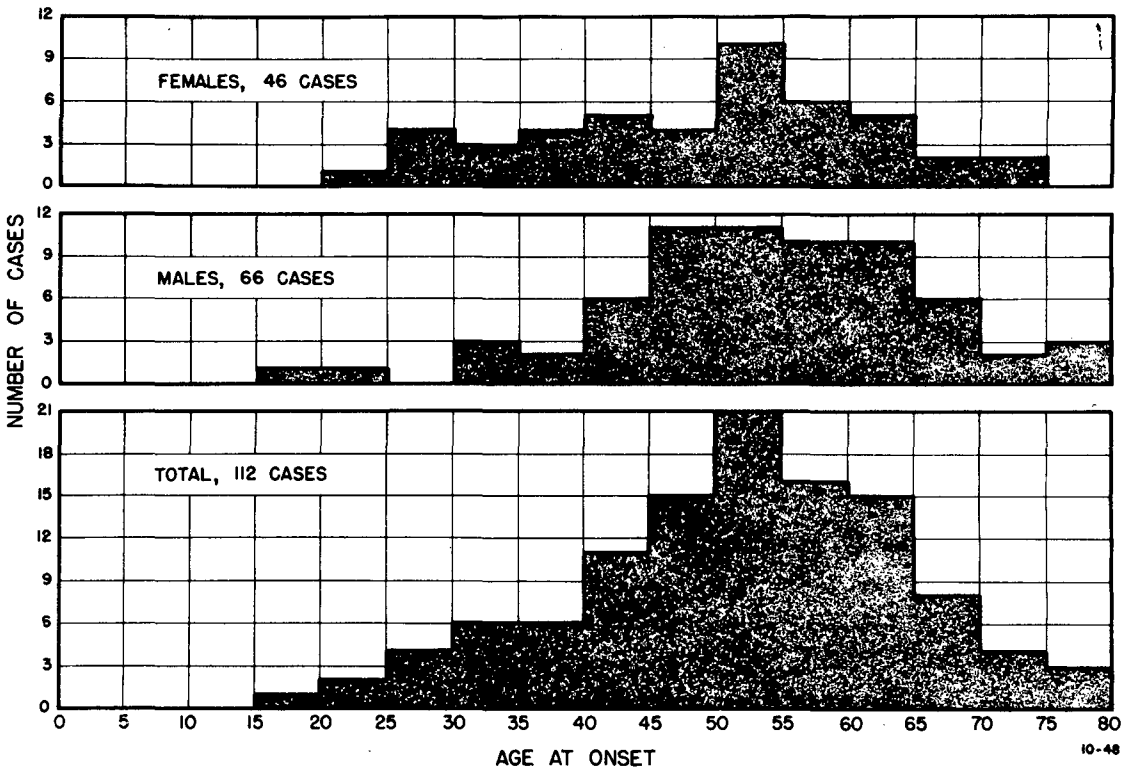
Fig. 6. Graph showing distribution of 66 male and 46 female patients with polycythemia vera treated with P^{32} according to age at onset (horizontal values). The vertical column of figures at the left shows the number of cases.

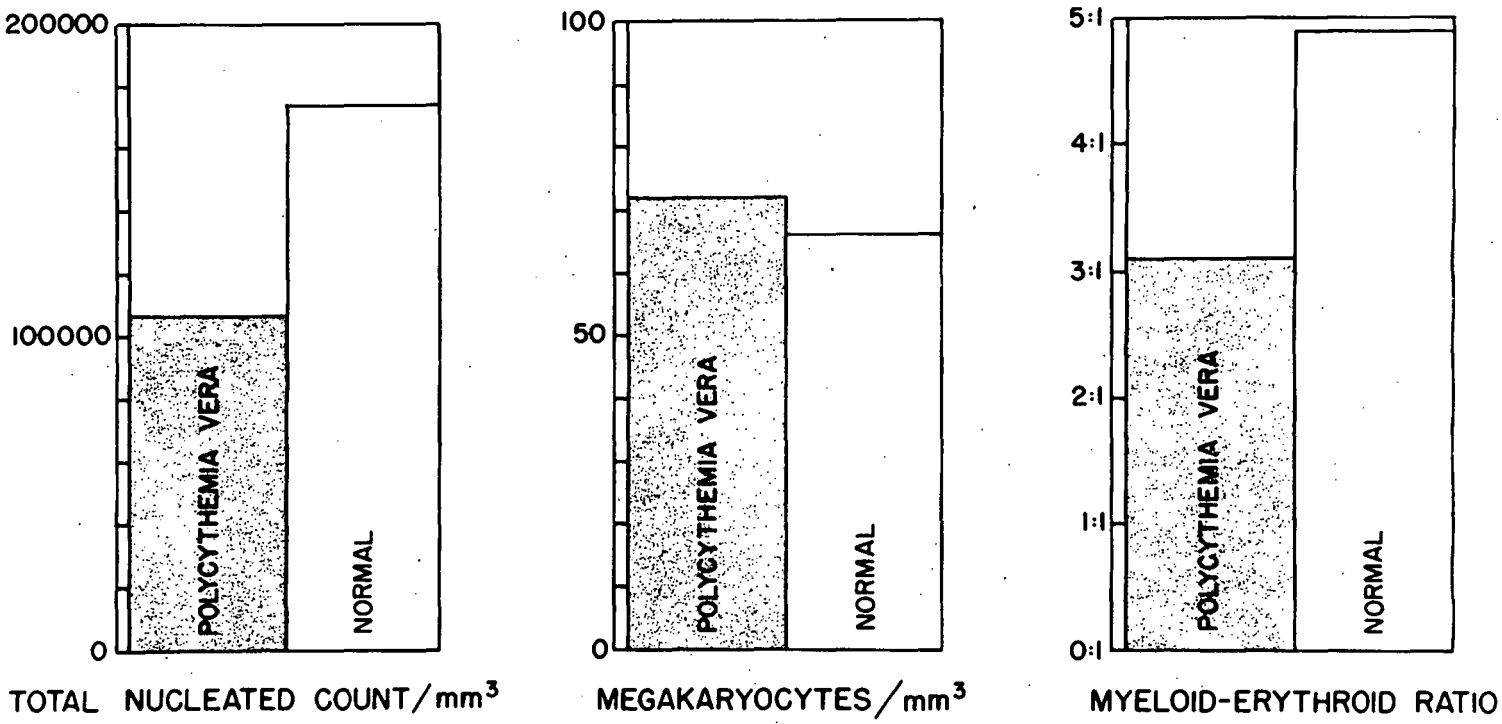
V.B. POLYCYTHEMIA VERA (Age 53, Male)

POLYCYTHEMIA

P^{32} RADIATION THERAPY

DISTRIBUTION OF 66 MALE AND 46 FEMALE CASES ACCORDING TO AGE AT ONSET.





STERNAL MARROW FINDINGS IN 20 NORMAL CASES AND 94 CASES OF POLYCYTHEMIA VERA (PRE TREATMENT)