TREATMENT OF POLYCYTHAEMIA VERA WITH RADIOACTIVE PHOSPHORUS

BY

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Since the introduction by Lawrence (1940) of radioactive phosphorus (^{32}P) for the treatment of polycythaemia vera, several reports concerning its effectiveness have appeared in the world literature. In the United Kingdom the largest reported series is that of Harman *et al.* (1955), comprising 48 cases, two smaller groups of patients having previously been described by Bodley Scott (1953) and Abbatt *et al.* (1954).

^{32}P , because of its being chemically indistinguishable from ordinary stable phosphorus, enters into all phases of phosphorus metabolism. After administration it is rapidly concentrated in phosphorus-containing tissues, and Lawrence *et al.* (1940) have demonstrated in animals that the majority becomes localized in bone and bone marrow, while only slightly smaller quantities become localized in the liver, spleen, and lymph nodes. In leukaemic patients a similar distribution of ^{32}P has been demonstrated (Erf, 1942). According to Reinhard *et al.* (1946) the selective uptake of phosphorus by cells is dependent principally on three factors: (a) total amount of phosphorus in the tissues, (b) rate of turnover of phosphorus in the tissues, and (c) rate at which new tissue is formed. ^{32}P would therefore seem to be a rational and satisfactory approach to the treatment of a myeloproliferative disease such as polycythaemia vera.

^{32}P can be administered orally or intravenously. As about 25% is lost in the stool when given by mouth, it is generally given by the intravenous route as dibasic sodium phosphate. After intravenous injection it is taken up by myeloid tissue during the first 24 hours, and it has been shown that in leukaemic subjects 5–25% of the isotope is excreted, mostly in the urine, during the first six days (Erf and Lawrence, 1941). Patients with polycythaemia vera excrete similar amounts, but in normal subjects 25 to 50% is excreted within the same period. In all cases, however, the rate of excretion falls after the first few days to less than 1% of the injected dose.

Since 1952, 47 patients with polycythaemia vera have been treated with ^{32}P at the Leeds General Infirmary, of which 40 have been followed up for periods longer than three months. The main purpose of this paper is to record the clinical and haematological effects of ^{32}P on this series of patients.

Age and Sex.—All patients were over the age of 40 years when the diagnosis was made, the range being 42 to 74 years (Table I). A slight preponderance (3:2) of females was observed.

TABLE I.—Ages of Patients at Time of Diagnosis

Under 40	40–49	50–59	60–69	Over 70
Nil	11 (23.4%)	24 (51%)	10 (21.3%)	2 (4.3%)

Dosage

The initial dose of ^{32}P recommended by various workers varies from 3 to 7 millicuries (mC.), depending to some extent on body build and the red-cell mass as indicated by blood-volume studies, haematocrit readings, and the height of the red-cell count. In the present series 3 mC. of ^{32}P has been given routinely to all patients as the first dose. Venesections at the outset have been recommended to relieve symptoms and prevent further thrombotic episodes before ^{32}P becomes effective. This has not been done routinely in Leeds, but in 10 patients initial venesection was considered desirable to relieve symptoms. No attempt, however, was made to reduce the red-cell mass to normal by massive venesection as suggested by Harman *et al.* (1955). Patients were treated as out-patients and usually seen at monthly intervals after the first injection. Changes in symptoms and in erythrocyte, leucocyte, and platelet counts were noted on each visit, and, depending on these findings, further doses of 3 mC. of ^{32}P administered when necessary.

In general, a falling red-cell count associated with clinical improvement, or evidence of depression of granulocytopoiesis or platelet production, was an indication against further treatment with ^{32}P . In view of the delayed effect of ^{32}P Lawrence *et al.* (1953) recommended an interval of 10 to 12 weeks before a second injection was given. In their series, however, it was the practice to carry out initial venesection in all cases. In the absence of such a procedure in the present series it has been the rule to give further injections of 3 mC. of ^{32}P during the second and third months after the initial injection if the haematological state warranted them. Experience suggested that such a scheme probably leads to a more rapid control of the disease in the absence of venesections.

The total dose of ^{32}P required to produce a haematological remission, using a red-cell count of 5,500,000 per c.mm. as the upper limit of normal, was variable, but in over half the patients a return of the blood state to normal occurred after a total dose of 3 to 6 mC., and in approximately 90% an initial remission was induced by a total of 9 mC. or less (Fig. 1). Occasional patients required larger doses, and in two cases adequate control was not obtained by ^{32}P therapy alone. In one a total of 34 mC. of ^{32}P was given over a period of two and a half years, and in another 55 mC. in four years, without producing a remission of over three months' duration. These two instances indicate that a small number of patients are resistant to therapeutic doses of ^{32}P , which has been suggested previously by Wiseman *et al.* (1951).

FIG. 1.—Dose of ^{32}P in mC. required to induce an initial remission (38 patients).

Clinical Manifestations before Treatment

The frequency of the various symptoms and signs, together with the complications which occurred, are shown in Table II. All patients were found to have a high colour, while the commonest group of presenting symptoms comprised headache, dizziness, dyspnoea, and increased fatigability. Pruritus occurred in nine patients, and in some was severe and the major complaint; it was generally worse after taking a hot bath. Nine patients complained of dyspeptic symptoms, in four of which a duodenal ulcer was demonstrated radiologically. Two patients had gout, in both for more than five years before polycythaemia was

TABLE II.—Presenting Symptoms and Signs in 47 Patients With Polycythaemia Vera

	No.	%
High colour	47	100
Headache, dizziness, dyspnoea, and fatigability	35	74.5
Hypertension (diastolic over 100 mm. Hg)	30	64
Splenomegaly	25	53
Cardiovascular disease other than hypertension	24	51
Phlebotrombosis	12	25
Angina pectoris	7	15
Intermittent claudication	5	11
Gangrene	4	8.5
Pulmonary embolism	4	8.5
Coronary thrombosis	2	4
Cerebral	1	2
Hepatomegaly	15	32
Haemorrhagic phenomena	9	19
Dyspepsia	9	19
Peptic ulcer proved by radiograph	4	8.5
Pruritus	9	19
Gout	2	4

diagnosed. Haemorrhage was not so common as in other reported series (Harman *et al.*, 1955), and was never serious. Cardiovascular disease, and in particular thrombotic phenomena, were common, however, half of the patients giving a history of one or more of the following: phlebotrombosis, pulmonary embolism, coronary thrombosis, angina pectoris, cerebral thrombosis, intermittent claudication, and gangrene. Hypertension as judged by a diastolic pressure of over 100 mm. Hg was present in about two-thirds of patients. Splenomegaly was present in 25 cases before treatment, but in only a few did the spleen extend further than the umbilicus. The liver edge was palpable in 15 of the 47 patients, but never extended more than two finger-breadths below the costal margin.

Effect of ^{32}P Therapy on Clinical Manifestations

It is generally accepted that most of the common symptoms of polycythaemia vera are due to the increased blood volume consequent upon the red-cell mass. Support for this belief is obtained from observing the effect of treatment, which in most cases results in a disappearance of symptoms as the red-cell count and total red-cell volume fall to normal levels. In this series it was usually found that symptomatic relief was complete before the arbitrary upper limit of normal of 5,500,000 red cells per c.mm. was reached, but in some instances symptoms such as headache, dizziness, and breathlessness persisted after the red-cell count and haematocrit reading had returned to normal. It seems not unlikely that in such cases these symptoms were due to causes other than polycythaemia, such as hypertension and arteriosclerosis, which one would expect in a group of people in this relatively older age group. In 75% of patients, however, headache, dizziness, fatigability, and dyspnoea were completely relieved or substantially improved.

Pruritus was completely relieved in five out of nine patients; in three only partial improvement occurred; while one failed to obtain any relief, although the blood picture returned to normal following treatment. Haemorrhagic phenomena and further thrombotic episodes were not observed after the disease was controlled, but established cardiovascular disease, such as intermittent claudication and angina pectoris, was unaffected by treatment. In the hypertensive patients a consistent fall in the diastolic blood pressure below 100 mm. Hg was observed in only 10 out of 30 patients. This finding indicates that the raised blood pressure in polycythaemia vera is not always due to increased blood volume alone, and in many instances is largely unrelated to the haematological state.

A reduction in the size of the spleen to a greater or lesser extent was observed in all 25 patients in which the spleen was enlarged, and in seven it became impalpable. The liver, although never greatly enlarged before treatment, returned to a normal size after treatment apart from one instance. Features common to all—namely, plethora, reddened conjunctiva, and highly coloured palms—disappeared as the red-cell volume diminished with treatment. Dyspeptic symptoms were not significantly affected by treatment, and one patient with gout has required regular treatment for this complaint irrespective of his haematological state.

Haematological Manifestations Before Treatment

The blood findings in the 47 patients at the time of diagnosis and preceding treatment are recorded in Table III.

TABLE III.—Blood Findings in 47 Patients With Polycythaemia Vera at Time of Diagnosis

Red blood cells:	No.	%
Range 6.5 to 9.6 millions per c.mm.	47	100
6.5 " 7.9 " " "	33	70
8.0 " 8.9 " " "	11	23
9.0 and over " " "	3	7
Packed cell volume:		
Range 60–77%	47	100
White blood cells:		
Range 5,000 to 40,000 per c.mm.	47	100
5,000 " 10,000 " " "	21	44
10,000 " 20,000 " " "	23	49
Over 20,000 " " "	3	7
Platelets:		
Range 125,000 to 615,000 per c.mm.	47	100
Below 150,000 " " "	2	4
150,000 to 350,000 " " "	28	60
Over 350,000 " " "	17	36

In most subjects the red-cell count ranged from 6,500,000 to 8,000,000 per c.mm., while the P.C.V. was over 60% in all. Leucocytosis, defined as a white-cell count of over 10,000 per c.mm., was present in 26 patients, but in only three was the leucocyte count higher than 20,000 per c.mm. The differential leucocyte count showed a well-marked preponderance of polymorphonuclear cells in approximately 75% of all patients, but myelocytes and nucleated red cells were observed in the peripheral blood in only five patients (11%). Although thrombocytosis occurs in polycythaemia vera, analysis of the present series suggested that a normal platelet count was more common. If a range of 150,000–350,000 per c.mm. is taken as representing normal, 60% of the patients were found to have platelet counts within this range, while 36% had counts higher than normal.

Thrombocytopenia—that is, less than 150,000 platelets per c.mm.—was detected in only two patients prior to treatment.

Bone-marrow aspiration was carried out in 14 patients. The marrow was found to be hypercellular in all, but no characteristic cellular pattern was observed. Marrow examination is of no diagnostic help in polycythaemia vera, and shows no features that might permit of differentiation from secondary polycythaemia (Lawrence *et al.*, 1953).

Haematological Changes After Therapy

The therapeutic effect of ^{32}P on the blood cannot be evaluated for at least 30 to 60 days, since red cells have a life cycle of 120 days and ^{32}P brings about a reduction of red cells by decreasing their rate of formation. Thus the fall in the red-cell count is slow and not normally apparent for several weeks after treatment.

The time interval between the start of ^{32}P therapy and return of the red-cell count to within the normal range is variable. Of 33 patients in whom accurate analysis was possible, the red-cell count returned to normal within three months in 6, within four months in 15, within five months in 26, and in 7 patients the interval was longer than five months. The delay in return of the red-cell level to normal might be taken as an indication for more liberal use of venesections. In practice, however, symptoms usually disappear before the red-cell count reaches normal, and further thrombotic episodes have not been observed after treatment has been instituted.

Forty patients have been seen regularly for periods of over three months following their initial injection of ^{32}P . In these patients the effect of ^{32}P on the blood can be assessed. In only two have the red cells not been satisfactorily reduced. In the remainder a normal red-cell count has been attained. Severe anaemia has not been observed to follow treatment, but in a few instances the red-cell count has temporarily fallen to a level of 4,000,000 per c.mm.

It is well recognized that ^{32}P not only reduces the red-cell level but also has a profound effect on the leucocyte and platelet counts. Over half the patients in the present series had an initial leucocytosis of over 10,000 per c.mm. After treatment the white cells fell below this level in all cases, together with a return of the differential count to normal. In 15 out of the 40 patients (37.5%) under analysis a transient fall to a leucopenic level (below 4,000 per c.mm.) occurred. In no instance did the leucopenia reach below 3,000 per c.mm. or result in any adverse effect upon the patient. A similar fall in the platelet count was observed to follow treatment, and in 17 patients (42.5%) the platelets fell below 150,000 per c.mm. In one the count fell to 48,000 per c.mm., but in all cases thrombocytopenia was transient, and no instances of spontaneous haemorrhages or purpura were observed. Thrombocytopenia, however, is a potentially dangerous state and may appear before the red-cell count falls. In such circumstances, and similarly when leucopenia is present, it has always been the practice to withhold treatment until the platelets or leucocytes have returned to normal numbers.

Fig. 2 shows graphically the haematological course of events in a woman treated with a total of 6 mC. of ^{32}P . A remission of one year resulted, and following relapse a second course of ^{32}P induced a further remission.

Fig. 2.—Effect of ^{32}P on the blood of a woman aged 58 with polycythaemia vera. (Dotted lines represent upper limits of normal.)

Duration of Remissions

Remissions following initial courses of treatment have been observed in 38 patients. Two were not controlled by ^{32}P , while five have been followed for periods of less than three months. Two others left the district after their first injection and were not seen again. Of 25 patients followed until relapse occurred, 20 (80%) had a first remission of over one year, as calculated from the date the red-cell count fell below 5,500,000 per c.mm., 14 (56%) had remissions longer than 18 months, while in 10 (40%) the initial remission was over two years. The longest remission was 37 months and the shortest two months. In the latter patient a second course of treatment was followed by a prolonged remission. The average length of the first remission in this group of 25 patients was 19 months. In 13 patients the initial remission continues, in 8 being shorter than six months, while in the remainder it ranges from 8 to 36 months.

Remissions followed a second course of therapy in 22 of the 25 patients relapsing after their initial course. Of the other three, two failed to be satisfactorily controlled by ^{32}P a second time, while one left the district. Eleven of this group of 22 patients have since relapsed after second remissions of up to 20 months' duration, while the remaining 11 continue satisfactorily controlled up to 15 months after their second course of treatment. Third and subsequent

remissions of as long as 22 months have occurred in nine patients to date.

Two patients have died. One, a woman aged 67, has been mentioned previously as not responding satisfactorily to ^{32}P therapy. She died of acute myeloblastic leukaemia five years after the diagnosis of polycythaemia vera was made. The other, a woman aged 54, was controlled satisfactorily with ^{32}P until she developed a severe terminal leuco-erythroblastic anaemia.

Comment

Venesection, phenylhydrazine, nitrogen mustard, and external irradiation are all therapeutic methods by which the total red-cell volume can be reduced and hence relieve symptoms in polycythaemia vera. Radioactive phosphorus can likewise effectively reduce the red-cell mass, and on account of the ease of administration, out-patient treatment, and absence of unpleasant side-effects it is now generally regarded as the most satisfactory form of therapy. Under careful supervision prolonged remissions can be expected in most patients and a life expectancy of only a few years under the normal for this age group (Lawrence *et al.*, 1953). The same authors are also of the opinion that the incidence of leukaemia is not higher than in previously reported series treated by other methods, while the incidence of deaths from vascular complications has been reduced by about one-half since the institution of ^{32}P treatment.

^{32}P is, however, not without certain practical disadvantages. Overdose must, of course, be guarded against, and thrombocytopenia and leucopenia, which may precede a fall in the red-cell count, are temporary contraindications to further therapy. Secondly, owing to the rarity of the disease, and the need for skilled technical staff, treatment must be carried out in clinics at the major hospital centres, which entails long journeys for many of the patients. Finally, the relatively long latent period of from 30 to 60 days before the red-cell count begins to fall may necessitate initial venesections to relieve symptoms until the ^{32}P becomes effective.

The excellent results of therapy, however, outweigh any of the disadvantages, and at the present day ^{32}P would seem to be the treatment of choice for patients with polycythaemia vera.

Summary

Forty-seven patients with polycythaemia vera have been treated with radioactive phosphorus (^{32}P).

A description is given of the clinical and haematological findings in this group of patients, and the results of treatment are assessed.

^{32}P was given intravenously in doses of 3 mC. In approximately 90% of patients an initial remission was induced by a total dose of 9 mC. or less.

Of 40 patients who have been observed for more than three months after their initial treatment, all but two developed remissions of up to 37 months' duration. Subsequent remissions usually followed further courses of treatment.

I would like to express my gratitude to Mr. G. W. Reed, senior lecturer, and Miss P. Morris, senior technician, of the Department of Medical Physics, University of Leeds, for their valuable assistance.

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