Age, *per se*, plays no direct part in determining rate of change of pressure in these populations even though, as is seen in Figs. 1 and 2, mean pressures are much higher in the old than in the young and even though almost all old people in these populations have high pressures. Age appears to play a part solely because the blood-pressure changes on average are positive and increase with higher pressures.

The relation between change of pressure and mean pressure also appears to be a graded phenomenon—the higher the pressure the greater the rate of increase—and seems partially to reconcile the conflicting views on the nature of unexplained hypertension.

If this relation were found to be causal it could explain the observations that some individuals and some races show no apparent increase in pressure with age. For example, the populations in Oceania studied by Maddocks (1961) and Lovell (1963), where old people have the same pressures as young adults, have mean pressures below the levels at which our data suggest that a self-perpetuating mechanism could be implicated. But our analysis has shown only an association between change of pressure and mean pressure, not a causal relationship. It is possible that minor but sustained increases of pressure, due to a variety of environmental and genetic influences, could lead to changes in function and structure which perpetuate a vicious circle, but some other factor acting in a similar fashion may underlie the relationship found.

A controlled therapeutic trial might show whether the pressure attained determines the subsequent increments in pressure; if, for example, it could be shown that after a reduction in pressure effected by hypotensive drugs the subsequent changes in pressure of previously hypertensive subjects revert to those occurring spontaneously in subjects with lower pressures, this would be strong evidence for a causal relationship.

Summary

Data obtained from the longitudinal surveys of arterial blood pressure in two general population samples have been used to examine the relation between change of blood pressure, the mean pressure attained, and age.

It has been shown, by multiple regression analysis of change of pressure on mean pressure and age, that in these popula-

tions changes in pressure during intervals of 10 and 8½ years are highly significantly related to mean pressures, but only indirectly related to age. This implies that ageing plays no direct part in determining the rate of change of pressure; age appears to play a part solely because the blood-pressure changes are positive and increase with higher pressures.

If change of pressure is determined by attained pressure, this would explain the observation that some individuals and some races show no apparent increase of pressure with age, and would partially reconcile the conflicting views on the nature of unexplained hypertension. However, the evidence has shown only association, not causality.

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Treatment of Polycythaemia Vera*

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The treatment of polycythaemia vera with radioactive phosphorus (³²P) was introduced in 1938 by Lawrence (1940); combined with venesection, it proved to be both effective and free from side-effects and was accepted as the best form of treatment (Scott, 1953; Harman, Hart, and Ledlie, 1955). Aplastic anaemia was its greatest hazard, but usually followed its use in unsuitable cases or in excessive dosage (Calabresi and Meyer, 1959). The association of acute leukaemia with the use of ³²P has been suspected for many years, and the evidence to substantiate this is considered. It is chiefly on account of this danger that some authorities (Perkins, Israëls, and Wilkinson, 1964) believe that ³²P should be replaced by chemotherapy (busulphan, thiotepea, nitrogen mustard, and pyrimethamine

being most frequently used); they regard this as equally effective but free from the risk of inducing acute leukaemia.

This paper reviews the results of irradiation (with ³²P or radiotherapy) in 81 patients with polycythaemia vera. Their survival, the incidence of acute leukaemia, and the causes of death are considered in detail, and the position regarding the use of ³²P is discussed.

Material

Polycythaemia vera was diagnosed when the haemoglobin was greater than 17 g./100 ml. or the red cell count greater than 6,000,000/cu. mm., together with one other feature—namely, a leucocyte count greater than 12,000/cu. mm., a platelet count greater than 300,000/cu. mm., or splenomegaly. Acute leukaemia was diagnosed when both blood and marrow were

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infiltrated with "blast cells." The incidence of chronic myeloid leukaemia is not discussed because of the inadequacies of definition.

Eighty-one patients were treated at St. Bartholomew's Hospital from 1947 to 1963 inclusive and followed up to 1965. Some of these cases were initially diagnosed elsewhere. The sex ratio of 1.5:1 showed a predominance of males. Seventy-six patients were treated with ^{32}P , two received ^{32}P together with radiotherapy for coincidental malignant disease, and three received radiotherapy only.

Forty-six patients have died. Of these, 43 had been treated with ^{32}P , 24 receiving less than 15 mCi and 19 receiving 15 mCi or more. Three had received radiotherapy only.

Results

A survival curve is shown (see Chart). The median survival (the time at which 50% of patients have died) is almost 11 years after the date of diagnosis.

Causes of Death

Acute Leukaemia.—Of the 46 patients who have died, one developed acute leukaemia and one acute erythraemic myelosis, or erythroleukaemia (Di Guglielmo's disease), both confirmed by sternal marrow puncture and both having been treated with ^{32}P . The latter case was initially diagnosed and treated with ^{32}P in South Africa. There are, so far, no cases among the living patients.

Vascular Causes.—In this category have been included cerebrovascular accidents, gastrointestinal haemorrhage, pulmonary embolus, myocardial infarction, and deaths from ischaemic heart disease and one death after amputation of a gangrenous leg. Twenty-three of the 46 deaths (50%) were from such vascular causes (see Table I). If the two deaths

TABLE I.—Causes of Death of Irradiated Patients

	Deaths	
	No.	%
Vascular causes:		
Cerebrovascular accident	6	13
Myocardial infarct	10	22
Cardiac failure	2	4.5
Pulmonary embolus	1	2
Gangrene (postoperatively)	1	2
Haematemesis	3	6.5
Total	23	50
Other causes:		
Acute leukaemia	1	2
Erythroleukaemia	1	2
Chronic myeloid leukaemia	3	6.5
Neoplasms	6	13
Pneumonia	4	9
Surgery	2	4.5
Other	6	13
Total	46	100

from ischaemic heart disease are omitted, as in many series, this figure is reduced to 46%.

Other Causes (see Table I).—These include pneumonia and postoperative deaths not due to haemorrhage; neoplasms were responsible for six deaths and include bronchial carcinoma (3), carcinoma of the ovary (1), rhabdomyosarcoma (1), and hypernephroma (1). Little information was available regarding the three patients reputed to have died from "chronic myeloid leukaemia."

There were two cases of myelofibrosis (confirmed by iliac trephine biopsy) in patients who have died. No cases have yet been detected among the living patients.

Discussion

The prognosis of untreated polycythaemia vera is very poor. Chievitz and Thiede (1962) have shown that the survival of these patients may be as little as 18 months, and also suggested that venesection alone is inadequate. The outlook is greatly improved by treatment with chemotherapeutic agents or ^{32}P , each combined with venesection. Modan and Lilienfeld (1965) compared the survival of 300 patients treated with ^{32}P and 133 treated without irradiation during the same period, and showed no significant difference in the survival (a median survival of between 10 and 11 years from the date of diagnosis), which is very similar to that of the present series. Halnan and Russell (1965) have treated 107 patients with ^{32}P and have shown that there is no significant difference in the survival from that of the 127 nonirradiated patients of Perkins *et al.* (1964) treated during a similar period, and having a median survival of 13.6 years from the date of onset of symptoms. This is also similar to the median survival of 13.3 years from the onset of the disease shown by Lawrence (1955) in a series of 231 patients treated with ^{32}P . It is important to remember that the date of onset of symptoms precedes that of diagnosis by about two years (Calabresi and Meyer, 1959); this difference has often led to confusion when comparing different series. If this difference is taken into account the evidence suggests that survival is improved equally by ^{32}P and chemotherapy.

The incidence of acute leukaemia in irradiated (^{32}P and/or radiotherapy) polycythaemic patients varies widely between 0 and 30% of deaths in different series (considering only the larger series), and in half is 15% or more (see Table II). In the present series of 46 deaths there was one case of acute leukaemia and one of acute erythraemic myelosis. The absence of acute leukaemia in irradiated series is exceptional, but has been reported by Calabresi and Meyer (1959) (28 deaths) and by Halnan and Russell (1965) (43 deaths).

Reports of acute leukaemia occurring in nonirradiated series have been infrequent, and are certainly much less common than in irradiated series. For example, among the 69 deaths in this group reported in the review of Modan and Lilienfeld (1965) there was one case of acute leukaemia; a single case was reviewed by Williams and Mendel (1954); Dameshek (1950) reported only two cases when reviewing 150 patients. Perkins *et al.*

TABLE II.—Incidence of Acute Leukaemia

	Total Dead	Acute Leukaemia	
		No.	%
<i>Nonirradiated</i>			
Chievitz and Thiede (1962)	111	0	0
Perkins <i>et al.</i> (1964)	44	1†	2
Modan and Lilienfeld (1965)	69*	1*	1.4
<i>Irradiated (³²P and/or DXR)</i>			
Wiseman <i>et al.</i> (1951) (review)	40	12	30
Stroebel (1954)	39	8	20.5
Lawrence (1955)	73	6	8
Calabresi and Meyer (1959)	28	0	0
Ledlie (1960)	21	5	24
Halnan and Russell (1965)	43	0	0
Modan and Lilienfeld (1965) (review)	110*	17*	15
Present series	46	2†	4

* These patients comprised a subgroup first seen in hospital in the year of diagnosis and first treated the same year.

† The patient of Perkins *et al.* and one of the present series had acute erythraemic myelosis.

(1964) reported a case of Di Guglielmo's disease in one of their nonirradiated series (44 deaths).

The occurrence of acute erythraemic myelosis, or erythro-leukaemia, in polycythaemic patients is rare. A case of acute erythroleukaemia was reported by Dameshek and Gunz (1964), and cases of acute erythraemic myelosis by Dammert and Kaipainen (1960) in a ^{32}P -treated patient, and by Perkins *et al.* (1964) in a patient treated by venesection, intravenous nitrogen mustard, and thiotepea.

That ^{32}P induces acute leukaemia has been suggested from other evidence. Thus MacDiarmid (1965) has found chromosomal damage after ^{32}P administration. Ledlie (1960) has pointed out that the occurrence of acute leukaemia in her series was two and a half to four years after ^{32}P administration and similar to the time interval after whole-body irradiation. Also, Modan and Lilienfeld (1965) have shown a correlation between the dose of ^{32}P and the incidence of acute leukaemia. However, Osgood's interpretation of the same data suggests that the ^{32}P -treated patients actually survive longer than any other group and that the frequency of acute leukaemia actually decreases with the time at risk after irradiation (Osgood, 1964a, 1964b).

The vascular complications of polycythaemia are responsible for much of the morbidity and mortality. Cerebrovascular accidents, gastrointestinal haemorrhage, severe haemorrhage at surgery, myocardial infarction, and pulmonary embolism are often causes of death. Deaths from ischaemic heart disease have been included in this group, as they have in many other series. The precise definition of "vascular complications" is difficult, and consequently the percentage of deaths from this cause in different irradiated series varies widely from 36 to 67% (see Table III, in which the calculations have been made according to the above definitions), and in the present series was 50% (23 out of 46 deaths), or if deaths from ischaemic heart disease are omitted, 46%. In the *nonirradiated* series of Perkins *et al.* (1964) 46% of deaths (20 out of 44) were due to vascular causes, which is similar to the incidence in this and other irradiated series. On the other hand, Modan and Lilienfeld (1965) showed a diminished incidence of vascular complications during the early years after starting treatment with ^{32}P which in the later years equalled or possibly exceeded that in patients treated without irradiation.

The value of any treatment is assessed by its efficacy at reducing both morbidity and mortality of the disease, balanced against both its toxicity and side-effects. It has been shown that either ^{32}P or chemotherapy (each combined with venesection) is equally effective in improving survival in polycythaemia. The most serious toxic effect of treatment is aplastic anaemia. It rarely occurs in ^{32}P -treated patients and then often follows excessive dosage, but it is a very real danger to patients treated by chemotherapy, particularly busulphan, and is especially likely to occur in those who fail to attend clinics and are therefore inadequately controlled haematologically.

There are negligible side-effects after the administration of ^{32}P , but patients on chemotherapy are liable to develop many disagreeable reactions—nausea, vomiting, diarrhoea, impotence, and loss of hair are fairly common—and those taking pyrimethamine not infrequently develop thrombocytopenia, some-

times with haemorrhage; in one series 30% of patients on this drug developed side-effects (Perkins *et al.*, 1964). In spite of the side-effects and toxic effects of these drugs, their use has been advocated particularly for patients under the age of 50 (Lancet, 1965; *British Medical Journal*, 1966).

Conclusions

Treatment of polycythaemia vera with ^{32}P has proved to be extremely successful, and its use should not be abandoned in favour of newer forms of treatment unless these have very definite advantages. Survival in polycythaemia vera is improved equally by venesection combined with either ^{32}P or chemotherapy. The use of ^{32}P is free from side-effects, its administration is simple, and it certainly allows patients to live normal and active lives. There is an increased incidence of acute leukaemia in ^{32}P -treated patients which does not occur in those treated by chemotherapy. However, side-effects often occur with chemotherapy, are extremely disagreeable, and there is a very real danger of aplastic anaemia. We therefore agree with Osgood (1964b) that "most persons would rather run some risk of dying of leukaemia at an advanced age than of dying younger without leukaemia," and believe that ^{32}P combined with venesection is still the best treatment for polycythaemia vera. However, we agree with Szur and Lewis (1966) that there is a great need for a controlled trial to establish statistically significant data regarding the best mode of therapy.

Summary

The results of treatment of 81 patients with polycythaemia vera attending St. Bartholomew's Hospital are reviewed. The median survival among them (78 of whom were treated with ^{32}P) was between 10 and 11 years; 23 (50%) of the 46 deaths were due to "vascular causes." There was one case of acute leukaemia and one of acute erythraemic myelosis (Di Guglielmo's disease) among this group.

These results are compared with those of other series of both irradiated and nonirradiated patients. Though the incidence of acute leukaemia in the irradiated groups is increased, the survival of both groups is very similar. Moreover, the use of ^{32}P is free from side-effects and allows patients to live absolutely normal lives; this is in marked contrast to the many unpleasant side-effects which occur during chemotherapy. We conclude that ^{32}P in association with venesection continues to be the best treatment for polycythaemia vera.

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TABLE III.—Deaths from Vascular Causes

	Total Dead	Deaths from Vascular Causes	
		No.	%
<i>Nonirradiated Patients</i>			
Perkins <i>et al.</i> (1964)	44	20	45.5
<i>Irradiated Patients</i>			
Stroebe, Hall, and Pease (1951)	22	7	32
Stroebe (1954)	39	14	36
Lawrence (1955)	73	31	42.5
Calabresi and Meyer (1959)	28	13	46.5
Szur, Lewis, and Goolden (1959)	19	8	42
Ledlie (1960)	21	10	45.5
Halnan and Russell (1965)	43	29	67.5
Present series	46	23	50