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Treatment of Polycythæmia by ^{32}P

Radioactive phosphorus was first used for the treatment of polycythæmia and leukæmia by Lawrence in California in 1938 (Lawrence 1940). Preliminary experimental work with mice had shown that a large proportion of an injected dose became rapidly localized in bone marrow and a few days later in bone, while smaller quantities found their way to liver, spleen and lymph nodes. In 1942 a similar distribution in leukæmic patients treated with ^{32}P a few days or weeks before death was demonstrated by Erf (1942). Although other radioactive isotopes, particularly when in colloidal form, were found to be equally effective in producing a remission in polycythæmia, ^{32}P was selected as the isotope of choice on account of its suitable half-life of 14 days, facility of preparation, cheapness and the absence of harmful local effects at the site of administration if leakage should occur. The chemical form is sodium orthophosphate in isotonic solution containing phosphate buffer. The volume is made up with normal saline so that 5 mc are contained in about 10 ml of liquid. The dose can be given orally but, as up to 25% may be lost in the stools, the intravenous route is preferred. After intravenous injection, approximately 10% of the dose is excreted in the urine in the first twenty-four hours and up to 25% in the first six days. Since the radiation emitted is pure β, the protection problems for the staff are minimal. No radiation reactions whatever are experienced by the patients with the doses used.

The installation of a total body counter of sufficient sensitivity to count the Bremsstrahlen from ^{32}P has recently enabled us to measure directly the total body dose in one new patient treated with radioactive phosphorus (Fig 1). These measurements were made in the Physics Department at the Surrey branch of the Royal Marsden Hospital on a patient who had been given 4·9 mc of ^{32}P intravenously. The $t_{\frac{1}{2}}$ was shown to be 11 days and the whole body dose calculated to be 46 rem. Measurements were made up to seventy days.

At the Royal Marsden Hospital ^{32}P has been used for the treatment of polycythæmia rubra vera since 1949. Mild cases have sometimes been maintained by venesection only for months or years before the administration of phosphorus. A few patients with so-called 'stress' polycythæmia, that is with an unexplained erythræmia, attend the hospital, but have not been treated

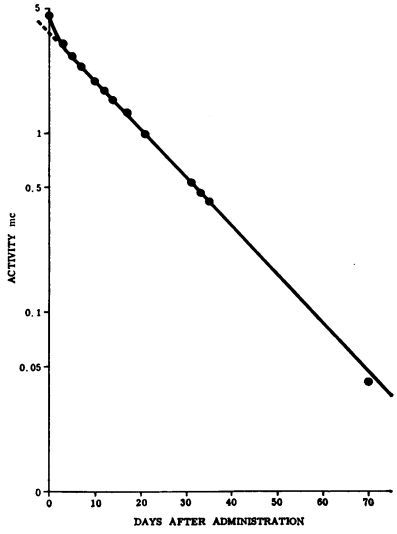

Fig 1 *Polycythæmia vera treated with ^{32}P. Total body activity. $t_{\frac{1}{2}}$, 11 days. Whole body dose, 46 rem*

with any form of radiation. An attempt has been made to treat some patients with secondary polycythæmia, particularly from chronic chest disease, who have been thought to have symptoms from overcompensation, by venesection and ^{32}P, but it has invariably been found that the symptomatic improvement achieved has not been maintained for more than a few months and we have been reluctant to pursue treatment of this group with a radioactive agent. Up to the end of 1963 the number of patients with polycythæmia vera treated with ^{32}P was 132, 79 male and 53 female. The average age at first treatment was 59; the youngest was 33 and the oldest 85. The earlier patients in the series were admitted to the ward for full investigation and for collection of the excreta for measurement of radioactivity. Isovolumetric venesection with replacement by Plasmosan or dextran was often done as a preliminary procedure, but this is not now our usual custom unless symptoms are severe. Most of our patients are now treated by injection of ^{32}P intravenously in the outpatient department. A single dose is often sufficient for a remission, but if necessary a second slightly smaller dose can be given not less than six weeks later. The average first dose is approximately 5 mc. It has varied between 3 mc for a small woman and 8 mc for a large man with a very high count. Small fractionated doses, that is 1 or 2 mc once a week, were tried in an attempt to obtain reduction of the count with a lower total dose of ^{32}P, but this objective was not realized as no effect was obtained on the count and a larger single dose had to be given. Ineffective

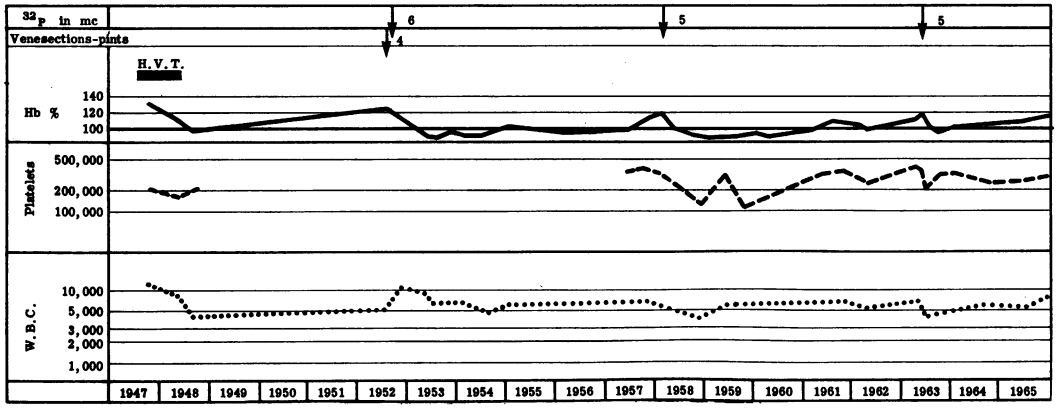

Fig 2 *Polycythæmia vera treated with ^{32}P. Woman, aged 40 in 1952. Long remission after ^{32}P therapy. Alive and well*

small doses of ^{32}P add to the amount of total body irradiation administered without achieving any useful purpose and should be avoided. The dose of ^{32}P given when relapse occurs is usually rather smaller than the initial dose, though in a few long-lived patients a phase of increased activity necessitating a higher dose of ^{32}P may occur. In our series the average time between retreatments is about twenty-three months, though the variation is great.

Fig 2 shows the blood chart of a woman, aged 40 in 1952, when she first presented at a general hospital in this country complaining of headaches, unilateral deafness and ataxia. Various neurological abnormalities were found on examination and a diagnosis of disseminated sclerosis suggested. But it was then discovered that she had had multiple venesections and several courses of external irradiation in France five years previously. A blood count in 1952 showed polycythæmia and iron deficiency. The main findings were Hb 126%, PCV 68%, and WBC 6,000. She was treated with oral iron and has had three single injections of ^{32}P at infrequent intervals since then. Her symptoms and abnormal physical signs disappeared shortly after the first injection, and she has been well since 1953, complaining only of a little lassitude and sleepiness.

Fig 3 is the chart of an average patient. He presented in 1957 at the age of 58 as an abdominal emergency, and was found to have an enlarged, acutely tender, spleen and a much raised blood count: Hb 157%, PCV 86%, and WBC 14,000/c.mm. We have kept his count at more normal levels by one venesection and ^{32}P injections. He has had no further vascular accidents, his spleen has regressed, and he remains in good health. The total dose of ^{32}P up to date is 37 mc.

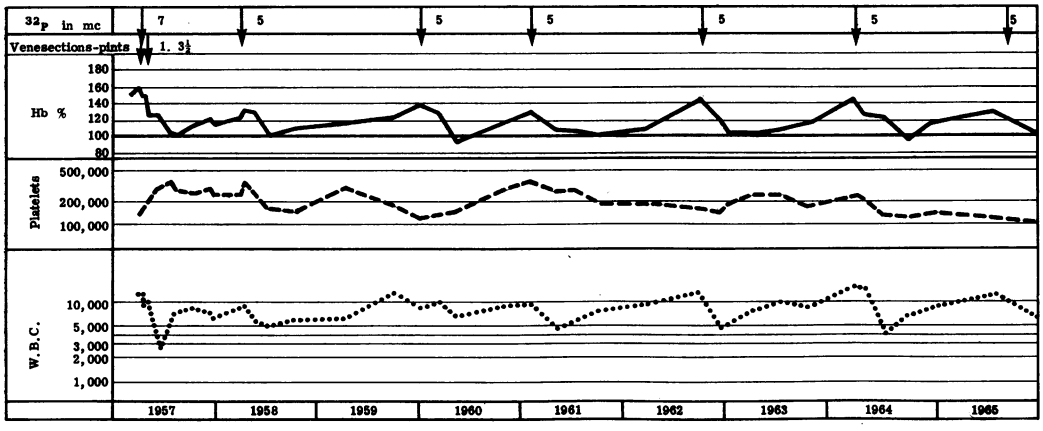

Fig 3 *Polycythæmia vera treated with ^{32}P. Man, aged 58 in 1957. Average response to ^{32}P. Alive and well*

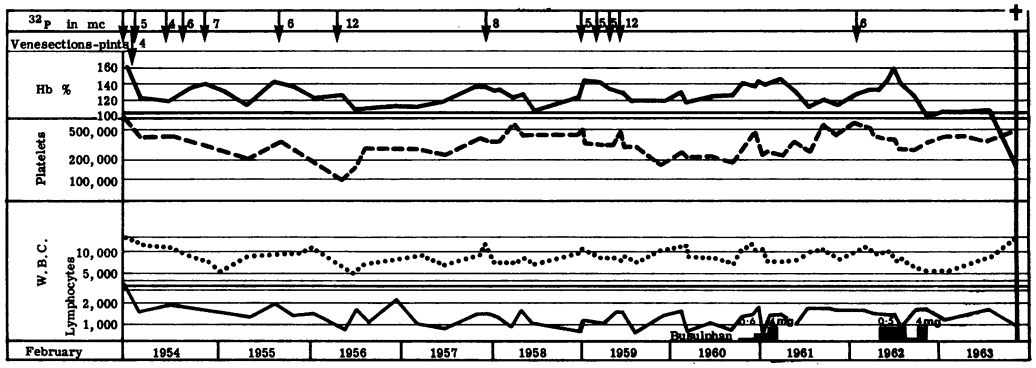

Fig 4 *Polycythæmia vera treated with ^{32}P. Man, aged 57 in 1954. Given large doses of ^{32}P, then busulphan. Died 1963*

Fig 4 shows the blood picture of a patient aged 57 in 1954 when he suddenly became blind in one eye. Physical examination showed a heightened colour of the skin and mucous membranes, a central retinal thrombosis and a palpable spleen. Hb was 164%, PCV 74%, WBC 15,600/c.mm, and platelets 715,000. He was given the largest doses of ^{32}P which we have been prepared to administer in an attempt to reduce his count, but good maintenance was not obtained. After a total dose of 75 mc, including one single dose of 12 mc, busulphan was tried in 1960 with moderate success; one further dose of ^{32}P was also given, but he died from marrow failure ten years after his first treatment.

Of our 132 patients, a total of 6 have been treated with busulphan on account of inadequate control with ^{32}P. No other chemotherapeutic agent has been tried. The dose of ^{32}P given to a new patient is adapted, in the light of our experience, to the sex, age and weight of the patient and the severity of the polycythæmia. Realizing, however, that this estimate can be only a rough approximation, we have been gratified to find, in common with other workers, that in patients with active polycythæmia anæmia due to overdepression of erythroblasts has not occurred. In explanation of this it has been postulated by Lawrence (1940) that in polycythæmia vera it is possible that a second population of abnormal red cells, more radiosensitive than the normal ones, arises in the marrow. Depression of the white cell count has not prevented treatment with ^{32}P in any patient and thrombocytopenia has been a limiting factor in only one. Patients in whom thrombocythæmia is a prominent feature of their dyscrasia respond particularly well to ^{32}P. Fig 5 is the chart of a patient aged 48 in 1956 who has been treated for nine years with ^{32}P for this condition. She has had a total dose of 27·5 mc. She presented complaining of severe headaches, epistaxis, melæna, hæmaturia and spontaneous bruising. The spleen was easily palpable. Hb was 102%, WBC 11,000, and platelets 960,000. Reduction of the platelet count with ^{32}P rapidly relieved all her symptoms and she has been maintained in good health with infrequent injections of phosphorus. When her platelet count has risen above about 500,000/c.mm minor hæmorrhagic episodes and one thrombotic one have occurred.

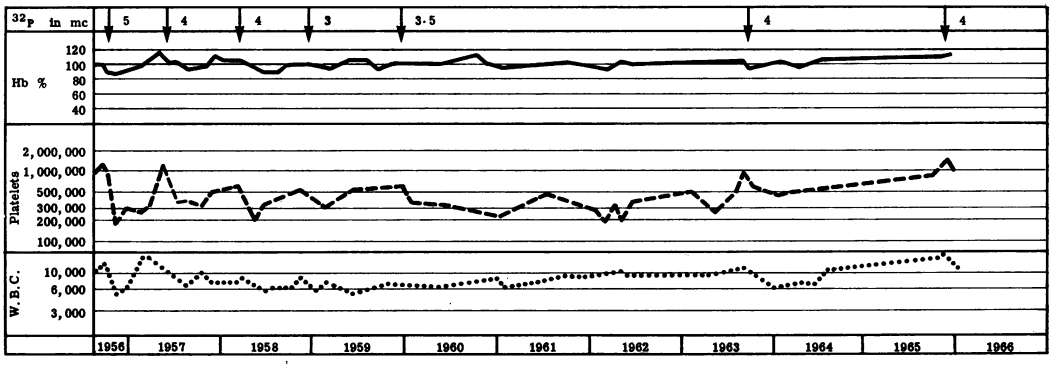

Fig 5 *Thrombocythæmia treated with ^{32}P. Woman, aged 48 in 1956*

Among the few women of child-bearing age in our series, no pregnancy or attempt at pregnancy has been reported. Amongst the men the evidence concerning the possible effect of ^{32}P in reducing fertility is equivocal. Our youngest male patient, who presented at the age of 33, was found at the age of 40 to have a low sperm count on two occasions. His wife, however, had had 4 pregnancies in the preceding twelve years, the last one occurring after the patient had had 16 mc of ^{32}P. The first patient in our series died at the age of 75, having received 47 mc of phosphorus. Death occurred from cerebral hæmorrhage ten days after his last dose of 7 mc. Autoradiographs were done on many tissues obtained at autopsy, including the testicles. Although uptake of phosphorus was shown, histological examination showed active spermatogenesis and apparently normal spermatozoa.

Survival

This has been calculated from the time of first treatment with ^{32}P. Although the survival rate is still less than that of healthy persons, the situation has improved when compared with results published before modern methods of treatment were available. Fig 6 shows a chart constructed in 1961 to show the survival times of our polycythæmic patients compared with people of the same age and sex distribution in the Greater London area. The third curve shows the survival of a series of polycythæmic patients treated in Scandinavia before ^{32}P was available and published in 1950 by Videbæk.

Fig 7 shows the survival of our 132 patients at five and ten years compared with a series treated by chemotherapy and recently published by Dr

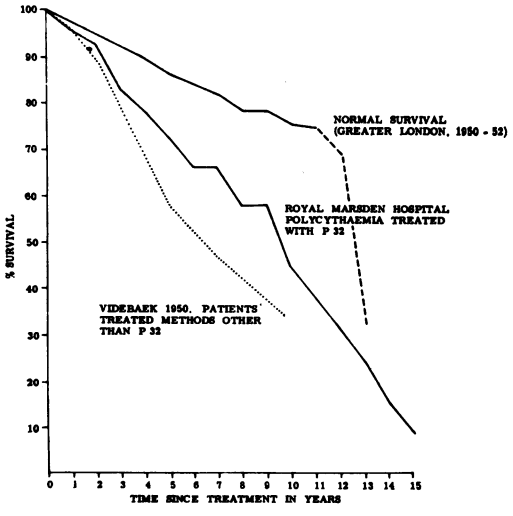

Fig 6 *Polycythæmia vera. Survival times 1949-63*

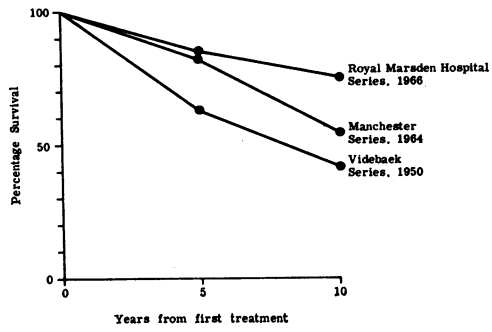

Fig 7 *Polycythæmia vera. Corrected survival curves*

Israëls and his colleagues (Perkins *et al.* 1964). Information to enable this comparison to be made was kindly supplied to us by the authors in addition to their published work. Videbæk's cases are again shown. The median survival of the ^{32}P treated patients is over twelve years, a similar figure to that obtained at Hammersmith Hospital and at the Christie Hospital and Holt Radium Institute (Halnan & Russell 1965, Szur, Lewis & Goolden 1959).

Causes of Death

Sixty-five of our 132 patients have died (Table 1). The causes of death are here shown together with a group published from Scandinavia in 1962 by Chievitz & Thiede. These authors state that they avoided the patients included in Videbæk's 1950 paper, but included all other patients with polycythæmia from most medical departments in Scandinavia who died during the period 1933–61. They were treated by a variety of methods including small doses of ^{32}P in a few patients. One-fifth of the group had no treatment. The number of deaths from vascular accidents in our series is a quarter of the total deaths, compared with half the total deaths in the Scandinavian series. One-third of our patients, however, have died from marrow failure compared with one-fifth of the Scandinavian ones. The other causes of death show little of note in this connexion. Although it has been known for a long time that death from one of the myeloproliferative disorders may occur in the course of untreated polycythæmia vera, it has become clear that the proportion of phosphorus-treated patients dying from marrow failure is higher than in untreated ones. The marrow shows hypo- or hyper-plasia; myelofibrosis, excessive blast cell formation, granulocytosis or megakaryocytosis may also be found. The fact that there is no clear dividing line between these various groups and that overlap is often present is, we believe, one cause of the discrepancy in the number of patients reported to

Table 1
Causes of death in polycythæmia vera

	Number of deaths			
	Chievitz & Thiede 1933–1961		*Royal Marsden Hospital 1948–1963*	
Thrombosis or embolus	100	51%	11	25%
Hæmorrhage	28		5	
Marrow failure Anæmia/myelosclerosis/ leukæmia	25	10%	22	34%
Urinary tract disease (excluding cancer)	17			
Heart disease (excluding thrombosis)	21		9	
Miscellaneous (chest diseases, cancer, accidents etc.)	61		18	
Total deaths	250		65	

have died from leukæmia in published reports. The process of marrow failure may be a gradual one prolonged over many years, and in no patient has it occurred under two years.

In a very few the peripheral blood picture has shown a sudden rapid deterioration with the appearance of primitive cells including blasts. Fig 8 shows the chart of one such patient. He had been referred for an opinion in 1957 at the age of 64 on account of the high colour of his skin and conjunctival suffusion. He said that his father had had very purple cheeks and had dropped dead in the street at the age of 59. His spleen was found to be easily palpable. Hb 139%, PCV 70%, WBC 12,200/c.mm (normal differential), platelets 590,000. He was treated with a total dose of 20 mc of ^{32}P over the next two-and-a-half years. He then developed a right-sided pneumonia for which he was admitted to hospital. Examination of his blood showed a falling hæmoglobin and a rising white cell count with the appearance of primitive cells including blasts. He showed no response to therapy and died within a few weeks.

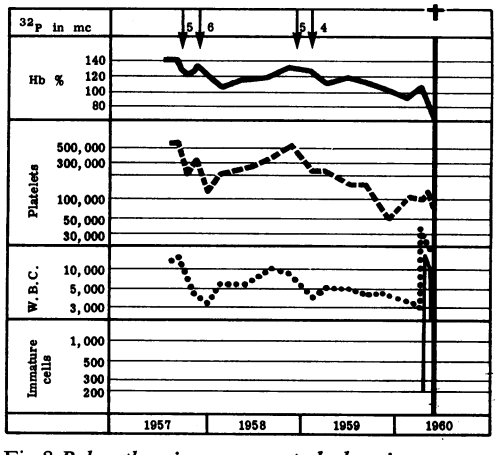

Fig 8 *Polycythæmia vera – acute leukæmia. Man, aged 64 in 1957*

Death from marrow failure may occur early or late in the course of the disease and is not apparently related to the overall dose of ^{32}P given. The total dose of ^{32}P given to the 22 patients who died from marrow failure has been charted in Fig 9 against the survival in years of each patient. The doses are similar to those given to patients who died from other causes. These 22 patients, moreover, did not have higher white cell counts or a greater degree of splenomegaly when first seen than the other patients who have died. Fig 10

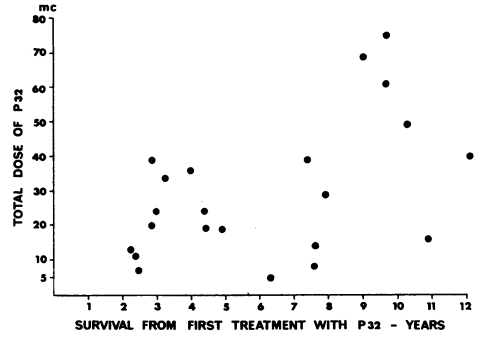

Fig 9 *Polycythæmia vera treated with ^{32}P, 1949-63. Patients dead from marrow failure*

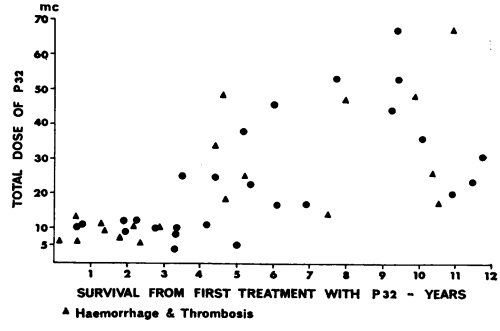

Fig 10 *Polycythæmia vera treated with ^{32}P, 1949-63. Patients dead from causes unassociated with marrow failure*

gives similar information for the 43 patients who died from causes unassociated with marrow failure. The most striking difference in distribution from Fig 9 is due to the patients who died in the first three years from vascular catastrophes. Dramatic and distressing though the few acute blastic terminations have been, it should be noted that this transformation has never occurred less than two-and-a-half years after the first treatment.

Had we a method of ascertaining which patients were going to undergo acute marrow failure in the course of their illness, there might be a case for withholding irradiation and trying other forms of treatment. But as there is no such method, we feel that in the present state of our knowledge there is no absolute contraindication to ^{32}P in any patient with polycythæmia vera.

Acknowledgments: I am grateful to the staff of the Royal Marsden Hospital, and particularly Dr J B Harman under whose care the great majority of the patients have been, for allowing me to discuss this group. My thanks are also due to Professor D W Smithers for asking me to undertake this work, to Dr H E M Kay for the hæmatology, to Dr R A M Case for the statistical work and to Dr N G Trott and Dr M Cottrall for the physics measurements.

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Treatment and Prognosis of Polycythæmia Managed by Non-radioactive Methods

Mild cases of polycythæmia vera can be managed for a time without any drugs by the simple use of venesection. This relieves the symptoms quickly and reduces the risk of thrombosis, but sooner or later venesection alone becomes inadequate. An odd blood picture develops with high red cell count, low hæmoglobin and low MCHC; if this happens more active treatment is needed. Venesection has its place in the relief of symptoms before radioactive phosphorus or chemotherapy can act, a period of three to six weeks. Various drugs have been proposed from time to time for the management of polycythæmia. Before 1940 phenylhydrazine was used; this is a dangerous hæmolytic substance and it was replaced when the nitrogen mustard group came into use.

Originally intravenous nitrogen mustard was used, but this is rather a violent drug and its use is now confined to severe and late cases. Other alkylamines have been tried for the control of polycythæmia as they have been introduced, but few have been successful. Thiotepa, introduced in 1956 by Leonard *et al.*, was useful because it could be given intramuscularly; up to fourteen months' remission was obtained from a single course of treatment. Mannomustine produced remissions up to ten months, but other alkylating agents, including the recently introduced uramustine, have been disappointing; triaziquone, an oral preparation, is at present under trial and so far has given encouraging results.

The two drugs most used at present are busulphan and pyrimethamine. Busulphan was originally introduced by Galton (1953) for the treatment of chronic myeloid leukæmia and was first used by Wald *et al.* (1958) for polycythæmia. We have treated some thirty patients with it and obtained reasonable initial results in most patients. Remissions of up to three years without treatment have been recorded, but most patients need further treatment within eighteen months. A small dose, 4 mg daily, is given initially; it is about eight weeks before real changes in the blood levels and the size of the spleen appear, and then the dose is reduced to 2 mg daily or even less; usually a course of treatment lasting about three months is needed to obtain normal levels. Busulphan reduces the raised alkaline phosphatase in the granulocytes and also reduces the platelet count; one of the undesirable effects of busulphan is that sometimes the platelets are selectively affected and treatment has to be stopped because the level is too low. But busulphan produces no other undesirable side-effects and it is very useful as initial treatment for the first few years.

Pyrimethamine was originally introduced in 1954 but first reports were unfavourable. In 1961 Pegg & Ford presented a dosage scheme which was satisfactory and gave encouraging results. In Manchester we have found it useful and have treated some 40 patients. Troublesome side-effects occur more often than with other drugs, but if the patient reacts satisfactorily, good control can be obtained. The usual dose is 25 mg daily at first, reducing to alternate days as soon as the PCV begins to fall. The platelet count must be watched since a symptomless thrombocytopenia can develop; if this happens, halving the