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Chemotherapy in Polycythemia Vera *

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Polycythemia vera is a disease in which chemotherapy has been used extensively for only a few years. Much more common has been the treatment with irradiation of all bones, and later — in the last thirty years — with radiophosphorus. Of particular concern has been the question of whether such treatment would increase the incidence of terminal acute leukemia in these cases. Since 1905 it has been known that polycythemia vera can terminate in acute leukemia. However, only after Modan *et al.* (1965) reported an analysis of 1222 cases did it become clear that therapy with P^{32} may be followed by a higher incidence of acute leukemia.

It is the purpose of this paper to indicate the difficulties of the clinician in choosing between various agents and in predicting the responseto any one of them, in particular to P^{32} and Myleran. There are no criteria by which the clinician can predict the final outcome of the disease, even when the initial treatment is successful. From this experience one becomes quite hesitant about judging the success of any one treatment only by short-term observations, and it appears to us that the final evaluation of the effectiveness of any one chemotherapeutic agent can only be made after many more years have passed during which very careful observations of the various episodes and phases of the disease have been made. With this in mind, we would like to demonstrate the course of a patient with polycythemia vera treated repeatedly with P^{32}. As shown in Fig. 1, P^{32} was administered 4 times over a period of 8 years. Unfortunately, such a typical case of an uncomplicated course of polycythemia vera is quite rare. However, one may find complete remission followed by a long period of no treatment after only one single administration of P^{32}, or, on the other hand, a variety of drugs may become necessary because P^{32} became ineffective.

In the following, we present varying results obtained in a few selected cases from a group of 210 patients with polycythemia, studied by us at the University Hospital in Cologne during the last 15 years. Up to 1965 the majority of them received P^{32}, since then all new cases have been treated with Myleran. In addition, a small number

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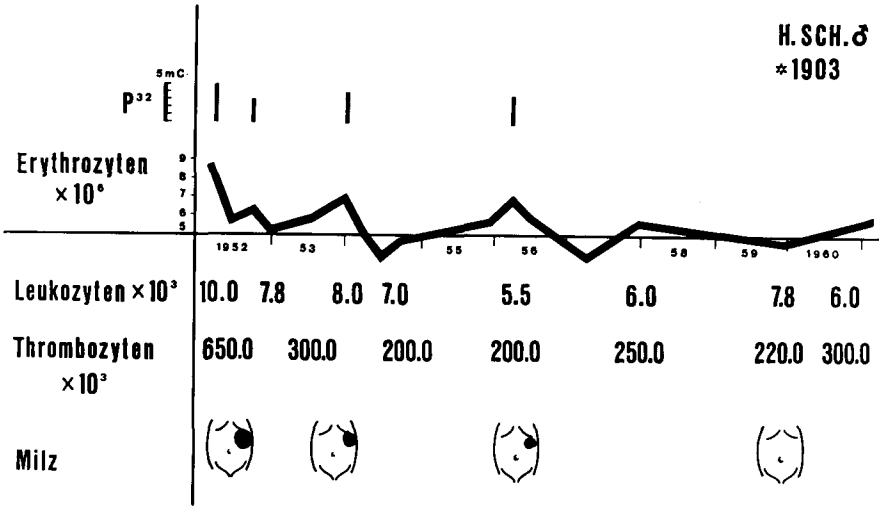


Fig. 1. Polycythemia vera-treatment with Radiophosphorus

of patients received chemotherapy in single or repeated courses: Myleran or another cytotoxic substance was administered either alone or concomitantly or alternately with radiophosphorus. This group included cases who had been treated elsewhere before being referred to us for re-evaluation. Furthermore, some patients were seen first after chemotherapy had been given during the pre-polycythemic phase, their hematological abnormalities having been taken as symptoms of early chronic myeloid leukemia.

A detailed report on our ten years' experience with P^{32} treatment was published in 1961, but no observations are available in our series to evaluate likewise the long-term effect of chemotherapy when given alone (Stecher *et al.*, 1961). However, the long observation period of the patients who received alkylating agents in addition to radiophosphorus provided the opportunity to compare the effect of either treatment at different stages of the disease.

First, we should like to mention the result of routine treatment with Myleran instead of with radiophosphorus, which in new cases was instituted only recently. Three patients are now being observed up to one year after the first course of the drug. The total dose varied between 200 and 400 mg, administered over a period of 1 to 4 months. No maintenance therapy was given. Complete remission was obtained in these three cases, lasting almost a year up to now. In one patient moderate thrombocytopenia, in another slight leukopenia developed transiently, and in both the red cell count dropped to 3 and to 2.6 mill/cmm respectively. In our series of P^{32} treated patients a decrease of erythrocytes below 3.5 mill/cmm was very rare after the first dose of radiophosporus, and the leukocytes as well as the platelets did not fall below normal. The unusually low drop of the red cell count after P^{32} was

mostly followed by remarkably long remissions, even lasting 6 to 9 years in two patients. As far as we know, similar results with chemotherapy have been obtained only with maintenance therapy or repeated courses of treatment.

The response to either P^{32} or Myleran in two further previously untreated patients is illustrated in Fig. 2. Both were known to have had some abnormal hematological findings up to 8 years before typical symptoms of polycythemia were present. One patient suffered from anemia which was occasionally treated with iron. There was no history of blood loss or increased bleeding tendency. Examinations at the time when erythrocyte values had become normal revealed leukocytosis and a palpable

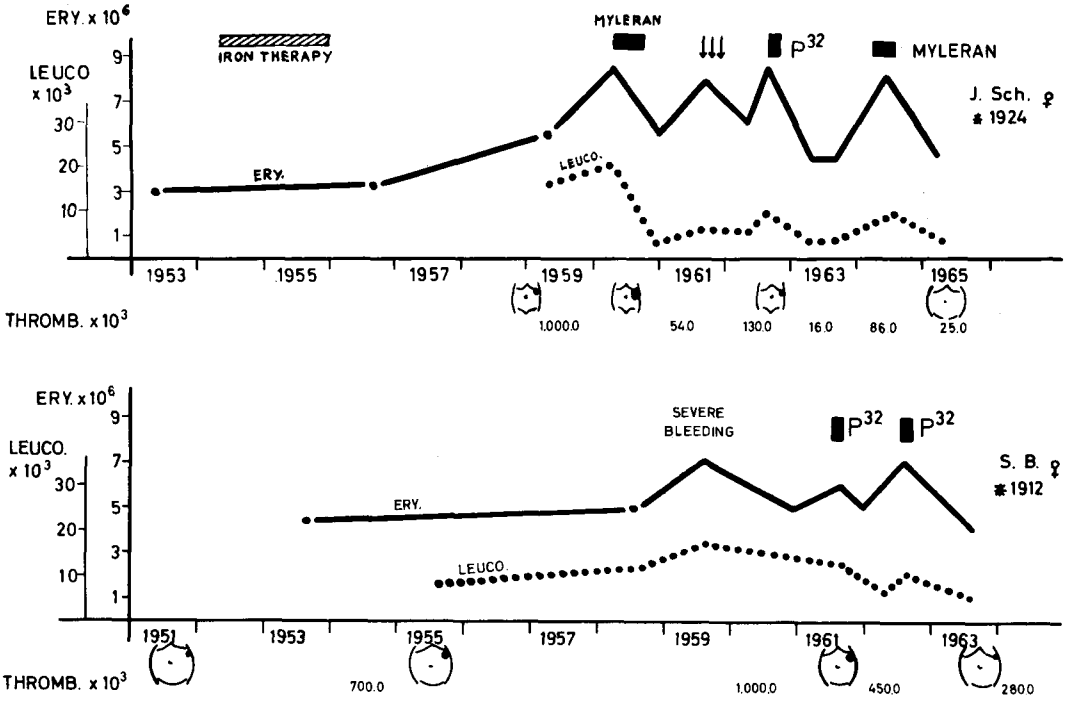
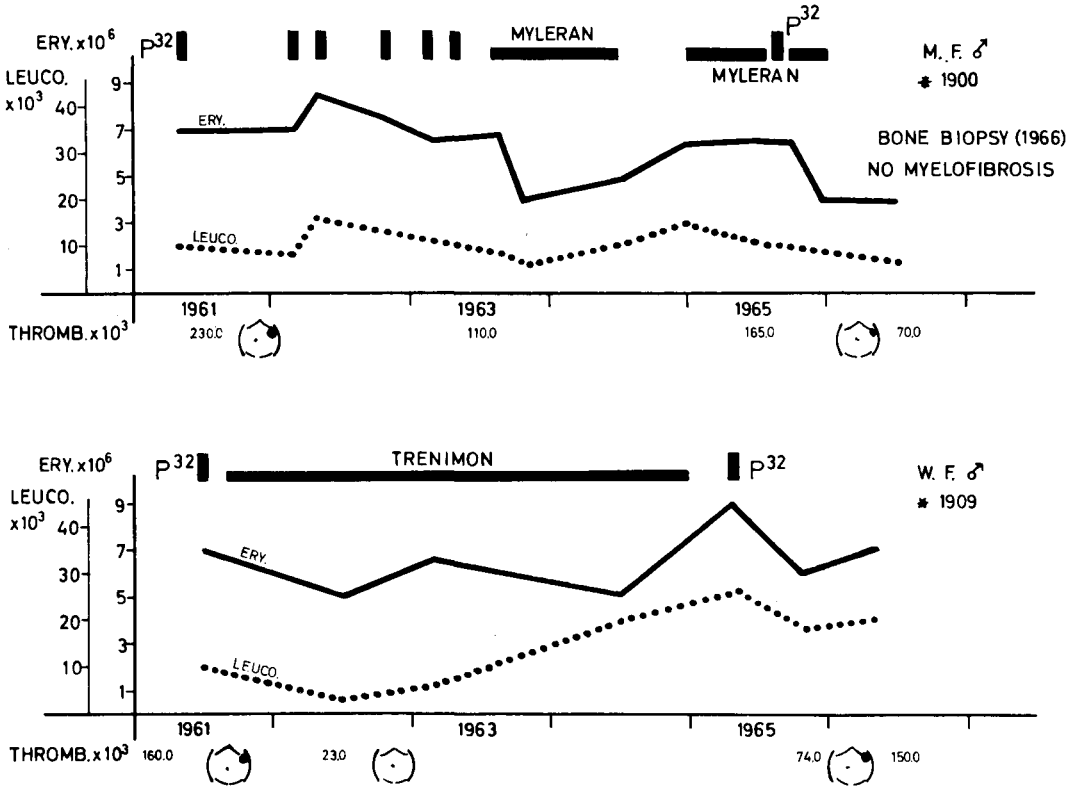


Fig. 2. Effect of Myleran or/and P^{32} in polycythemia vera with marked thrombocytosis

spleen. Twelve months later a fully developed picture of polycythemia with marked thrombocytosis was present. In the second case, who once during the pre-treatment period suffered from severe bleeding, splenomegaly and thrombocytosis were reported many years before diagnosis of polycythemia was made. Previous history and symptoms at the time of diagnosis in both cases were quite similar. Since previous therapy had not been given, increased sensitivity to any kind of specific agent could not be expected. However, the response to P^{32} and Myleran was shown to be very different. Myleran caused thrombocytopenia which subsided but reappeared after

the next treatment with P^{32} and persisted. It should be noted that this patient presented with cerebral symptoms characteristic of chorea minor, which became worse as soon as relapse of the basic disease occurred. Therefore, treatment had to be continued in spite of the thrombocytopenia. In the second case, no adverse effect of P^{32} was seen, and complete remissions were obtained following repeated doses of radiophosphorus.

The effect of combined treatment is demonstrated in Fig. 3. Two cases were seen



Rig. 3. Therapy with P^{32} and Myleran or Trenimon in polycythemia vera

after Myleran and Treminon in very small doses had been given elsewhere almost continuously over a period of 2 to 4 years. P^{32} treatment preceded and followed administration of alkylating agents. By this method the disease was well controlled in both patients now being observed under treatment for 5 years. The first patient had not responded at all to rather vigorous treatment with radiophosphorus. After Myleran therapy had been discontinued, bone marrow smears showed normal cellu-

larity and no fibrosis was present in a bone trephine specimen. These findings should be kept in mind when looking at the effect of treatment in more advanced stages of polycythemia.

Five patients were started on Myleran after resistance to P^{32} had developed. The total dose of radiophosphorus per person varied between 23 and 50 mC given over a period of 5 to 10 years. Myleran was given in daily doses of 2 to 4 mg in courses of 2 weeks to 4 months, total doses ranging between 150 and 580 mg. The occurrence of thrombocytopenia necessitated withdrawal of the drug at a time when the red cell count was still highly elevated. In three patients, a precipitous fall of hemoglobin and erythrocytes, however, was seen within the next months. In one of them, sternal puncture did not yield any marrow cells, and typical myelofibrosis was demonstrated histologically in a bone section (Fig. 4, lower half). Concomitantly the spleen increased rapidly in size. Two cases presented with similar hematological findings, but unfortunately no bone biopsy was done to establish whether myelofibrosis had also developed. In the remaining two patients of this group, there was a delay of 15 and 20 months before anemia became apparent, one dying of acute leukemia two years after Myleran had been administered.

We should like to comment that according to our experience a rather characteristic pattern may be seen in the development of resistance to therapy. Sooner or later after treatment has been instituted, there is no further effect at all, and the red cell count may even rise when therapy with radiophosphorus is continued. As reported already some time ago, the paradoxical response to P^{32} in some cases was followed by a rapid downhill course of the disease. The sequence of hematological and clinical changes in some of the resistant patients, who were finally treated with Myleran instead of with P^{32}, was almost identical. The disease almost invariably terminated in either acute or chronic myeloid leukemia or in myelofibrosis with myeloid metaplasia (Figs. 4 and 5).

Finally, a group of four patients is demonstrated, in whom the presence of some atypical symptoms could be traced back for a considerable length of time before polycythemia was diagnosed. These patients had been presenting elsewhere with normal red cell values, moderate splenomegaly and an increase of white blood cells. Treatment with Urethane, TEM or Myleran was given because the hematological abnormalities had been taken as symptoms of early chronic myeloid leukemia. As shown in Fig. 6, two patients became pancytopenic and there was a time lapse of 1 to 3 years before the onset of typical polycythemia. In one case, erythrocytes and hemoglobin values increased steadily while under Myleran therapy. The disease, then treated with P^{32}, was well controlled in one patient, who died after 8 years of observation from a cerebrovascular accident. In the two patients with transient pancytopenia, the further course of the disease was characterized by recurrent thrombocytopenia in one and by increasing splenomegaly in the other. The fourth case, pre-treated with Urethane followed by P^{32} with a total dose of 6 mC, died of chronic myeloid leukemia, which was confirmed by autopsy.

The first findings in this group of patients were almost identical and indeed sug-

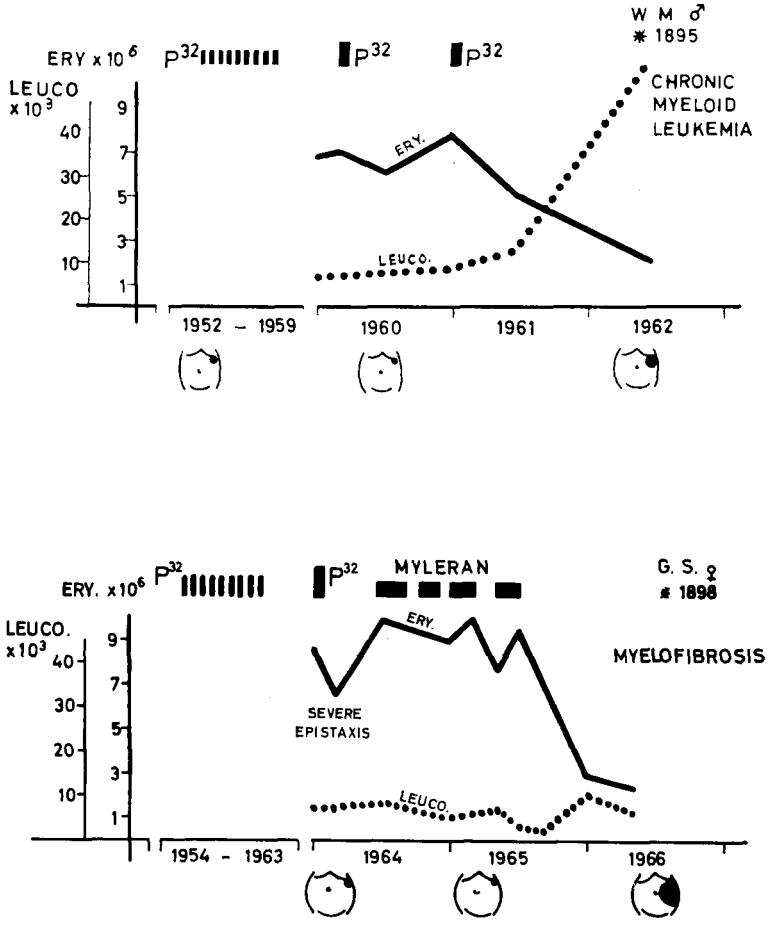


Fig. 4. Chronic myeloid leukemia or myelofibrosis following polycythemia vera

gestive of chronic myeloid leukemia in an early stage. Unfortunately, diagnostic procedures such as chromosome studies or determination of leukocyte alkaline phosphatase activity had not been done at that time. In all patients the full-blown picture of polycythemia developed after administration of alkylating agents or Urethane. Calabresi in 1958 reported about a patient with a similar course following irradiation of the spleen. After reviewing the literature for other characteristic cases, he stated that transition from a leukemic phase to polycythemia invariably took place after x-ray treatment. Similar cases were reported by Braunsteiner *et al.*, (1961) and Lopas *et al.*, (1964) respectively, but here, as in our observations, Myleran was given instead of irradiation.

Looking back on our quite limited experience with Myleran in new cases, the

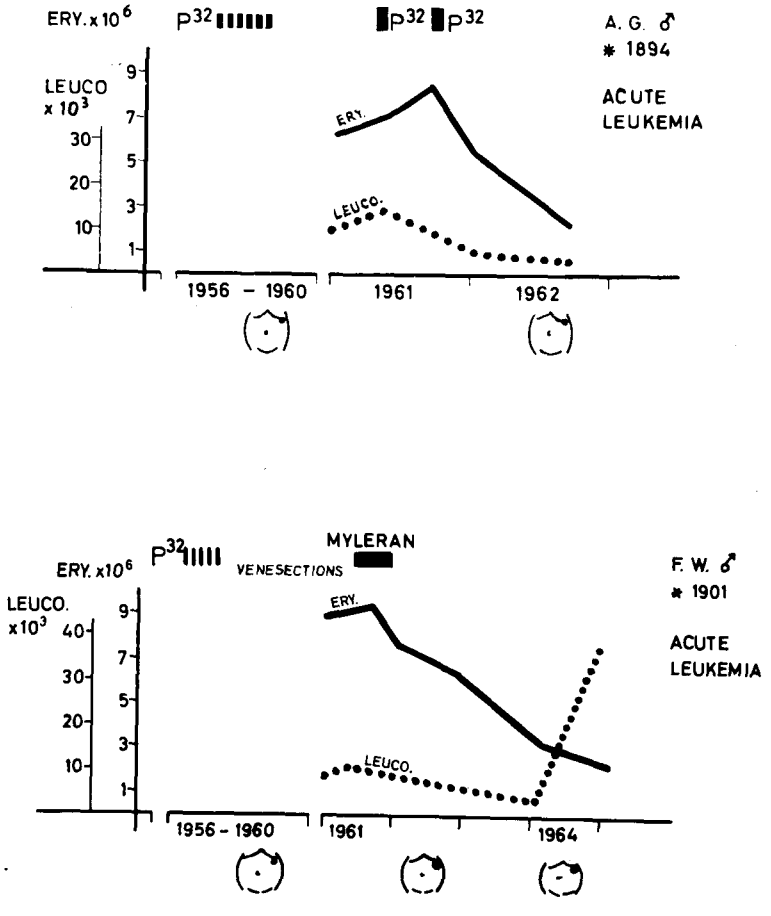


Fig. 5. Acute leukemia following polycythemia vera

preliminary results obtained are in agreement with those reported in the literature (Wald *et al.* 1958; Louis, 1958; Killmann and Cronkite, 1961). The response to a given amount of Myleran varied much more than we would have expected after a single dose of radiophosphorus. The remarkable and sometimes selective effect on platelets, which has been described by many investigators, was demonstrated in one of the two patients with outstanding thrombocytosis. The other responded very well without any side effects from radiophosphorus. Further evidence of the unpredictability of the response to Myleran was demonstrated by showing the opposite effects. In two cases already treated, a reduction in hemoglobin and red cell values was obtained, whereas the platelet count, which was already slightly decreased when therapy was instituted, remained unaffected. Similar results were obtained when

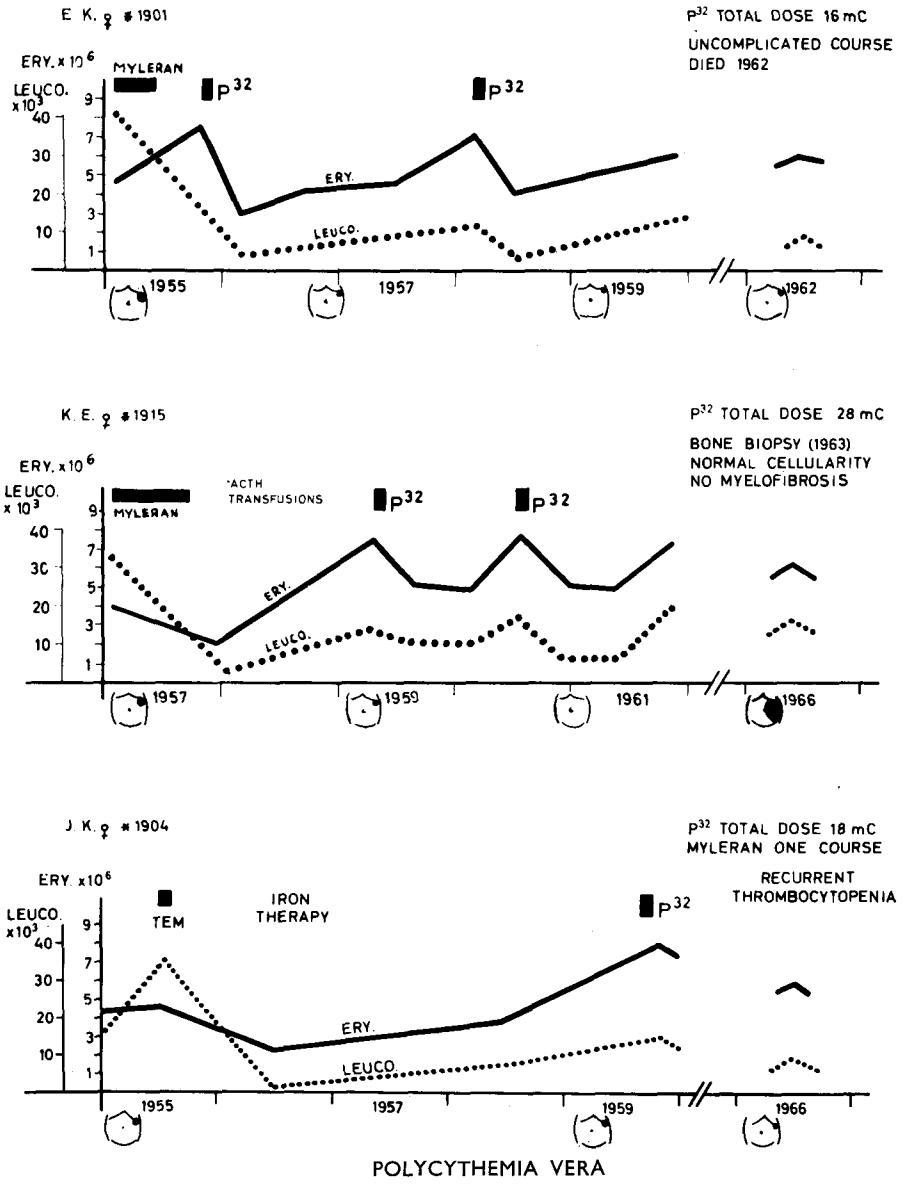


Fig. 6. Course of the disease after pretreatment with Myleran or TEM

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Myleran was given in very low doses as maintenance therapy alternating with radiophosphorus.

Administration of Myleran or TEM in the pre-polycythemic phase was certainly not indicated (Fig. 6). Nevertheless, the patients treated likewise were presented because the various response pattern following such interference with the natural development of the disease process apparently bore some relationship to the further course of polycythemia. It may be remembered that the same sequence in changes of clinical and hematological symptoms has been seen after radiation therapy. The reaction to Myleran or P^{32} when given to far advanced cases in whom transition to one of the chronic myeloproliferative disorders ultimately took place was most unexpected. After resistance to previous treatment had developed, both agents seemed temporarily to stimulate erythropoiesis, but finally had a pronounced depressive effect. In two patients of this group, one terminating in chronic myeloid leukemia after P^{32}, the other in myelofibrosis after P^{32} and Myleran, similar cytological abnormalities were also present. Their blood smears showed a considerable number of Pseudo-Pelger cells at the time when anemia became apparent. Furthermore, striking mitotically connected abnornalities in the red cell precursors were found in the bone marrow of the P^{32} and Myleran treated case, with acute leukemia in the terminal stage. It should be mentioned that out of 8 patients who died from acute leukemia in our series of 210 cases, this was the only one who received Myleran in addition to radiophosphorus.

There is no doubt that polycythemia can terminate as leukemia or myelofibrosis without any specific treatment at all. Nevertheless, it should be questioned whether treatment with radiation, P^{32} and/or alkylating agents increases the risk of developing such a fatal outcome or precipitates the onset of it. Evidence for a causal relationship has been presented repeatedly, most recently in the large group studied by Modan *et al.*, (1965). Besides the higher incidence of acute leukemias, there was also a higher percentage of chronic myeloproliferative disorders in the P^{32} treated cases compared to patients not treated in this way. No figures were given for patients receiving chemotherapy alone. Perkins *et al.* (1964), however, observed myelofibrosis in 4 cases among 125 patients treated with various cytotoxic substances. It is of interest that Hunstein *et al.* (1965) reported an increased incidence of myelofibrosis after Myleran treatment in chronic myeloid leukemia. The same author, however, when examining a group of patients with polycythemia for myelofibrosis before and after treatment with P^{32}, did not find fibrosis in the marrow, although total doses given were as high as 36 mC (1966). In the whole of our group, 11 patients were seen who developed myelofibrosis, which was either confirmed by biopsy or diagnosed by typical hematological and clinical findings. Three cases had received P^{32} and alkylating agents, 7 had only P^{32} and one had chemotherapy alone.

In summarizing our observations, it appears that therapy with alkylating agents may be as hazardous as treatment with radiophosphorus or with a combination of both. This refers to any treatment schedule described above, regardless of whether it was applied early or late in the course of the disease. One explanation for the un-

predictable response to treatment and the possible influence of treatment on the final outcome of the disease may be that we do not actually know what we are treating. The typical hematological picture of polycythemia vera very often seems to mask a variety of underlying diseases of the bone marrow, the nature of which is not understood. In fact, nothing is known about the etiology and pathophysiology of the disease. If an experimental model for polycythemia were available, perhaps it would be possible to evaluate the proliferative activity of each of the three cell groups in the marrow and to determine their sensitivity to a given cytotoxic agent. However, up to the present time attempts to induce polycythemia permanently in experimental animals have not been successful.

Summary

210 cases of polycythemia vera were observed over a period of 15 years. The majority of them received P^{32}; treatment with Myleran instead of with radioactive phosphorus was instituted only recently. To a small number of patients chemotherapy was given alternately with P^{32}. The differing response pattern to either kind of treatment and the possible interference of therapy with the natural development of the disease process are demonstrated in a few selected cases.

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RIASSUNTO

Sono stati osservati per un periodo di 15 anni 210 casi di policitemia vera. La maggior parte di essi sono stati trattati con P^{32}; il trattamento con myleran invece che con fosforo radioattivo è stato istituito solo recentemente. Alcuni pazienti sono stati trattati alternativamente con P^{32} e chemioterapia. La diversa risposta a ciascun tipo di trattamento e le possibili interferenze della terapia con la normale evoluzione del processo morboso sono state dimostrate in alcuni casi.

RÉSUMÉ

210 cas de *polycytemia vera* ont eté observés pendant une période de 15 ans. La plupart des cas ont été traités par P^{32}, le traitement avec myleran ayant été introduit récemment. Dans quelques cas la chimiothérapie a été alterné avec le P^{32}. La différente réponse à chaque type de traitement et les possibles interférences de la thérapie avec l'évolution naturelle de la maladie ont été démontrées dans quelques cas.

ZUSAMMENFASSUNG

Während eines Zeitraumes von 15 Jahren wurden 210 Fälle von Polycythämia vera beobachtet und die Mehrzahl von ihnen mit Radiophosphor behandelt. Die übrigen Patienten erhielten nur Myrelan oder P^{32} und ein Cytostaticum. Es wird die Wirkung der verschiedenen Behandlungsmethoden geschildert und an einigen Beispielen gezeigt, dass in manchen Fällen die Therapie den natürlichen Verlauf der Erkrankung zu modifizieren scheint.

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