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Polycythemia Vera

II. Transgression Towards Leukemia with Special Emphasis on Histological Differential Diagnosis, Cytogenetics and Survival *

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Summary. Of 113 Patients with polycythemia vera (P. vera) who had been followed for the last 8 years, 30 cases (27%) developed myeloid leukemia with fibrosis of the bone marrow. Core biopsies of the bone marrow including sequential examinations in several cases revealed neoplastic proliferation of neutrophil granulopoiesis and an atypical megakaryopoiesis with accompanying fibrosis of varying degrees. These alterations were consistent with a subtype of chronic myeloid leukemia – the so called chronic megakaryocytic-granulocytic myelosis (CMGM) – and correspond to (agnogenic) myeloid metaplasia with osteomyelofibrosis/-sclerosis. 5 of those 30 patients showed spontaneous transgression into myeloid leukemia, none of them had received any ionizing radiation or cytostatic therapy. A blast crisis or so called acute leukemia in P. vera was seen only in one patient who was treated by an overdose of radioactive phosphorus and later evolved into osteomyelosclerosis with blastic transformation.

These findings of a chronic leukemia or CMGM arising from P. vera was further confirmed by atypia of ultrastructure and particularly by our cytogenetic evaluation. Chromosomal studies showed a Ph'-chromosome to be present in 5 of 8 patients with CMGM and myelofibrosis.

Clinical and statistical evaluation of survival times showed a median survival expectation of all P. vera patients of 15 years. Life expectancy of the patients who still displayed P. vera was more favorable than those cases with transformation into CMGM, disregarding any therapy. Transformation of P. vera into CMGM occurred about 8 years after the onset of disease and following transgression into leukemia, half of these patients were dead after 2.5 years. Our results demonstrate that P. vera represents a "panmyelosis" with an inherent malignant nature, or a neoplastic proliferation of all three cell lines. This concept is supported by several facts: atypia of cytologi-

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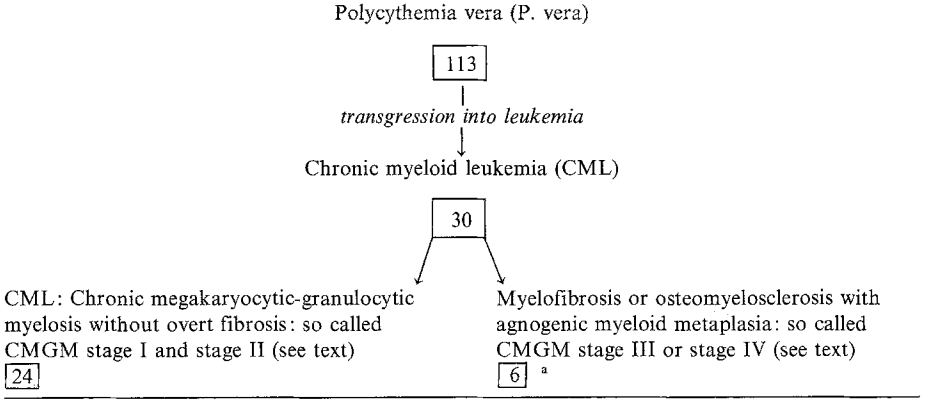
cal differentiation as observed by light- and electron microscopy of the bone marrow, chromosomal anomalies with aneuploidy and an infrequent Ph'-marker, spontaneous transgression into chronic myeloid leukemia or its subtype CMGM without relevant therapy and a clonal evolution as shown by enzymatic studies reported in the literature.

Key words: Polycythemia vera – Myeloid leukemia – Histopathology – Ultrastructure – Cytogenetics – Survival.

Introduction

Polycythemia vera (P. vera) may be regarded as a myeloproliferative disorder with a malignant potential, or as a presumptive preleukemic lesion since it is well known that a fraction of patients eventually evolve leukemia irrespective of their treatment (Wasserman 1976). To investigate this problem of leukemic

Table 1. Survey of patients who progressed from P. vera into chronic myeloid leukemia (CML with its subtypes CMGM with and without myelofibrosis/osteomyelosclerosis; for further detail see Georgii, 1979)



[a] One of these has further transgressed into blast crisis

Table 2. Principle clinical and hematological data of 6 patients with P. vera and transgression into CML with its subtype of CMGM (with and without myelofibrosis) diagnosed and treated at the Medical School Hannover, Department of Immunology and Blood Transfusion ($\bar{x}$ mean and standard error Sx of the mean for each variable). ALP = alkaline leukocyte phosphatase score

Final diagnosis	No.	Sex (ratio)		Age (years)	Hemoglobin g%	Hematocrit %
P. vera with transformation into chronic myeloid leukemia	6	2F/4M	$\bar{x}$	71.5	19.4	59.3
			Sx	8.7	2.3	9.6

transformation in P. vera several methods of approach are possible: The first and most essential however, is the histopathology of the bone marrow. Although the value of a bone marrow biopsy for the differentiation of the so called polycythemic disorders – secondary polycythemia and P. vera – is emphasized in a number of comprehensive papers (Burkhardt et al. 1969; Duhamel et al. 1970; Lundin et al. 1972; Ellis and Peterson 1979) morphology of the transition into chronic myeloid leukemia (CML) has rarely been described. In addition to the morphological and clinical findings (Silverstein 1974; Landaw 1976) one of the most successful ways is by study of chromosomal abnormalities as shown by Wurster-Hill and McIntyre (1978) for P. vera. A morphological and cytogenetic investigation was therefore performed to increase our knowledge of the histopathology, differential diagnosis and expected chromosomal anomalies occurring during transgression of P. vera towards leukemia. Further, we wished to compare clinical data of survival in P. vera and evolved CML in regard to the different regimens of treatment. In our first paper we reported morphological and clinical findings in P. vera and secondary polycythemia with special reference to histopathology (Vykoupil et al. 1980). This paper is intended to continue and complete our study on polycythemic disorders, with emphasis on transformation into leukemia.

Patients and Methods

Patients. From a total of 113 cases with P. vera 30 patients revealed transition into CML (Table 1) with and without accompanying fibrosis of variable degree (so called myelofibrosis/osteomyelosclerosis with myeloid metaplasia). The mean age was 60 years and the sex ratio F:M/1.7:1. Of these 30 cases 25 patients received treatment with radioactive phosphorus (^{32}P) and cytostatics, whereas 5 cases had phlebotomies only. The main clinical and hematological data of a group of 6 patients diagnosed and treated at our university hospital are listed in Table 2 and correspond to the findings of the remaining cases from outside (see acknowledgements, Vykoupil et al. 1980).

Methods. The methods applied for the examination of corings of the iliac crest and further processing for light- and electron microscopy and cytogenetic investigations have been recorded (Vykoupil et al. 1980). Statistical evaluation of the survival times and life expectancy was performed using the method of Cutter and Ederer (1958), for more details see Table 8.

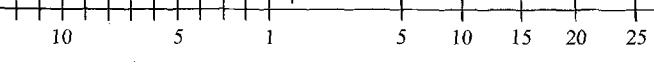
Results

The gradual and insiduous transgression of P. vera towards CML with its subtype chronic megakaryocytic-granulocytic myelosis or CMGM and different

Peripheral blood count (cu mm)			ALP	Total red cell volume cc/kg	Plethora (ratio)	Splenomegaly (ratio)
Erythrocytes $\times 10^3$	Leukocytes $\times 10^3$	Thrombocytes $\times 10^3$				
7.9	20.8	479	293	86	−3/+3	++3/−3
0.5	6.9	408	201	6.8		

Table 3. Transformation of P. vera into chronic myeloid leukemia with and without accompanying fibrosis (CMGM I–IV), as evaluated from sequential biopsies in 7 patients and course of disease until now (for details of CML-classification see Georgii 1979). Arrows indicate approximate time of core biopsies of the bone marrow and resulting diagnosis

No.	Initials	Sex	Age (years)	Course of disease	Therapy: ^{32}P cyto-statics	Ph'-chromo-some
				P. vera / CML with / without myelofibrosis		
1.	Sch. M.	F	77	P. vera → CMGM II	–	
2.	H. H.	M	60	P. vera → CMGM I	–	
3.	V. A.	F	77	P. vera → CMGM I	–	
4.	S. H.	M	60	P. vera → CMGM II → blast crisis → CMGM III	+++^{32}P	+
5.	B. M.	F	73	P. vera → CMGM III → CMGM III	+	+
6.	H. A.	F	74	P. vera → CMGM III → CMGM IV → CMGM IV	+	+
7.	T. K.-F.	M	41	P. vera → CMGM II → CMGM II	+	



in years

in months

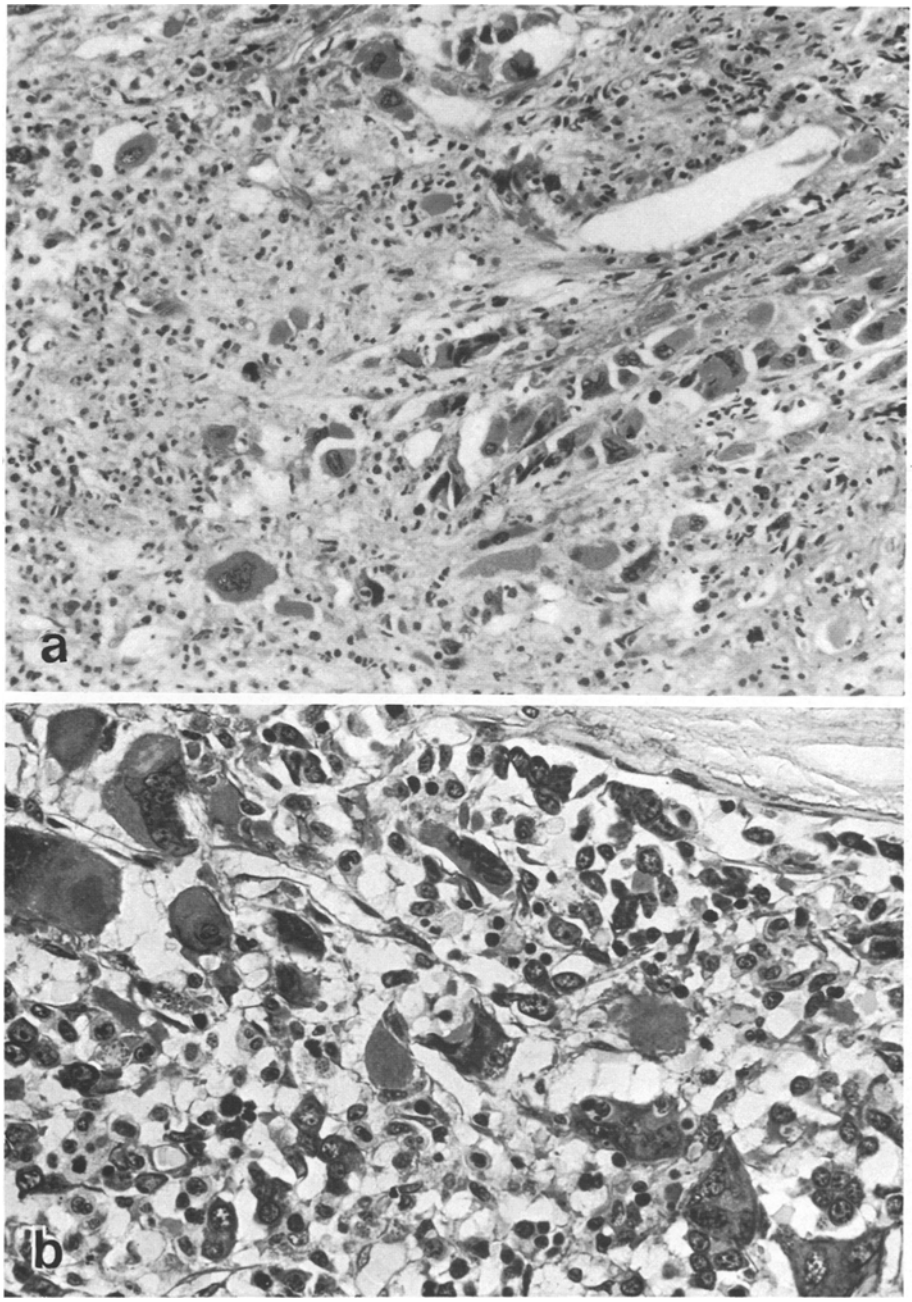


Fig. 1a and b. Transgression of P. vera into CML. **a** Chronic megakaryocytic-granulocytic myelosis (CMGM) with conspicuous proliferation of granulopoiesis, decrease of erythropoiesis and many bizarre megakaryocytes with a variety of sizes and irregular shapes. There is a remarkable increase in reticulin and single collagen fibers corresponding to early myelofibrosis (CMGM II). **b** A conspicuous increase of fibers (myelofibrosis, CMGM III) is accompanied by an atypical growth of megakaryopoiesis and paratrabecular clusters of neutrophilic granulopoiesis. **a** × 280 – Giemsa stain; **b** × 480 – Gomori stain

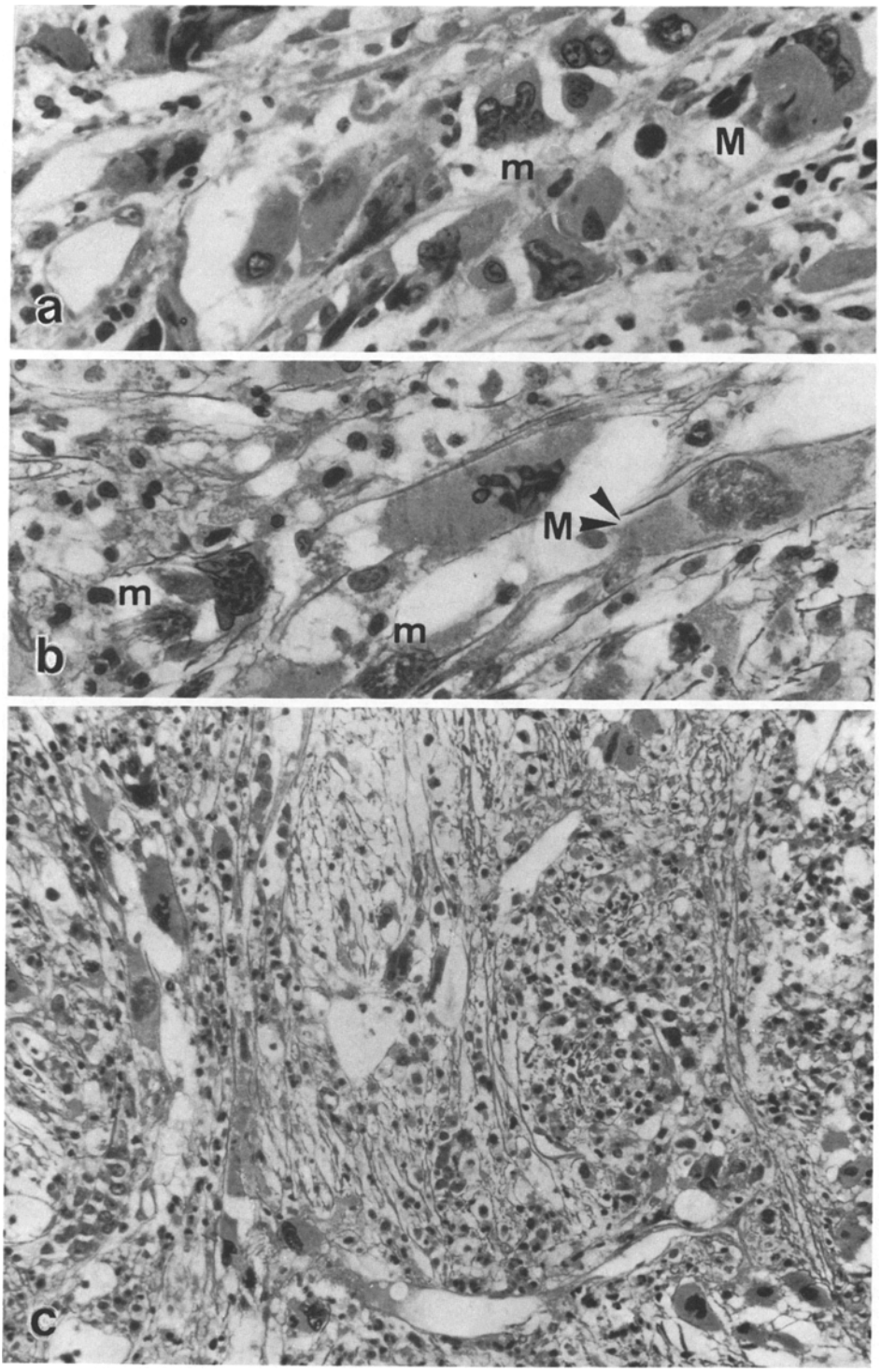

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Table 4. Erythropoiesis: Histological criteria of erythropoiesis in polycythemic conditions evaluated by semiquantitative gradings (0→3=$\bar{x}$, □ $P<0.001$), abbreviations: not evaluable: –; not applicable: n.a.

Entity	No.		Hyper-plastic	Hypo-plastic	Normo-cytic	Macro-cytic	Shift to the left	Arrest of maturation	Localization of erythrons[a] normal	Localization of erythrons[a] atypical	Iron[b] (siderin storage)
Polyglobuly	51	$\bar{x}$	1	0	–	–	–	0	n.a.	n.a.	1.6
		%	94	0	96	4	6	0	92	8	90
P. vera (phlebotomy only)	56	$\bar{x}$	2.8	0	–	–	–	–	n.a.	n.a.	0
		%	100	0	73	27	12	4	8	92	0
Transformation P. vera → CML	30	$\bar{x}$	0.3	0.6	–	–	–	–	n.a.	n.a.	0.4
		%	48	38	79	21	14	14	76	24	31

[a] Localization of erythrons: *normal* (diffuse and perisinusoidal), *atypical* (diffuse and peritrabecular)

[b] Iron storage (siderin): total sideropenia –0, hyposiderosis –1, normal –2, hypersiderosis –3

degrees of myelofibrosis/osteomyelosclerosis (for classification see Georgii, 1979) is most striking if sequential trephine biopsies of the bone marrow are performed (Table 3). Spontaneous transformation was observed in the first three patients who did not receive any substantial therapy and the fourth patient (S.H.) evolved a blastic crisis with the clinical symptoms of an acute leukemia following excessive ^{32}P treatment.

Histopathology of P. vera with evolution of CML is illustrated firstly by micrographs of light- and electron microscopy (Figs. 1 a, b to 4 a–c) and secondly by a semiquantitative evaluation of the different cell lineages of the bone marrow which are involved in the process of proliferation including a comparison of the three main groups of polycythemic disorders: secondary polycythemia, P. vera and particularly P. vera with transgression into CML (Tables 4–6). This synopsis of histopathology of the polycythemic conditions was done to point out clearly the fundamental cellular alterations which occur in the bone marrow in evolving leukemia and myelofibrosis arising from P. vera.

Fig. 2a–c. Atypia of myelofibrosis (with agnogenic myeloid metaplasia, CMGM III) arising from P. vera. **a** Abnormal differentiation of megakaryocytes lying along a sinus and showing microforms with pyknotic nuclei (*m*) and larger cells (*M*), all with a dissociation of the nuclear-cytoplasmic development. **b** Disorganization of megakaryocytic maturation in CMGM III (myelofibrosis) of a patient (S.H., case 4 in Table 3), who received an overdosis of ^{32}P. Besides pyknotic microforms resembling naked nuclei (*m*), there are large cells either with a hyperlobated nucleus with dense chromatin (*M*) or an immature nucleus with finely dispersed chromatin like a megakaryoblast (*arrow heads*). **c** Light microscopy of the bone marrow of patient S.H. with a CMGM III (myelofibrosis) after prolonged ^{32}P therapy of a P. vera displaying bundles of collagen and reticulin fibers enmeshing bizarre megakaryocytes and abnormal nests of proliferating granulopoiesis. **a** × 620 – Giemsa stain; **b** × 620 – Gomori stain; **c** × 280 – Gomori stain

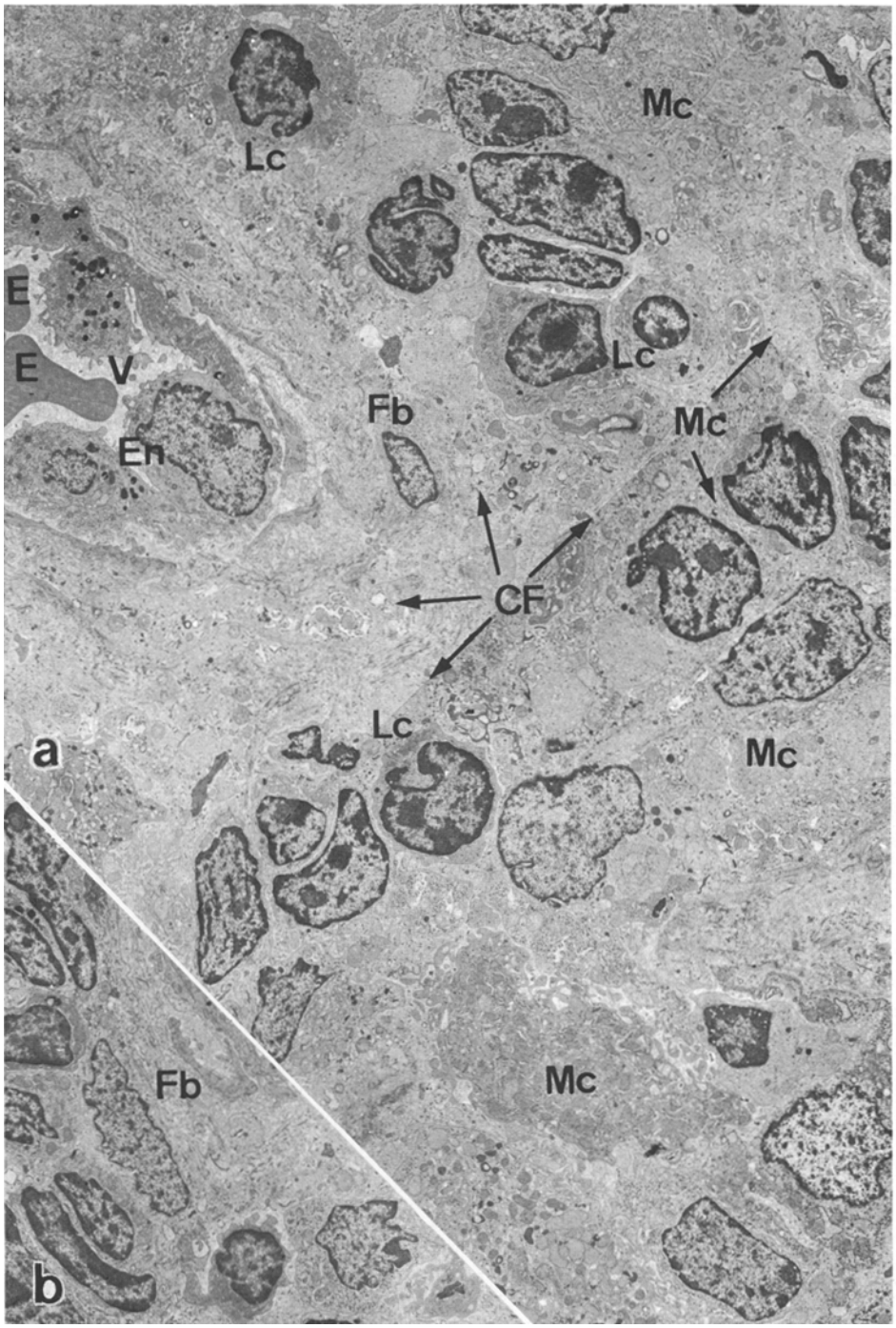


Fig. 3a and b. Ultrastructure of the patient S.H. with CMGM III (myelofibrosis, see also Figs. 2b, c). **a** Survey with cells of myeloid origin (*Mc*) mostly belonging to an abnormally differentiated granulopoiesis intermingled by lymphocytes (*Lc*) and surrounded by extensive bundles of collagen fibrils (*CF*) with fibroblasts (*Fb*). There is also a capillary (*V*) with endothelial cells (*En*) and erythrocytes in the lumen (*E*). Because of the small magnification no further differentiation of the cells of apparently myeloid derivation (*Mc*) is possible. **b** Fibroblast (*Fb*) surrounded by collagen fibrils, lymphocytes and fibrocytes. **a** × 4,000; **b** × 3,500

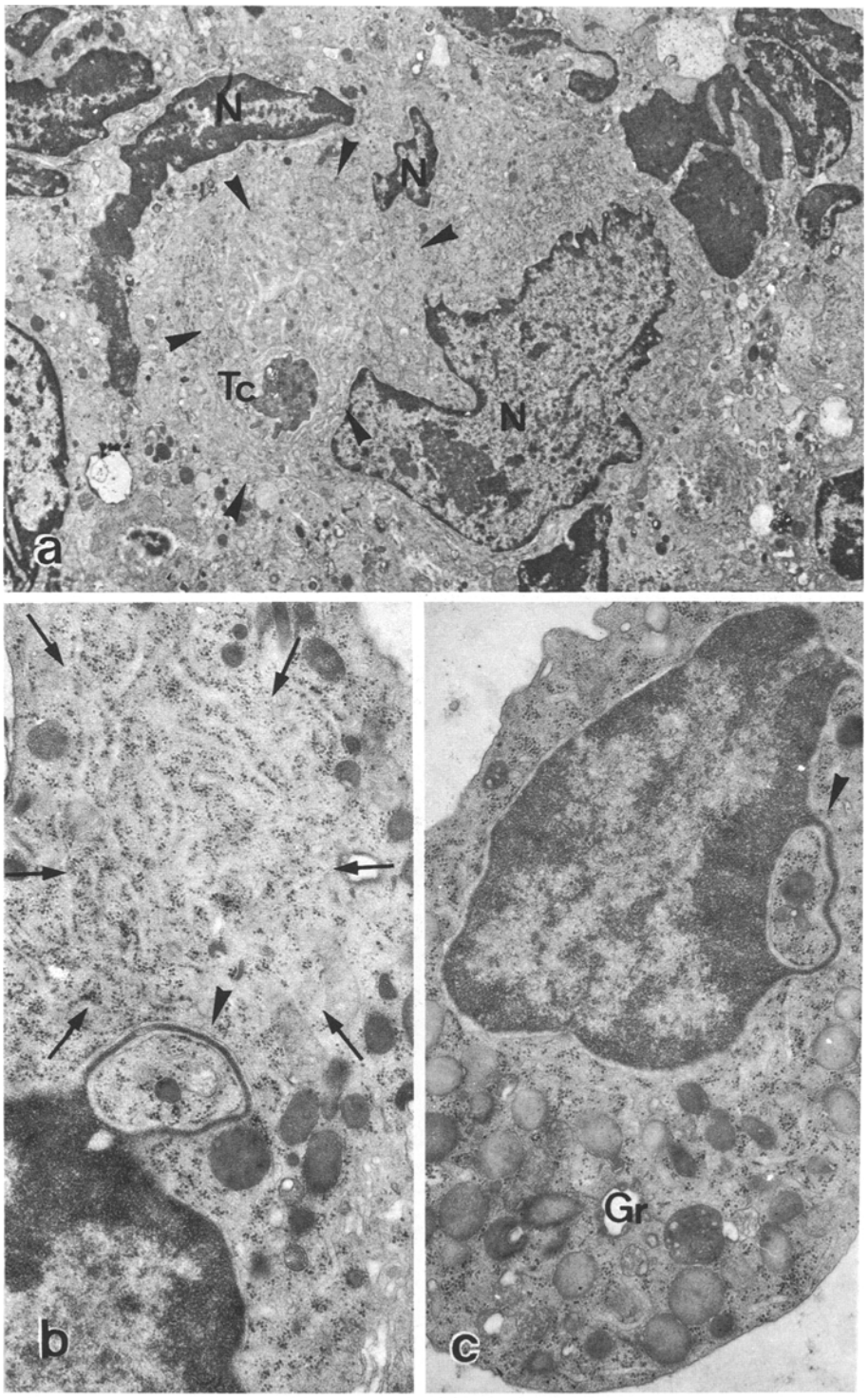
Table 5. Granulopoiesis: Histological criteria of neutrophilic granulopoiesis in polycythemic conditions evaluated by semiquantitative gradings with special emphasis towards progression into CML ($0 \rightarrow 3 = \bar{x}$, □ $P < 0.05$)

Entity	No.		Hyperplastic	Hypoplastic	Shift to the left	Arrest of maturation	Eosinophils	Basophils
Polyglobuly	51	$\bar{x}$	0.3	> 0.1	0.2	0	0.3	0
		%	27	2	18	0	24	0
P. vera (phlebotomy only)	56	$\bar{x}$	1.3	0	0.8	> 0.1	0.6	0
		%	100	0	77	4	42	0
Transformation P. vera → CML	30	$\bar{x}$	1.7	0.1	1.2	0.3	1	> 0.1
		%	90	6	97	28	45	3

Table 6. Megakaryopoiesis: Histological criteria of megakaryopoiesis in polycythemic conditions evaluated by semiquantitative gradings with special emphasis towards progression into CML ($0 \rightarrow 3 = \bar{x}$, □ $P < 0.05$), n.a.: not applicable

Entity	No.		Hyperplastic	Hypoplastic	Megakaryoblasts	Polymorphy	Atypias (mostly microforms)	Pyknotic cells (naked nuclei)	Giant megakaryocytes	localization	
										Perisinusoidal	Diffuse
Polyglobuly	51	$\bar{x}$	0.1	> 0.1	0	0.2	0	0.4	0.1	n.a.	n.a.
		%	8	4	0	20	0	43	6	0	100
P. vera (phlebotomy only)	56	$\bar{x}$	1.9	0	0.8	1.2	0.7	0.5	1.4	n.a.	n.a.
		%	100	0	65	100	73	50	96	0	100
Transformation P. vera → CML	30	$\bar{x}$	2	0	1.2	1.9	1.1	1.1	1.2	n.a.	n.a.
		%	100	0	87	100	93	80	80	80	20

Light microscopy of core biopsies of the bone marrow in P. vera with transgression into CML with minimal or overt myelofibrosis displayed a decrease of the extensive erythropoiesis seen in P. vera and showed a minimal storage of iron in the (histiocytic) reticulum cells (Table 4). Moreover there was an atypical proliferation of neutrophilic granulopoiesis with a shift to the left and arrest and disturbance of maturation (Fig. 1 a, b, Table 5). In comparison with secondary polycythemia and P. vera, gradually developing myelofibrosis of different degree occurred simultaneously with striking atypia of megakaryopoiesis. These abnormalities were consistent with a dissociation of nuclear-cytoplasmic maturation and appeared as irregularly shaped outlines of the megakaryocytes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besides micro- and macroforms (Figs. 1b, 2a, b; Table 6). The anomalies of cellular differentiation were most conspicuous in the case of a 63 year-old male patient (S.H., case 4 in Table 3, Fig. 2c), who received an overdose of radiophosphorus therapy in 5 successive years. He finally died in a blast crisis of CML with overt myelofibrosis (so called megakaryocytic-granulocytic myelosis, CMGM, stage III, see Georgii, 1979). *Ultrastructure* of the bone marrow about half a year before death of this patient revealed a bizarre population of cells lying between bundles of collagen fibers. These were not easily assigned either to the neutrophilic or megakaryocyte lineage (Fig. 3a, b). A further analysis displayed atypical micromegakaryocytes with an apparently mature nucleus and demarcation membrane system, but no specific granules in the cytoplasm (Fig. 4a). A similar anarchy of cellular development was observed in the neutrophilic granulocytic series. There were frequent formations of nuclear blebs (Fig. 4b, c), dissociation of granulogenesis with hypogranulation in comparison with the stage of nuclear maturation and large stacks of cisternae of rough endoplasmic reticulum (so called Döhle bodies, Fig. 4b).

Table 7. Cytogenetic findings in 8 patients who evolved chronic myeloid leukemia (CML) from P. vera; for classification of CML see Georgii (1979). The first patient (S.H.) developed a blastic crisis as the only case of this study and cases 4 and 5 a Ph'-chromosome positive CML without previous cytostatic or radiomimetic therapy

	Initials	Chromosomal anomalies	Philadelphia chromosome	Ratio abnormal/metaphases	Classification of chronic myeloid leukemia	Treatment	
						^{32}P	phlebotomy
1.	S. H.	+13, +20, ringchr. 10	+	72/176	CMGM-III in blast-crisis	+++ (overdosis of ^{32}P	
2.	B. M.	+3, +17, +18, 14−, 13+	+	6/68	CMGM III	+	
3.	K. O.		+	3/17	CMGM II	+	
4.	G. M.	10−, +22	+	9/69	CMGM I		+
5.	V. A.	+15, +19	+	2/15	CMGM I		+
6.	M. C.	−	−		CMGM I		+
7.	R. J.	−	−		CMGM I		+
8.	H. A.	−	−		CMGM II	+	

Fig. 4a–c. Electron microscopy of atypia of megakaryopoiesis and neutrophilic granulopoiesis in CMGM III (myelofibrosis) of patient S.H. (see also Figs. 2b, c and 3a, b). **a** Abnormal micromegakaryocyte with mature lobated nucleus (*N*) and demarcation membrane system (*arrow heads*) but no specific granules. There is further an intussusception of a thrombocyte (*Tc*). **b** Neutrophilic segmented granulocyte with abnormal loop (*arrow head*) and peripheral condensation of chromatin in a mature nucleus but with stacks of rough endoplasmic reticulum in whorl-like arrangement ("Döhle body", *arrows*) surrounded by a few granules of the secondary type. **c** Neutrophilic metamyelocyte with abnormal nuclear loop (*arrow head*) and abundant granules exclusively of the secondary type (*Gr*). **a** × 7,000; **b** and **c** × 15,000

Table 8. Survival times with median life expectancy and 5- and 10-year survival rate in comparison with therapy and course of P. vera, particularly transgression into CML with the subtypes of CMGM (chronic megakaryocytic-granulocytic myelosis – osteomyelofibrosis/-sclerosis)

Groups of patients with P. vera	No.	Median survival expectancy (years)	Survival rate % 5 years	10 years
Total without and with transformation into CMGM treated and non-treated	113	15.1	93	75
No relevant treatment (phlebotomy)	31	10	83	50
^{32}P and/or cytostatics	26	24.5	100	92
Transformation into CMGM: phlebotomy	5	5.6	60	30
		$P: = 0.018$		
: ^{32}P and cytostatics	21	15.1	100	72
Total: without transformation into CMGM	57	24.5	93	87
		$P: = 0.05$		
: with transformation into CMGM	26	14.5	92	65
Period of latency: P. vera→CMGM	26	8.5	–	
Survival after transformation into CMGM	26	2.9	> 48	–

Cytogenetic findings in P. vera with transgression into CML and frequently accompanying myelofibrosis was indicated by the presence of a Ph'-chromosome in 5 of 8 patients (Table 7, see also Table 3). Only 1 patient (case 1, S.H.) had been treated with an overdose of ^{32}P as mentioned above but the 4 others either received cytostatics alone or had had phlebotomies only (2 patients). Further chromosome anomalies are listed in Table 7, but the 3 last cases are remarkable with no aberrations of their karyograms to date.

Finally some results concerning *survival times* and *life expectancy* of patients with P. vera in comparison with the transgression forms into CML and different therapeutic regimes are presented in Table 8.

Discussion

In our study of polycythemic disorders, transgression of P. vera into CML with accompanying myelofibrosis occurred in 30 out of 113 patients or 27% (see also Vykoupil et al. 1980). This transformation was more frequent in elderly patients with long lasting disease (Tables 3, 8) and was characterized by an increase of the leukocyte count in the peripheral blood consistent with subleukemic values (Table 2).

Histopathology of the bone marrow, particularly sequential corings, demonstrated that the evolving fibrosis of late stage P. vera was always connected with an atypical growth of the neutrophilic granulo- and megakaryopoiesis, irrespective of any treatment applied (Table 3). Analysis of the fine structure by light- and electron microscopy further revealed that this transgression towards CML actually resulted in the development of a subtype of myeloid leukemia, the so called chronic megakaryocytic-granulocytic myelosis (CMGM, for more details see Georgii, 1979) with different degrees of fibrotic alterations of the

bone marrow and (agnogenic) myeloid metaplasia of hematopoiesis (CMGM stage I, II – agnogenic myeloid metaplasia with no/or minimal fibrosis or stage III, IV – osteomyelofibrosis/-sclerosis). The relationship of P. vera with these entities, i.e., agnogenic myeloid metaplasia or myelofibrosis/-sclerosis has been frequently discussed and sometimes those disorders have been regarded as "burnt out stages" or the "natural outcome" of P. vera (Lopas et al. 1964; Ikkala et al. 1967; Roberts et al. 1969; Laszlo 1975; Wasserman 1976; Modan 1975; Burkhardt et al. 1979; Ellis and Peterson 1979). The similarity of P. vera in the cases of evolving fibrosis with the so called myelofibrosis/-sclerosis syndrome was emphasized by Lennert et al. (1975) who published an elaborate quantitative study of the reticulin and collagen fibers of the bone marrow in both disorders. Wasserman (1976) developed the concept that P. vera represents a dynamic process in which myeloid metaplasia and leukemia should not truly be classified as complications, but rather stages incident to the natural course and duration of this disorder. In the pertinent literature there are limited data regarding the development of CMGM or "agnogenic myeloid metaplasia" from P. vera. Burkhardt et al. (1969) reported 15 patients of a total of 144 (about 11%) to display CMGM or myelofibrosis respectively during the course of P. vera. Modan and coworkers (review by Modan 1975) found 6% and Silverstein et al. (1974) and Silverstein (1976) 14% (ratio 29/207), considerably less than in our study. This difference of transformation rates may have several reasons: Firstly most patients in the series of Modan (1975) and Silverstein et al. (1974) have been followed by clinical variables whereas in our cases early stages with minimal fibrosis (CMGM II) were detectable by the applied techniques of processing bone marrow biopsies. Further Silverstein et al. (1974) only considered an extensive marrow fibrosis (at least 40% of the cross-sectional area) as being compatible with myelofibrosis – myeloid metaplasia. In comparison with our classification of this disorder (Georgii, 1979) this would mean CMGM III, IV with 7 cases or about 6%, a value close to Modan (1975) or the estimated 5–15% by Silverstein (1976) and Ellis and Peterson (1979).

Most remarkable are however, the 5 cases with a spontaneous transgression into CMGM without cytostatic or radiomimetic therapy, of which two carried the Ph'-chromosome (cases 4 and 5, G.M., V.A.; Table 7). A spontaneous progression of P. vera into myeloid metaplasia (i.e. CMGM) was noticed by Silverstein et al. (1974) in 4 of 25 cases which had only had phlebotomies (as our patients) and pyrimethamine and therefore seems to be an infrequent event in the course of P. vera. In this context the assessment of the relationship between P. vera and CML with myelofibrosis as a sequel of ^{32}P or cytostatic therapy is clearly controversial. There is little evidence that the development of agnogenic myeloid metaplasia and osteomyelofibrosis (i.e., CMGM) can be attributed to this treatment (review by Ellis and Peterson 1979). Our concept that fibrosis in P. vera develops only in the course of a CMGM independently of whether ^{32}P, cytostatic or no treatment at all is applied, confirms the results of Modan and Modan (1968). These authors found no case of so called myeloid metaplasia in their large series of 129 treated patients (38 on ^{32}P and 91 with no radiation therapy) with so called benign erythrocytosis.

Eight patients with the subtype of CML (the so called CMGM) showed the Ph'-chromosome in 5 cases in which the chromosome studies of the bone

marrow was successful. This result should be expected since all these cases displayed the histological and clinical features of myeloid leukemia, which was, however, preceded by P. vera (see also sequential trephine biopsies, Table 3). In the early stages differentiation from P. vera may be difficult, but cytogenetic studies with the finding of a Ph'-chromosome are helpful in establishing the correct diagnosis, since this chromosomal marker is thought to be diagnostic for CML (Rowley 1976). Three similar cases of Ph'-positive CML evolving from P. vera were reported by Hoppin and Lewis (1975) with an review of the pertinent literature. These authors concluded that although uncommon, P. vera may on occasion progress to CML and the likelihood of this occurring by chance alone was assumed to be exceedingly small.

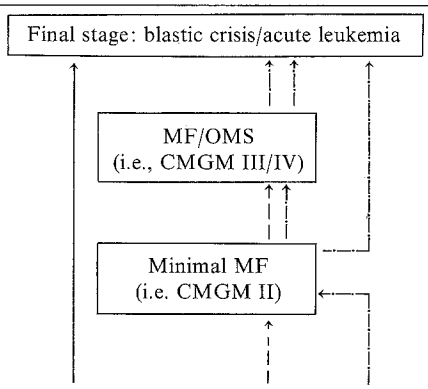
A further related and crucial point in the course and outcome of P. vera is the transformation into acute myeloid leukemia (AML). There is however, no unequivocal agreement as to the precise definition of AML arising from P. vera (reviews by Schwartz and Ehrlich 1950; Masouredis and Lawrence 1957; Ellis and Peterson 1979). The evolution of AML is sometimes regarded primarily or exclusively as sequel of radiomimetic therapy, but despite many clinical data and arguments definitive proof is lacking (Modan 1975; Landaw 1976). There are a very few cases of apparently spontaneous occurrence of AML in patients who only had phlebotomies (Wasserman 1976; Rosenthal and Moloney 1977). The frequency of development of AML is quite low and in the largest series of the Polycythemia vera-Study Group only 4.5% of 426 cases reviewed followed this course (Ellis and Peterson 1979). According to these findings, evolution of acute leukemia seems to present a blastic crisis of CML (or osteomyelofibrosis/-sclerosis/CMGM III, IV) rather than an AML in most patients. This statement not only supports our argument that the so called myeloid metaplasia and osteomyelofibrosis represent a neoplastic disorder or subtype of CML (Georgii 1979) but is further confirmed by the findings of Silverstein et al. (1974). These authors found 10 cases in their series of 207 patients with P. vera who progressed towards AML during the course of disease (mostly treated by ^{32}P); 5 of the 10 patients however, had agnogenic myeloid metaplasia (or a metaplastic phase) before the occurrence of so called acute leukemia. It must be added that these diagnoses had mostly been made by clinical data and not by a combination of sequential corings and cytogenetics (Ph'-chromosome) as in the majority of our patients. Similar results for acute leukemia superimposed on myeloid metaplasia and/or myelofibrosis were observed in the extensive review of Landaw (1976) and comparable findings at least in a few patients, seen in the series of Meytes et al. (1976), Weinfeld et al. (1977) and Rosenthal and Moloney (1977). Although virtually every aspect of the occurrence of acute leukemia in P. vera is controversial there are a few important factors which are believed to have importance in leukemogenesis: maleness, presence of myeloid metaplasia, prolonged survival and a questionable dose-response relationship with ionizing radiation treatment (Landaw 1976).

Concerning the clinical data and survival times or life expectancy in patients with P. vera with and without transgression towards leukemia we can say that the male: female ratio is approximately 1.3:1 in all P. vera patients (Vykoupil et al. 1980) which agrees with the results of large series of the Polycythemia vera-Study Group (Ellis and Peterson 1979). In contrast to this ratio, in reactive

polycythemia there is a thirty fold increase of males possibly due to underlying pulmonary disorders (Vykoupil et al. 1980). The median survival expectancy in our non-selected pool of all patients with P. vera is around 15 years (Table 8), 10 years in the non- or phlebotomy-only-treated cases and about 24 years in patients who received cytostatic or/and ^{32}P therapy. These values are slightly more favorable than those published by Halnan and Russell (1965) and Wasserman (1976). However, it should be mentioned that different therapeutic regimens were applied in our cases which have been derived from various hospitals (see acknowledgements). Therefore a comparison with such a homogenous group of patients as those reported by Wasserman (1976) is only limited in this regard. The length of the latency period (8.5 years) from the onset of P. vera until the transgression into CMGM confirms the clinical data of Landaw (1976) and Silverstein et al. (1974). This is conspicuous for the unfavorable prognosis after transformation into CMGM or myeloid metaplasia (osteomyelofibrosis/-sclerosis): Here a mean survival time of 2.9 ± 1.1 years was observed by Silverstein et al. (1974) in 29 patients which is in complete agreement with the 2.9 years of our cases.

The neoplastic or malignant nature inherent in P. vera is suggested by several facts as discussed in part above: (I) Spontaneous transgression into chronic myeloid leukemia (CMGM or agnogenic myeloid metaplasia) with osteomyelofibrosis/-sclerosis and development of acute leukemia, as a blastic crisis in most cases. (II) Clonal evolution as shown by enzymatic studies of the glucose-6-phosphate dehydrogenase (Adamson et al. 1976; Singer et al. 1979) and the response of the abnormal stem cell line to erythropoietic stimulation (Prchal et al. 1978).

Table 9. Polycythemia vera in the system of chronic myeloproliferative disorders with regard to the pathways of evolution into myeloid metaplasia and myelofibrosis/osteomyelosclerosis and so called acute leukemia



Histopathology	CGL	CMGM	P. vera
Neoplastic cell lineages	one	two	three

Abbreviations: CGL = chronic granulocytic leukemia, CMGM = chronic megakaryocytic-granulocytic myelosis with different stages of myelofibrosis/-sclerosis = CMGM II–IV, MF/OMS = myelofibrosis/-osteomyelosclerosis, P. vera = Polycythemia vera

Similar enzymatic studies revealed the clonal origin of CML (Barr and Fialkow 1973 and Fialkow et al. 1977) and of so called agnogenic myeloid metaplasia (Jacobson et al. 1978); all entities which belong to myeloproliferative diseases and frequently may show transition into each other. In addition disturbance in the phenotypic expression of glutamic-pyruvate-transaminase in P. vera was related to the clonal nature of this disease (Kirkland et al. 1980). (III) Cytogenetic abnormalities in non-treated patients, mostly consisting of aneuploidy and rarely a Ph'-chromosome marker (review by Vykoupil et al. 1980). (IV) Cytological atypia in the development and maturation of all three cell lines, revealed by the elaborate techniques of resin embedded core biopsies and ultrastructural findings (Burkhardt et al. 1969; Thiele et al. 1979; Vykoupil et al. 1980).

Consequently, in the myeloproliferative disorders P. vera may be regarded as a panmyelosis with a neoplastic proliferation of all three cell lineages, erythro-granulo- and megakaryopoiesis, with a natural course insiduously and unpredictably running towards CMGM with different degrees of myelofibrosis/-sclerosis. Because of the mixed cellularity of proliferating lineages in P. vera, transformation into leukemia should involve more than one line, i.e., the neutrophilic granulopoiesis and megakaryopoiesis and therefore results in CMGM rather than in chronic granulocytic leukemia (CGL). Included is the possible occurrence of a blastic crisis (so called acute leukemia). This concept of the position of P. vera and its relationships with other entities in myeloproliferative disease is depicted in Table 9 which summarizes the results of our present study and the findings of the pertinent literature.

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