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Chronic Megakaryocytic Granulocytic Myelosis – CMGM

A Subtype of Chronic Myeloid Leukemia

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Summary. In 1,083 core biopsies of the bone marrow with myeloproliferative diseases 454 cases or 42% were found to have neoplastic megakaryopoiesis. Neoplasia of megakaryocytes was assumed from the conspicuous cytological atypicality revealed by light microscopy, extending and confirming earlier ultrastructural findings. Histopathology of the bone marrow in these patients was described as chronic megakaryocytic-granulocytic myelosis – CMGM – since neutrophilic granulopoiesis is also apparently neoplastic and both cell lineages showed a complete differentiation to mature forms. CMGM should be separated from the chronic granulocytic leukemia – CGL – which consists of only a single line proliferation. The incidence of CGL in our total of 1,083 patients was 25%. Both entities are included in chronic myeloid leukemia – CML – because of the demonstration of the Philadelphia chromosome in the hematopoietic cells of these two groups of patients. Primary or idiopathic thrombocythemia has to be differentiated from CMGM since there is no evidence for malignancy of the granulocytic series.

Key words: Chronic myeloid leukemia – Chronic megakaryocytic granulocytic myelosis – Myelofibrosis, beginning – Histopathology – Philadelphia chromosome.

Introduction

In chronic myeloproliferative diseases, particularly myeloid leukemia (CML) histopathology of core biopsies of the bone marrow frequently reveals specimens with a conspicuous neoplasia of megakaryopoiesis (Georgii and Vykoupil 1976; Hill and Schäfer 1976). However, this is not a novel finding, since the so called megakaryocytic myelosis is a well known entity from individual case reports (review by Georgii and Vykoupil 1972) and has been described by

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several synonyms: aleukemic megakaryocytic myelosis/leukemia (Hewer 1937; Lindeboom 1938; Chien-Nai et al. 1960; Allegra and Broderick 1971; Kajita and Hirokawa 1973; Roessner et al. 1975), megakaryocytic leukemia/myelosis (McDonald and Hamrick 1948; Dougan et al. 1967; Iizumi et al. 1973), acute megakaryocytic myelosis (Rappaport 1966) and megakaryoblastic myelosis/leukemia (Demmler et al. 1970; Bain et al. 1977; Breton-Gorius et al. 1978; Den Ottolander et al. 1979).

Megakaryocytic myelosis is generally accepted to belong into the category of chronic myeloproliferative diseases (Georgii and Vykoupil 1972, 1976) or myeloproliferative syndromes (Burkhardt 1980). In addition, ultrastructural studies have demonstrated findings which suggest a neoplastic or malignant nature for both the granulocytic and megakaryocytic cell lines (Georgii and Thiele 1976; Thiele et al. 1977a, b, c). Consequently, this hematological neoplasia has been coined chronic megakaryocytic-granulocytic myelosis with the abbreviation – CMGM – (Thiele et al. 1977a; Georgii 1979). Although there are many papers published in recent years which discuss this or similar disorders, the relationship of the entity – CMGM – and chronic myeloid leukemia, or other myeloproliferative diseases such as myelofibrosis (MF) or osteomyelosclerosis (OMS) remains questionable (reviews by Block et al. 1975; Laszlo 1975).

In the present study the histopathology of the bone marrow is described in CMGM, the occurrence of the Philadelphia chromosome (Ph′-chromosome) investigated and the results are compared with those for chronic granulocytic leukemia (CGL).

Material and Methods

From our files of referred biopsies of the bone marrow all chronic myeloproliferative diseases have been selected and reviewed independently by three different pathologists. The principal clinical data such as courses of disease, peripheral blood counts and complications like blast crisis, hemorrhages or thrombotic diathesis, infections and cause of deaths, together with the mean age and sex ratio have been compiled from the clinical records but are not recorded in the present paper. All core biopsies of the bone marrow were performed by the method of Burkhardt (Burkhardt 1966) or as trephines after Jamshidi (Jamshidi and Swaim 1971). The bone cylinders obtained were fixed in a solution containing methyl-alcohol-formalin (Schaffer's solution) and were embedded in methyl-methacrylate mixture. Semithin sectioning was done without decalcification and further processing and staining procedures followed the methods described by Vykoupil et al. (1976).

Cytogenetic investigation was often performed from a second biopsy and included hematopoietic tissue and cellular material obtained by aspiration from the hole of the iliac bone after removal of the core, and extruded tissue from particles of the trephine itself. The tissue was mixed with Tc-chromosome medium (Difco Lab., No. 665822) and incubated at 37° C between 2 and 72 h without phytohemagglutinin (PHA) stimulation. Staining was done by conventional methods and the Giemsa banding technique and chromosomal analysis was performed on photographs. Evaluation included a mean of 16 metaphases per specimen with a range between 9–30.

Results

Chronic megakaryocytic-granulocytic myelosis – CMGM – refers to a lesion of the bone marrow which is characterized by a neoplastic proliferation of both the neutrophilic granulopoiesis and the megakaryocytes (Figs. 1b, 5a).

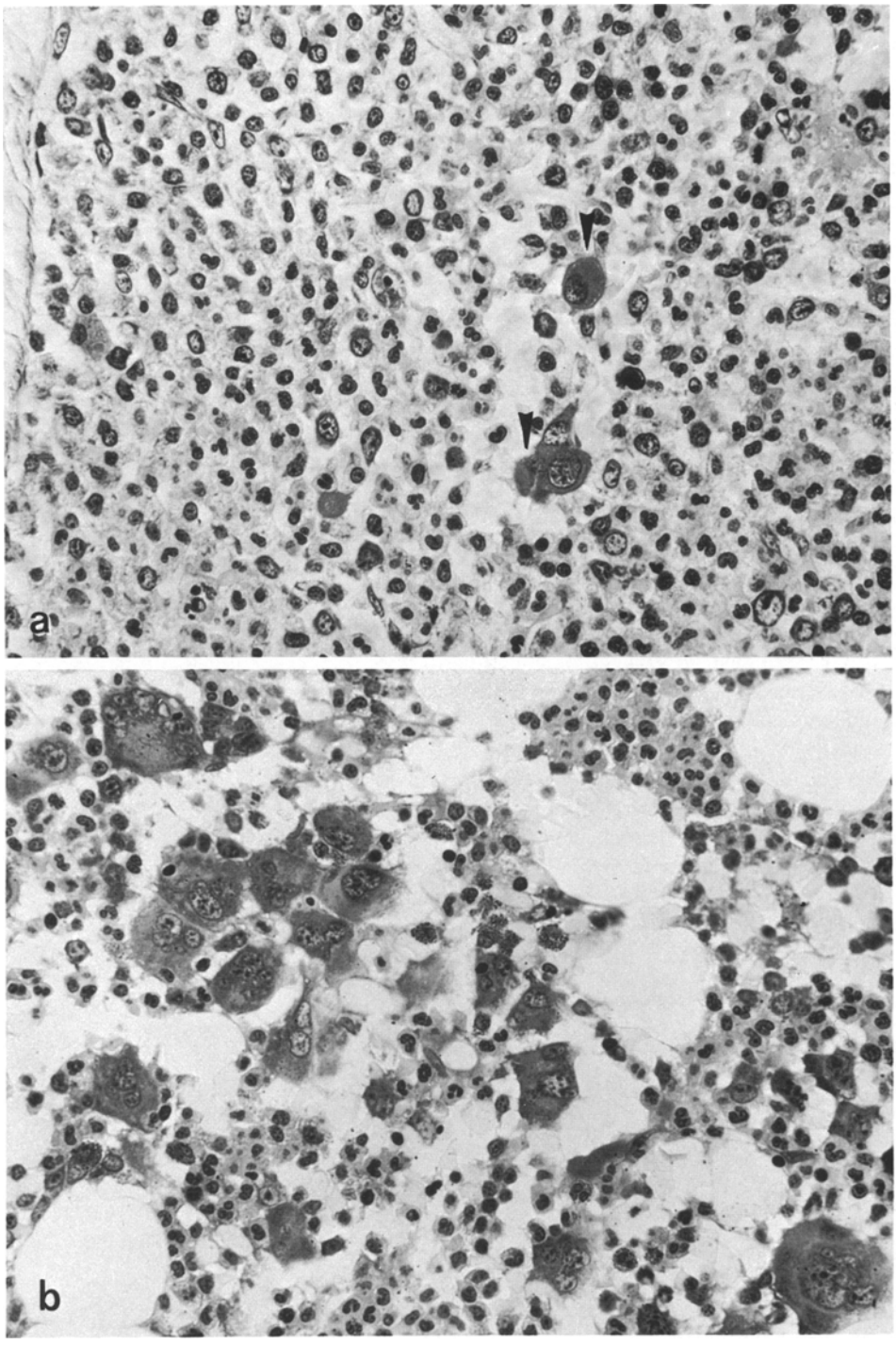

Fig. 1 a, b. Comparison of chronic granulocytic leukemia (CGL) and chronic megakaryocytic-granulocytic myelosis (CMGM). **a** CGL with overall proliferation of fairly differentiated neutrophilic granulocytes starting with precursor cells at the peritrabecular generation zone (*left half*). There are only a few megakaryocytes mostly of small size (*arrow heads*). **b** CMGM with abnormal increase of megakaryocytes showing remarkable clustering and a variety of forms surrounded by proliferating neutrophilic granulocytes, the last comparable with CGL. **a** × 300 – Giemsa; **b** × 280 – Giemsa

In contrast to this growth consisting of two different cell lineages (mixed cellularity) CGL is defined as a disorder with neoplasia of only neutrophilic granulopoiesis. Here megakaryocytes may display a slight to moderate possibly reactive increase (Figs. 1a, 3a).

Among a total of 1,083 cases with chronic myeloproliferative diseases we encountered 42% or 454 specimens which should be diagnosed as CMGM (Table 1). In comparison with this high frequency 25% or 266 cases with granulocytic leukemia – CGL – have been found, and the other subtypes of chronic leukemia are listed in Table 1.

In CMGM *atypicality of megakaryopoiesis* consist *firstly* of cytological anomalies of maturation and *secondly* of an abnormal site of growth. This means dislocation of megakaryocytes in the marrow space. These aberrations of megakaryopoiesis are often more conspicuous than the findings in granulopoiesis, which is increased but completely mature and well differentiated (compare Fig. 1a with 1b).

Cytological atypicalities of megakaryopoiesis are mostly characterized by an abnormal variation of cell sizes with bizarre outlines and similar abnormalities of the nuclei. The latter show irregular shapes and lobulations with a changing content and uneven distribution of chromatin depending on the stage of cellular maturation. These failures in megakaryocyte differentiation are described by the term nuclear-cytoplasmic disorganization (Figs. 2a, b and 4a compared with 4b). There is, further, a remarkable increase of microforms apart from the giant megakaryocytes and many promegakaryocytes and pyknotic cells (naked nuclei). Mitoses are frequently observed (Fig. 2a, b). A critical review of megakaryocyte maturation reveals that this process seems to be partially disturbed or dissociated. There are immature nuclei which are one- or bilobated, contain a finely dispersed chromatin and prominent nucleoli. There may be extensive (Fig. 1b) or, more often, rim-like portions of cytoplasm, producing microforms (Fig. 2a, b). Oversized megakaryocytes are seen with a hyperlobulation of their nuclei with a bizarre stag horn-like appearance and an extended veil-like area of cytoplasm (Fig. 2b). Another abnormality consists of a varying density of

Table 1. Survey of chronic myeloproliferative diseases as revealed in core biopsies from bone marrow during the years 1977–1979. A novel subtype is introduced in comparison with former classifications and presented by the term chronic megakaryocytic-granulocytic myelosis – CMGM

Histopathology	*n*	%
Chr. granulocytic leukemia – CGL	266	25
Chr. megakaryocytic-granulocytic myelosis – CMGM	454	42
Polycythemia vera – P.vera	72	6.6
Myelofibrosis, Osteomyelosclerosis – MF/OMS	252	23.3
Primary (idiopathic) thrombocythemia	5	0.5
Smouldering leukemia	11	1.0
Chr. monocytic leukemia	3	0.3
Others	20	1.8
Total	1,083	~100

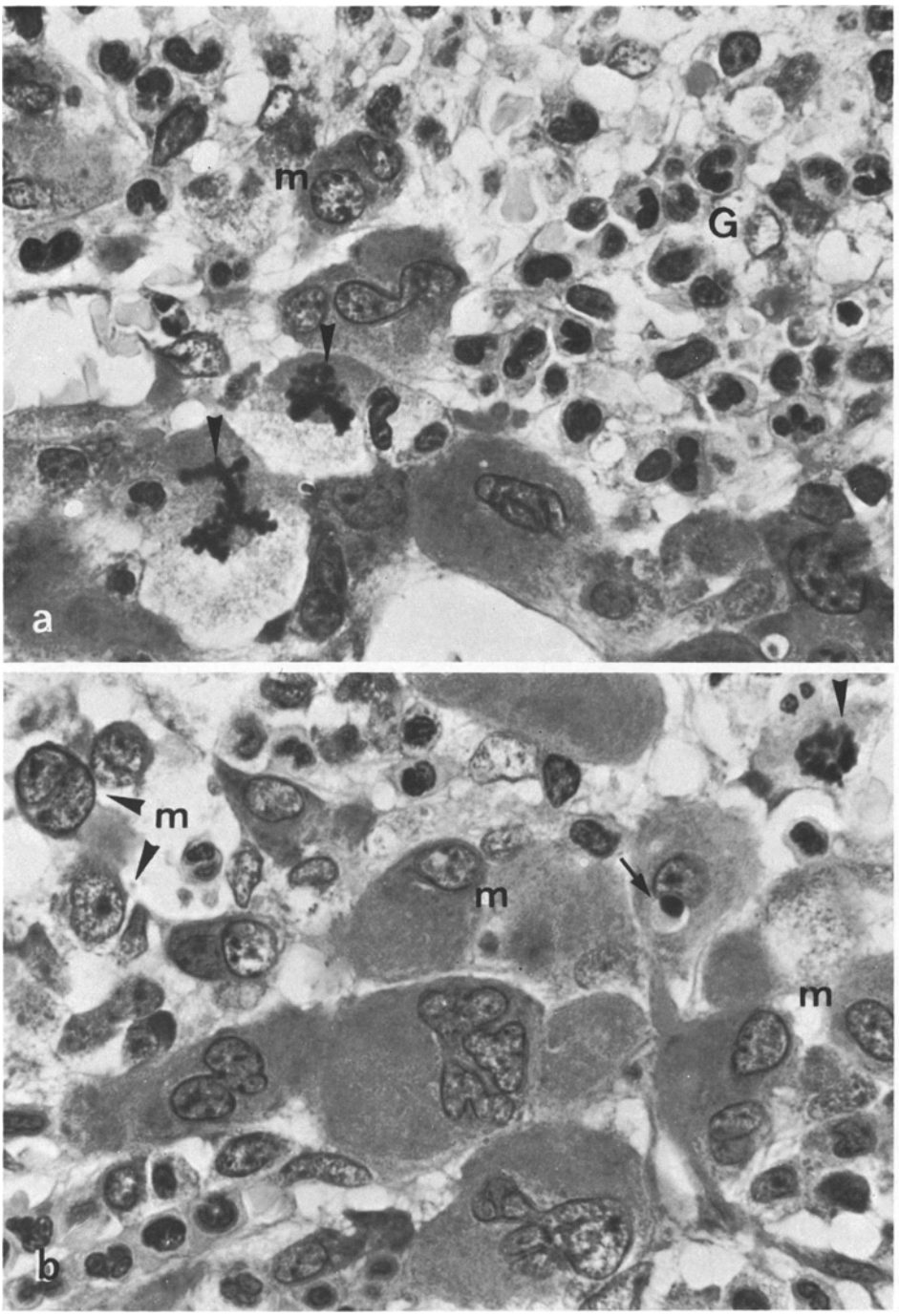

Fig. 2a, b. Atypia of megakaryopoiesis in CMGM. **a** In comparison with neutrophilic granulopoiesis (*G*) megakaryopoiesis displays a variety of forms with large cells and lobated nuclei besides many mitoses (*arrow heads*) and microforms (*m*). **b** Abnormalities of maturation consist of frequent megakaryoblasts (*m*) and microforms with a round or bilobulated nucleus and a small portion of cytoplasm lying nearby oversized megakaryocytes with hyperlobulation of their nuclei and extensive area of cytoplasm. A mitosis is indicated by an arrow head and a normoblast is engulfed by a megakaryoblast (intussusception, *arrow*). **a** and **b** ×780 – Giesma

the cytoplasm after routine staining methods. This is probably due to a lack of specific granules, glycogen and membranes of the demarcation system and may therefore indicate another failure of normal cellular differentiation (Fig. 4a). A frequent finding is an intussusception of segmented granulocytes or normoblasts which is comparable with an ameboid engulfment (Fig. 2b).

Abnormal dislocation of megakaryopoiesis means an extension of this lineage towards the osseous trabecula, the original generation zones of neutrophilic granulopoiesis, and a remarkable clustering around the sinuses in the marrow centers (Figs. 1b, 6a and especially 5b).

It should be emphasized that *neutrophilic granulopoiesis* is conspicuously increased in all cases with CMGM and displays an uninterrupted maturation starting in the peritrabecular areas and extending continuously towards the venous sinusoids of the marrow centers (Fig. 1b, 5a, b and 6a). This pattern of growth is identical with CGL, particularly since here a complete and step-wise maturation to segmented neutrophils is also recognizable and may be traced from the bone trabeculae to the central areas of the marrow spaces (Figs. 1a, 3a). Even precursor forms including myeloblasts and promyelocytes are not impressively increased and a proliferation of blasts over 10% clearly implies impending transformation or blast crisis which is shown in Fig. 3a for CGL. Erythropoiesis may be prominent in CMGM but does not disclose any abnormal proliferation of erythroblasts or proerythroblasts and shows no macro- or megaloblastic features or increase of sideroblasts or -cytes.

Chronic megakaryocytic-granulocytic myelosis – CMGM – has to be clearly distinguished from another entity, primary (essential, idiopathic) thrombocythemia. This disease is characterized by an enormous hyperplasia of megakaryopoiesis only with no gross abnormalities of maturation (Fig. 3b). In contrast to the obvious atypias of megakaryocytes in CMGM the primary thrombocythemia displays no severe polymorphism but a shift to the left and a conspicuous assembly in the surroundings of sinuses with predominance of precursor forms. The mature cells contain a reticulum-like fuzziness in their cytoplasm, probably consistent with the demarcation membrane system and regularly lobated nuclei (Fig. 4b). The fundamental difference to CMGM is that granulopoiesis is not neoplastic or even hyperplastic. Primary thrombocythemia is therefore compatible with single line neoplasia of the hematopoietic parenchyma, i.e., the megakaryocytes, and may thus be termed chronic megakaryocytic myelosis or – CMM.

The mesenchymal compartment shows only slight alteration, especially regarding its content of reticulin fibers. There is one fraction of patients where practically no changes may be found, while others display a minimal increase of the argyrophilic skeleton which can be recognized by polarization of silver impregnated specimens (Fig. 6b). The beginning of this minimal degree of fibrosis is located in the surroundings of the sinus walls in the centers of the marrow space and in the walls of the paratrabecular terminal sinusoids – sinus wall sclerosis (Figs. 5b, 6a). Thus augmentation of reticulin fibers is patchy and disseminated with concentration around the vessels, at least in the early stages. The earliest detectable alteration in one given area consists of a longitudinal course of 3–6 single fibers almost without cross links and thus without a lattice structure (Fig. 5a). In between this loose network of reticulin fibers megakaryo-

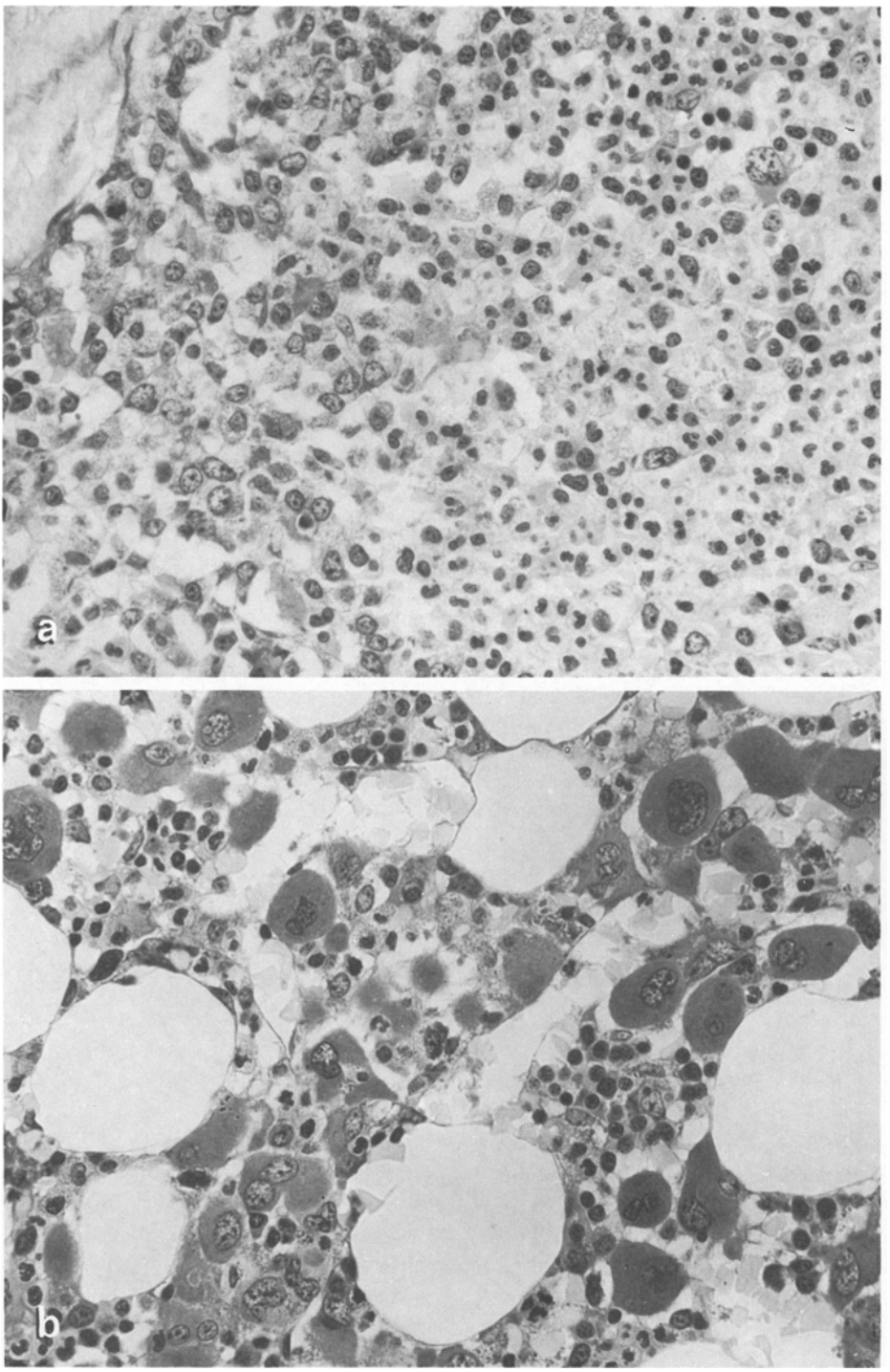

Fig. 3a, b. Comparison of chronic granulocytic leukemia (CGL) and chronic megakaryocytic myelosis (idiopathic thrombocytosis, CMM). **a** CGL in early blastic crisis which shows a proliferation of myeloblasts starting at the generation zone (peritrabecular, *left half*) and progressing towards the intermediate area of the marrow space with arrest of segmentation (hiatus leukaemicus). **b** CMM with an enormous proliferation of apparently mature megakaryocytes between clusters of granulopoiesis and erythropoiesis with no remarkable defect of differentiation (compare with Fig. 4b). **a** and **b** × 320 – Giemsa

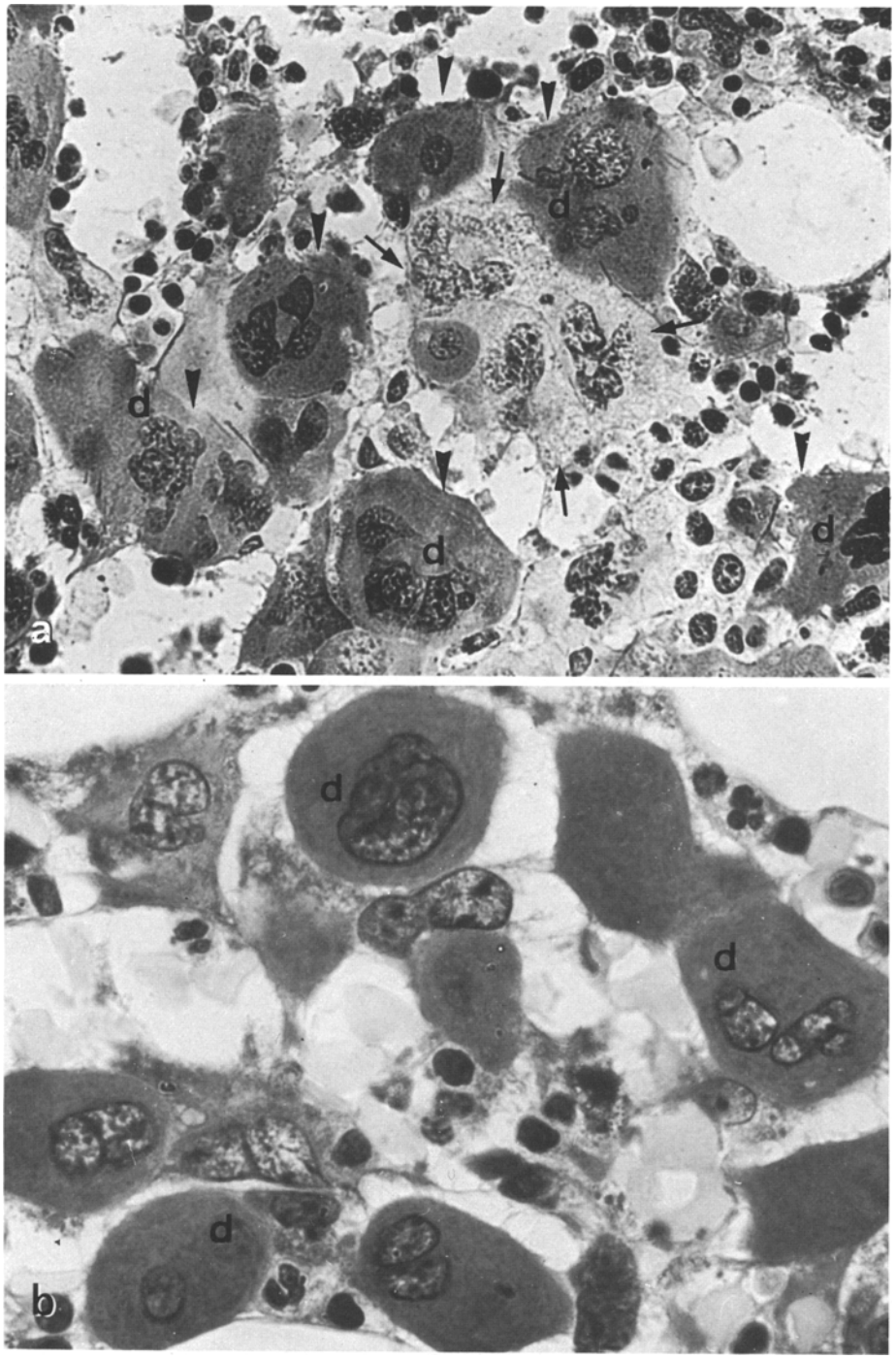

Fig. 4a, b. Comparison of megakaryopoiesis in CMGM and CMM. **a** CMGM with an abnormal variety of megakaryocytic differentiation showing large cells (*arrow heads*) with a fuzzy cytoplasm probably corresponding to the demarcation membrane system (*d*). There is also a cluster of micro-forms and megakaryocytes with a light cytoplasm (*arrows*) apparently due to a lack of specific granules and demarcation membranes which account for the density. **b** CMM with large mature megakaryocytes and precursor forms. The lobated nuclei containing megakaryocytes display a network or fuzziness of their cytoplasm corresponding to the demarcation membrane system (*d*). **a** × 620 – Giemsa; **b** × 780 – Giemsa

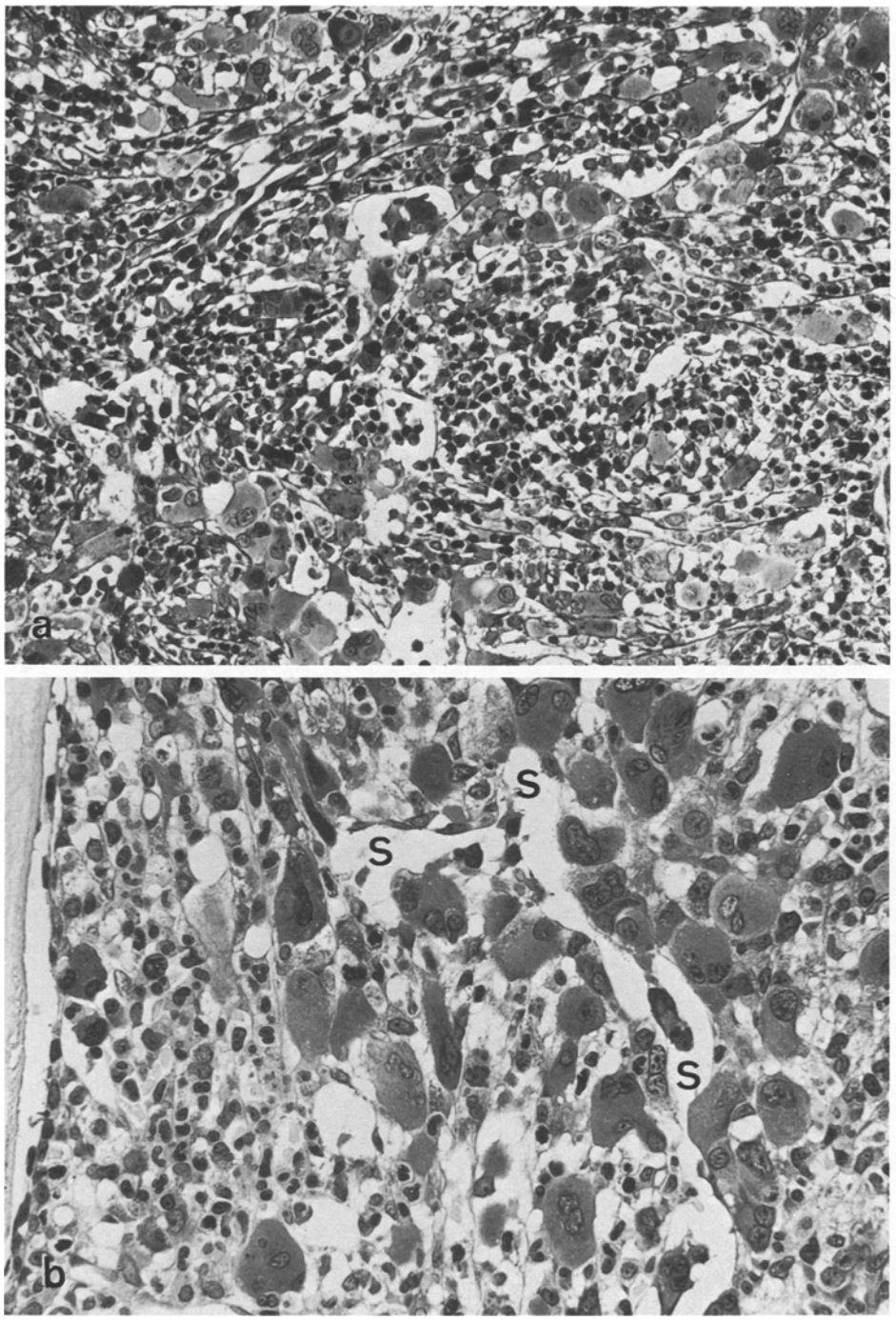

Fig. 5a, b. CMGM with commencing fibrosis (i.e., CMGM stage II, see text). **a** Minimal to slight increase of reticulin fibers enveloping clusters of megakaryocytes, neutrophilic granulopoiesis and erythropoiesis. **b** Perisinusoidal assembly of megakaryocytes with close attachments to the sinus wall and bulging forward into the lumen (*S*). Note the variety of megakaryocytic differentiation as expressed by size, lobulation, and density of the nuclei. Around the trabeculum (*left half*) there is only a small rim left of the neutrophilic granulopoiesis which is otherwise dispersed by the abnormal megakaryocyte proliferation. **a** × 180 – Gomori; **b** × 320 – Giemsa

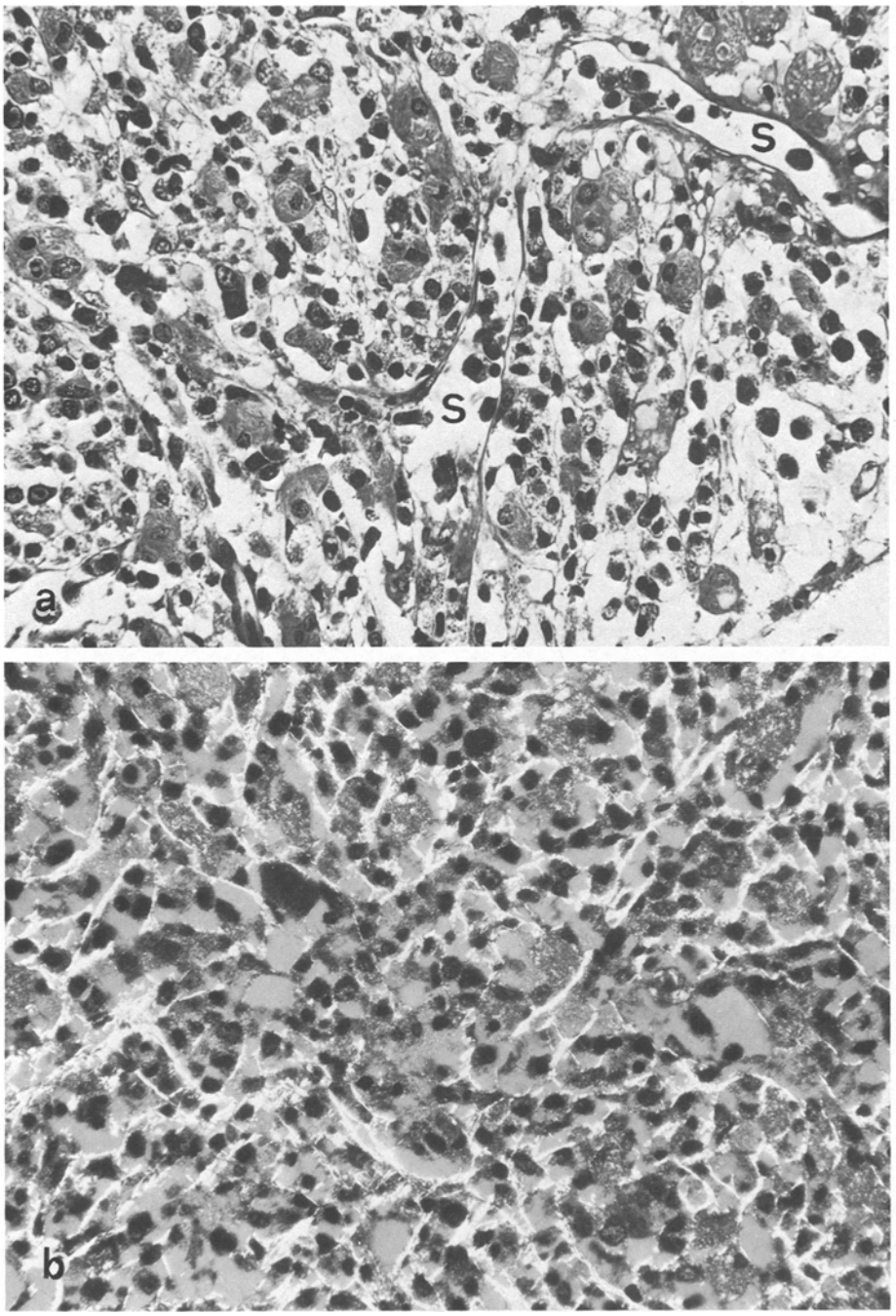

Fig. 6a, b. Reticulin fibers in CMGM (i.e., CMGM stage II, see text). **a** Numerous megakaryocytes, mostly microforms entrapped by a meshwork of reticulin fibers which are increased around a sinus (*S*), so called sinus wall sclerosis. **b** Polarization of silver impregnated specimen shows a dense network of small bundles of fibers with dark shadows of cells in between. **a** and **b** × 280 – Gomori

cytes are trapped. Especially around sinuses a clustering of many, often atypical and small forms, may be seen together with sclerosis of the sinus walls (Figs. 5b, 6a). However, as stated above only polarization of silver impregnated specimens of the bone marrow is able to show those findings. Collagen fibers which are easily recognizable without these methods or without polarization are indicative of the initiation of MF as endophytic bone formations characterize OMS.

Among the patients with CMGM from the years 1973–1980 there were 159/376 or about 42% without any increase in reticulin fibers, while 217/376 or about 58% revealed a scattered augmentation. In conclusion CMGM may be separated into two subtypes: The first group of bone marrow specimens has no increase of reticulin fibers at all, whereas the second displays a minimal fibrosis which is only recognizable by special methods of staining and light microscopy. Therefore, the first group is termed CMGM I or stage I and the latter CMGM II or stage II.

The remaining structures of the mesenchymal compartment are not remarkably altered in typical CMGM. There is no increase of the siderin storage in the (histiocytic) reticulum cells and occasionally there may be minimal to moderate arrangements of plasma cells along the capillaries or sinusoids. Scattered plasma and mast cells can be seen in the interstitium. However, focal lymphocytic infiltrates or small lymph nodes of the bone marrow occur and are the most characteristic lesion of the mesenchyme in CMGM. As a summary of these

Table 2. Schematic presentation of the histopathology of the bone marrow in chronic myeloproliferative diseases; + indicates a conspicuous increase compared with normal findings

Classification	Granulopoiesis	Megakaryopoiesis	Erythropoiesis	Focal lymphocytes	Reticulin fibers
CGL	+	0	0	0	0
CMGM I	+	+	+	+	0
CMGM II	+	+	(+)	+	+

Table 3. Cytogenetical findings in bone marrow cells from 41 patients with chronic granulocytic leukemia – CGL – versus 38 patients with chronic megakaryocytic granulocytic myelosis – CMGM – demonstrating a similar frequency of the Philadelphia chromosome in the latter

Histopathology	Ph′-chromosome positive		Clonal evolution		Aneuploidy				Metaphases examined (mean)
					Total		C/D-group		
	Ratio	Percentage	Ratio	Percentage	Ratio	Percentage	Ratio	Percentage	
CGL	25/27	93	7/27	26	15/27	56	11/27	41	16
in blastic crisis	13/14	93	3/14	21	8/14	57	7/14	50	18
CMGM	17/27	63	4/27	15	11/27	41	5/27	19	14
in blastic crisis	7/11	64	0/11	0	8/11	73	5/11	45	17
Total	62/79	78	14/79	17	42/79	53	28/79	36	16 (range 9–30)

results a schematic presentation of the histopathology of the bone marrow in CMGM is shown in Table 2 in comparison with CGL.

An evaluation of the results from *cytogenetic investigations* which are given in Table 3 demonstrates that in CMGM the Ph′-chromosome occurs in a comparable frequency to that seen in CGL. It has to be added that 3–4 metaphases exhibited the Ph′-chromosome in an average count of 16 per marrow specimen. Clonal evolution and other aberrations, especially of the C- and D-group chromosomes (in many cases trisomy +8) can be found in CMGM, as in CGL. Further, an identical aneuploidy was encountered in 3 of the 10 Ph′-negative CMGM patients, whereas only 5 of them showed normal karyograms. In CGL-patients who were Ph′-negative, an aneuploidy of C- and D-group-chromosomes has been observed as the only anomaly.

Discussion

The histopathology of the bone marrow alterations termed CMGM is in general agreement with findings of the case reports on the so called megakaryocytic myelosis (reviews by Georgii and Thiele 1976; Georgii 1979). Our findings are based on the evaluation of many samples of bone marrow which have been processed by a refined histological technique and a chromosomal analysis of 38 cases of this special subtype. However, this paper presents three arguments to stimulate and renew discussion of a more exact classification of myeloproliferative diseases.

1. The striking frequency of CMGM in comparison with CGL.
2. The neoplastic nature inherent to both neutrophilic granulopoiesis and megakaryopoiesis.
3. The general occurrence of the Ph′-chromosome in CMGM in a comparable frequency to that seen in CGL.

The frequency of CMGM is 42% in our material compared with 25% of granulocytic leukemia (CGL). Similar material was studied by the same technical procedure (Hill and Schäfer 1976) who reported a comparable incidence of megakaryocytic-granulocytic leukemias. Nevertheless, both their and our material is undoubtedly selected since it consists partially of reference specimens and of cases where a sternal puncture of the bone marrow and aspiration was unsuccessful (dry tap), particularly in those patients with minimal fibrosis (CMGM stage II).

The neoplastic nature of both granulo- and megakaryopoiesis implicates a mixed cellularity type of myelosis in contrast to the one line malignancy, granulocytic leukemia – CGL – which is often conveniently called chronic myeloid leukemia (CML). Neoplasia of the neutrophilic granulopoiesis in the cases of megakaryocytic leukemia (or myelosis) has been neglected or not mentioned (Prechtel et al. 1977; Burkhardt 1970, 1980). The malignant nature of the granulopoiesis is asserted for quantitative and qualitative reasons. Major arguments for this assumption are disturbances of maturation such as the pseudo-Pelger-Huët anomaly frequently seen by light microscopy. In confirmation and extension of these results ultrastructure displays an aberration of nuclear organization with formations of blebs and atypical loops besides arrest and defects of the

maturation procedure of the different types of granules. These findings of an abnormal fine structure have been recorded in detail in earlier studies (Thiele et al. 1977b) and correspond to identical alterations of neutrophilic granulocytes in CGL (review by Georgii and Thiele 1976). The simultaneously occurring neoplasia of granulocytes and megakaryopoiesis provides the evidence to support calling this hematological disorder mixed cellularity myelosis and this changes the meaning of the previously used term megakaryocytic myelosis. It should be added that comparable lesions of histopathology and ultrastructure which have been described by us (Thiele et al. 1977a, b, c; Georgii and Thiele 1976) are actually shown in several illustrations of other papers (Bain et al. 1977; Breton-Gorius et al. 1978; Den Ottolander et al. 1979).

The results of karyograms in those two myeloproliferative diseases point to a common pathogenetic origin since the Ph′-chromosome has been demonstrated to occur in CMGM as in CGL but with some differences in frequency. This difference of frequency of occurrence may be explained by difficulties of method, which are caused by the altered bone marrow condition in CMGM, the minimal fibrosis. Consequently cell material should be obtained by squeezing the cores of the biopsies or at least the biopsy particles, which was not performed in all cases of this study. By aspiration of liquid marrow from the hole of the removed trephine, the yield of cells of the hematopoietic tissue may be too small to trace the Ph′-chromosome among the metaphases which are to be karyotyped. This may be the main reason why a Ph′-chromosome was detected only very rarely in megakaryocytic myelosis (Dougan et al. 1967) or in so called megakaryoblastic leukemia (Bain et al. 1977). The Ph′-chromosome consists of a translocation between chromosome 9 and 22 (t (9q+, 22q−)) and occurred in 85–94% of patients as evaluated from larger series (reviews by Rowley 1978, 1979; van den Berghe et al. 1978). It is generally accepted that it represents a fundamental chromosomal aberration characteristic for CML or CGL respectively (Rowley 1976). Our high incidence of Ph′-positive cases with CGL corroborates this statement and proves the correct histological diagnosis of this diseases. A control group with 14 AML patients displayed aneuploidy with predominant anomalies of the C- and D-group chromosomes in a percentage of cases which is in agreement with other studies (Mitelman et al. 1976; Alimena et al. 1977; Rowley 1976, 1979; van den Berghe 1978). There was no Ph′-positive AML with a clinical acute leukemia of myeloblastic or lymphoblastic origin, as has infrequently been observed in adults (Bloomfield et al. 1977). Further support for the similarity of karyotypes in both entities (CGL and CMGM) is the occurrence of a Ph′-chromosome with clonal evolution in about 25% of cases in these two diseases. In our series no missing Y-chromosome was encountered in Ph′-positive CML or in AML in males which is an uncommon anomaly and which seems to be associated with an unfavourable prognosis (Lawler et al. 1975; Hossfeld and Wendehorst 1974; Sakurai and Sandberg 1976). Results of chromosomal analysis implicate that CMGM and CGL represent two different aspects of the same underlying disorder or subtypes of CML. This leads to the assumption that CML may be encountered at least histologically as a one cell line neoplasia – chronic granulocytic leukemia – CGL – or may evolve into a mixed cellularity neoplasm of megakaryocytes

and granulocytes – CMGM. The latter would mean ambivalent or biphasic differentiation and development from a common progenitor or committed stem cell which inherited the malignant tendency but did not loose potency for further cellular differentiation. This concept is in agreement with the hypothesis of a stem cell transformation as shown by enzymatic studies in CML (Fialkow et al. 1977; Fialkow 1979), Polycythemia vera (Adamson et al. 1976) and so called myeloid metaplasia consistent with myelofibrosis (Jacobson et al. 1978). However, we never observed CMGM arising from a CGL in our material, as was reported by Prechtel et al. (1977). Finally it should be considered whether such a different appearance in histopathology really warrants two confusing terms – CGL and CMGM – for one disease, CML, since both carry the Ph′-chromosome. An answer may be given only after completion of a review of all clinical data and the statistical evaluation of both entities to see whether there are differences in hematological findings and clinical outcome which justify our own nomenclature.

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