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Histopathology of the bone marrow in toxic myelopathy

A study of drug induced lesions in 57 patients

R. Krech and J. Thiele
Pathologisches Institut der Medizinischen Hochschule
Konstanty-Gutschow-Straße 8, D-3000 Hannover 61, Federal Republic of Germany

Summary. Following the introduction of numerous highly effective drugs in recent decades, haematologists are confronted with a panmyelopathy or "toxic myelopathy" originating from the exhibition of certain therapeutic regimens. Among 16,711 trephines referred to us in the last 5 1/2 years, 57 cases or 0.34 percent were found to have clear evidence of lesions caused by the ingestion of potentially toxic agents. The evaluation of the histopathology shows two groups of alterations which concern the haematopoietic parenchyma as well as the mesenchyme of the bone marrow. Different degrees of cellularity ranging from aplasia to regenerative hyperplasia and a pronounced mesenchymal reaction with proteinaceous oedema, perivascular plasmacytosis and frequent necrobiosis of neutrophilic granulocytes or cellular debris are the most conspicuous features. However, the histopathology of the bone marrow described gives no indication of the specific drug responsible and no specific suggestion of any group of drugs. Generally the histopathology allows the recognition of lesions which are induced by the toxicity of these agents. Therefore a bone marrow biopsy should be included in the diagnostic procedures whenever a toxic lesion is suspected of causing haematological disorders, particularly in all cases of uncertain pancytopenia.

Key words: Myelopathy – Drug effect – Toxicity – Histopathology – Bone marrow

Introduction

Following the introduction of numerous highly effective and aggressive drugs in recent decades, clinicians are increasingly confronted with haematological disorders which may range from granulocytopenia to anaemia and even pancytopenia (Bithell and Wintrobe 1967; Baudach 1972; Remmele

Offprint requests to: R. Krech at the above address

1972; Hausmann et al. 1974; Heimpel et al. 1975; Heimpel and Kern 1976; Alter et al. 1978; Kelton et al. 1979; Islam et al. 1980). However, only infrequently has attention been directed towards the histopathology of the bone marrow underlying these lesions (Heimpel et al. 1975; Shimamine et al. 1981; Fischer and Fohlmeister 1984). In this context, considerable difficulties have been reported which prevent an unequivocal classification of histological features related to certain drugs. This is mainly due to two reasons, first, the difficulty of obtaining precise data from the clinical history of those patients and second, the simultaneous application of a variety of therapeutic agents (Glogner and Heni 1976; Liu et al. 1978; Chang et al. 1979; Druart et al. 1979; Ell et al. 1982). Moreover, the diverse components of an ingested medicament which may have a toxic effect on the haematopoiesis provide further difficulties in the identification of the suspected agent (Heimpel and Kern 1976; Ring 1982). The routinely performed evaluation of bone marrow biopsies in patients with the peripheral findings of a refractory anaemia or pancytopenia reveals lesions which are thought to be of an exogenous or toxic origin. The present study was focussed on this problem of whether therapeutic or casual applications of drugs may generate alteraltions of such nature that they are recognizable by the histopathology of bone marrow biopsies.

Patients and methods

Bone marrow biopsies. Core biopsies of the marrow were performed by the method of myelotomy (anterior iliac crest; Burkhardt et al. 1982) or as trephines (posterior iliac crest) following Jamshidi's technique (Jamshidi and Swaim 1971). The bone cylinders obtained were fixed in a solution containing methyl-alcohol-formalin (Schaffer's solution) and were processed by embedding in a methyl-methacrylate mixture.

Semithin sections of 3 micron were done without decalcification and further processings and staining methods (Giemsa, Goldner's trichrome, silver impregnation after Gomori, Prussian blue reaction and methyl-green-pyronine) followed the procedures described elsewhere (Vykoupil et al. 1976).

Selection of patients. Among the 16,711 trephine biopsies of the bone marrow referred to us in the last 5 1/2 years (January 1977–July 1982), 173 cases (1.03%) were found with clinical evidence for a marrow failure, i.e. mild to severe pan- or bicytopenia (aplastic or hypoplastic anaemia). For technical reasons, sufficient haematological data and the clinical histories of patients were available only in certain hospitals affiliated with the Medical School in the vicinity of Hannover and therefore included a representative fraction of 69 patients from the total of 173. In only 22 cases of these 69 patients was the clinical finding of cytopenia thought to be generated from possible drug intake, whereas in the remaining 47 there was no primary indication for an exogenous origin by the clinicians, but characteristic features of the bone marrow were found which were suggestive for a toxic lesion. In all 69 patients the clinical data have been extracted from the files which were suitable to establish both drug ingestion and corresponding haematological alterations. Particular regard was taken of a possible abuse of drugs, an overdose or an abundant therapeutic application of medicaments. Finally, in 5 patients an improvement of pancytopenia started shortly after cessation of drug ingestion. The sequences of haematological findings were followed at least 2 months after the performance of the trephine biopsies and the suspected toxic agents are listed in Table 1. Twelve patients who originally entered this study had to be discarded since the thorough evaluation of the clinical findings revealed inflammatory diseases like hepatitis and chronic rheumatoid arthritis together with a drug intake. Thus these cases were considered not to

Table 1. List of drugs which are generally suspected by the clinicians to induce a bone marrow failure in regard to the specification of our 57 cases

Analgesics – antirheumatic drugs		26
Gold compounds	3	
Indometacine	7	
Phenylbutazone	3	
Antibiotics		13
Chloramphenicol	2	
Sulfonamides	6	
Penicilline	4	
Psychopharmaca		7
Phenothiacines	4	
Anti-gout drugs		3
Allopurinol	3	
Diuretics		2
Thyrostatic drugs		2
Anticonvulsives		2
Phenytoin	2	
Antidiabetics		1
Antiarrhythmics		1
Antihypertensive drugs		1
Environmental toxic agents		5
Total		57

present clear cut evidence for an exclusively toxic-exogenous cause of the bone marrow lesions and consequently of the total of 69 patients, 57 finally remained for the present study. These 57 cases included 22 male and 35 female patients with a median age of 58 years (range 12–88 years). An evaluation of all morphological features described in the following text as toxic myelopathy displayed no relation to the sex or any age group.

Results

Cellularity

As a general but not a particularly characteristic feature of a drug related toxic myelopathy, a variable decrease in cellularity is encountered (Table 2a; Figs. 1b; 2a, b; 3a). Haematopoiesis may be either partially hypoplastic or almost completely absent (aplastic) and replaced by extended fatty tissue. These latter findings were present in only 14 of our 57 patients (25%). This agreed with the haematological findings which, in the majority, were represented by a mild cytopenia. In only a few cases was aplastic anaemia diagnosed by the clinicians. This rather monotonous appearance of a cellular depletion may be interrupted by the occurrence of a regenerative proliferation of haematopoiesis which is either dispersed or in clusters, as "hot spots" around the vessels (Figs. 2a and 3c). In the following specification of the characteristic features of the histopathology, haematopoiesis and myeloid stroma are described separately for a more distinct presentation, al-

Table 2a. Haematopoiesis: Survey of prominent features which are found by a semiquantitative evaluation of the histopathology from cores of bone marrow in 57 patients with proven ingestion of myelotoxic drugs

Cellularity of parenchymal compartment (with specification of main lesions)		Cases	Percent	Comments
Aplasia	all 3 series	14	25	
	Erythropoiesis mainly	1	2	
	Granulopoiesis mainly	4	7	Decrease in cellularity
	Megakaryopoiesis mainly	2	4	as a general but not peculiar characteristic
Hypoplasia	all 3 series	33	58	feature of drug related
	Erythropoiesis mainly	8	14	toxic myelopathy
	Granulopoiesis mainly	12	21	
	Megakaryopoiesis mainly	4	7	
Hyperplasia	all 3 series	7	12	Regenerative
	Erythropoiesis mainly	6	11	haematopoiesis
	Granulopoiesis mainly	3	4	probably in a
	Megakaryopoiesis mainly	4	7	phase of recovery
Normoplasia	all 3 series	3	5	Additional and
	Erythropoiesis mainly	2	4	remarkable
	Granulopoiesis mainly	–	–	alterations of
	Megakaryopoiesis mainly	7	12	the mesenchyme

Table 2b. Myeloid stroma: Survey of prominent features which are found by a semiquantitative evaluation of the histopathology from cores of bone marrow in 57 patients with proven ingestion of myelotoxic drugs

Alterations of mesenchymal compartment	Cases	Percent	Comments
Oedema			
Proteinaceous type	46	81	Most marked lesion together with plasmacytosis
Sclerosing type	7	12	Increase of reticulin fibres probably leads to fibrosis in final stages
Fibrosing type	1	1.8	Non-neoplastic reaction
Cellular infiltration			
Plasma cells	30	53	Very frequent alterations of the mesenchyme
Mast cells	11	19	
Eosinophils	5	9	Allergic hyperergic reaction
Other alterations			
Necrobiosis	23	40	Phagocytosis of necrotic neutrophilic granulocytes (cellular debris)
Haemosiderin deposits	7	12	Hyperplasia of phagocytic reticulum cells – some patients with prior transfusion –

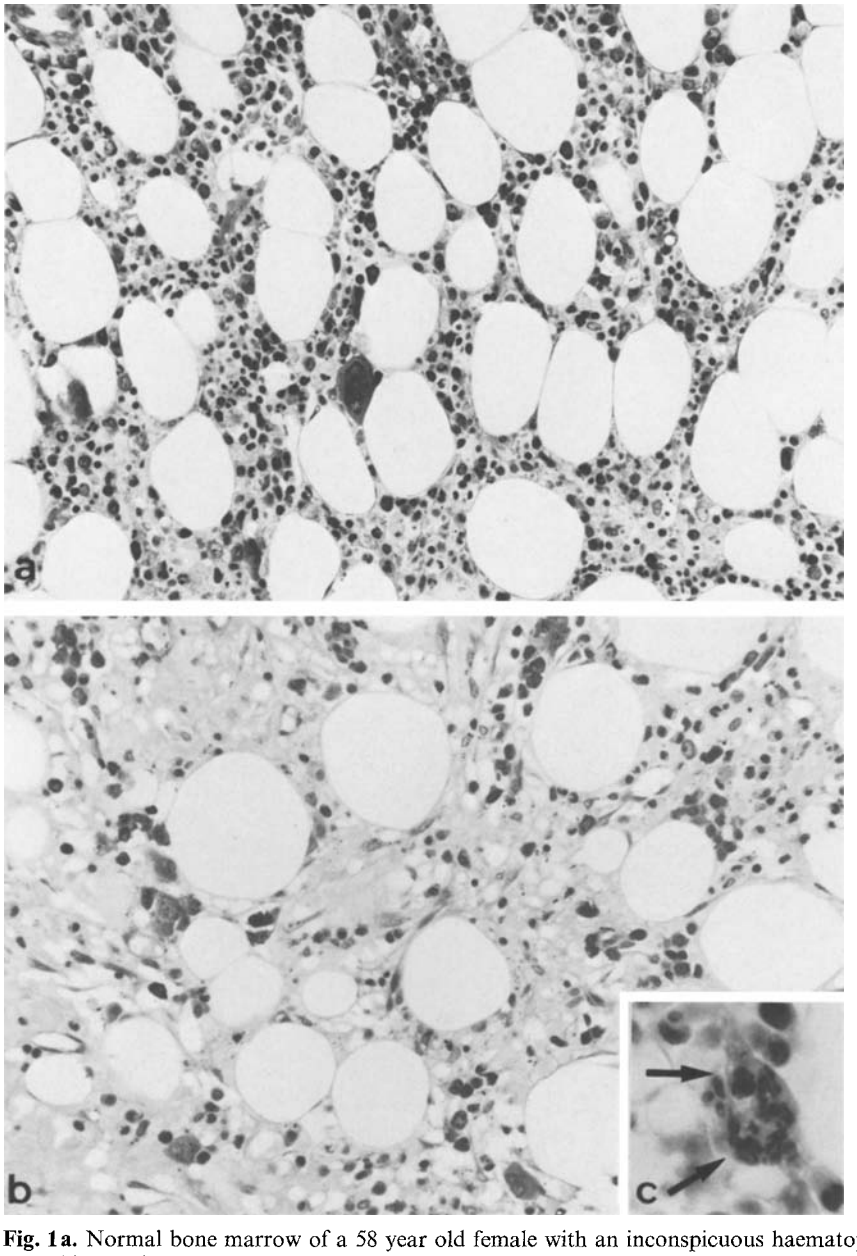

Fig. 1a. Normal bone marrow of a 58 year old female with an inconspicuous haematopoiesis. **b** Striking oedema of a proteinaceous type and reduced haematopoiesis. Focal regenerative proliferation of haematopoiesis after ingestion of Phenylbutazone. **c** Necrosis of neutrophilic granulocytes forming clusters and cellular debris (so called necrobiosis) which are engulfed by histiocytic reticulum cells (*arrow*). Giemsa **a** × 250; **b** × 350; **c** × 420

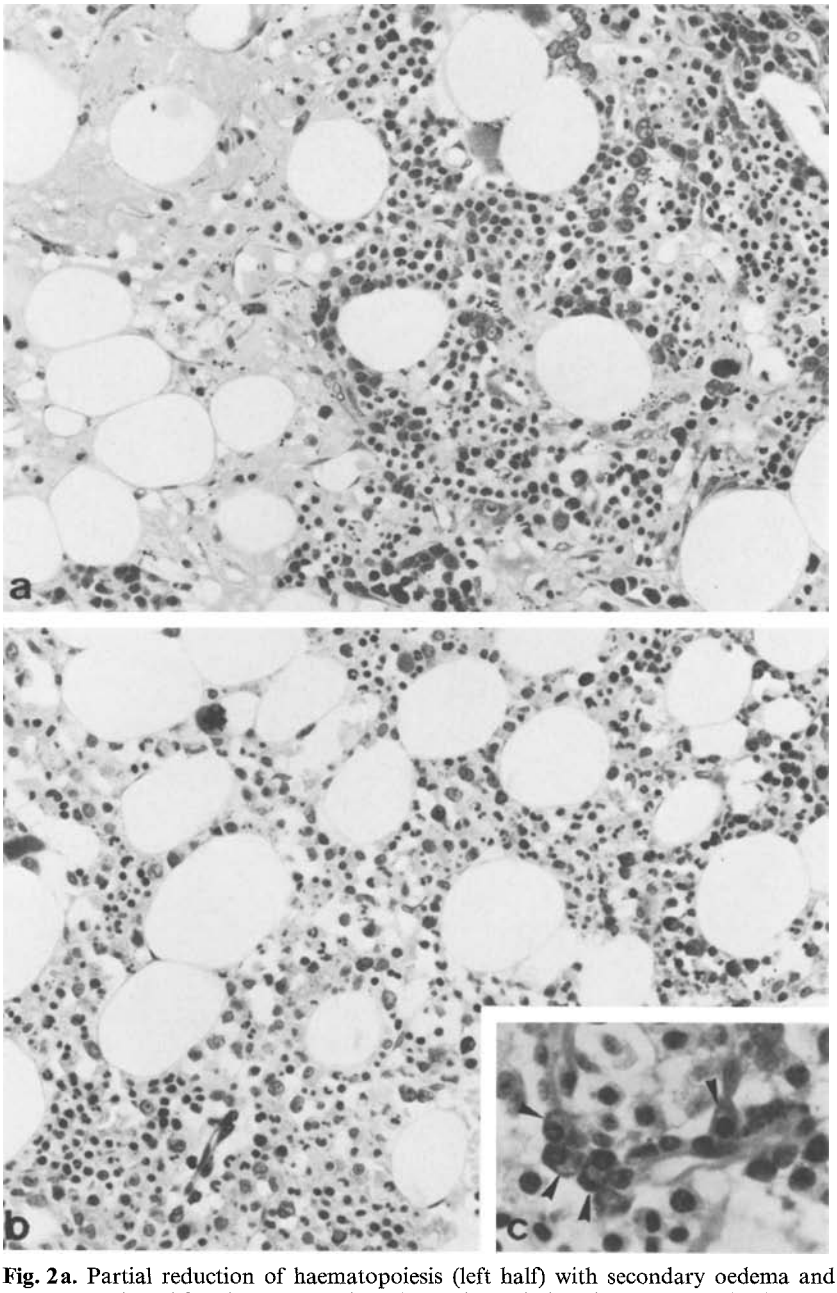

Fig. 2a. Partial reduction of haematopoiesis (left half) with secondary oedema and haemorrhage. Focal proliferation, predominantly erythropoiesis, with many erythroblasts in clusters or "hot spots" after ingestion of Phenylbutazone. **b** Toxic myelopathy after intake of Allopurinol displaying prominent changes of the mesenchymal compartment and a left shifted haematopoiesis without a remarkable decrease of cellularity (45 year old male). **c** Perivascular plasmacytosis showing a deployment of mature plasma cells (arrow heads) attached to the vessel wall. Giemsa **a** × 250; **b** × 250; **c** × 420

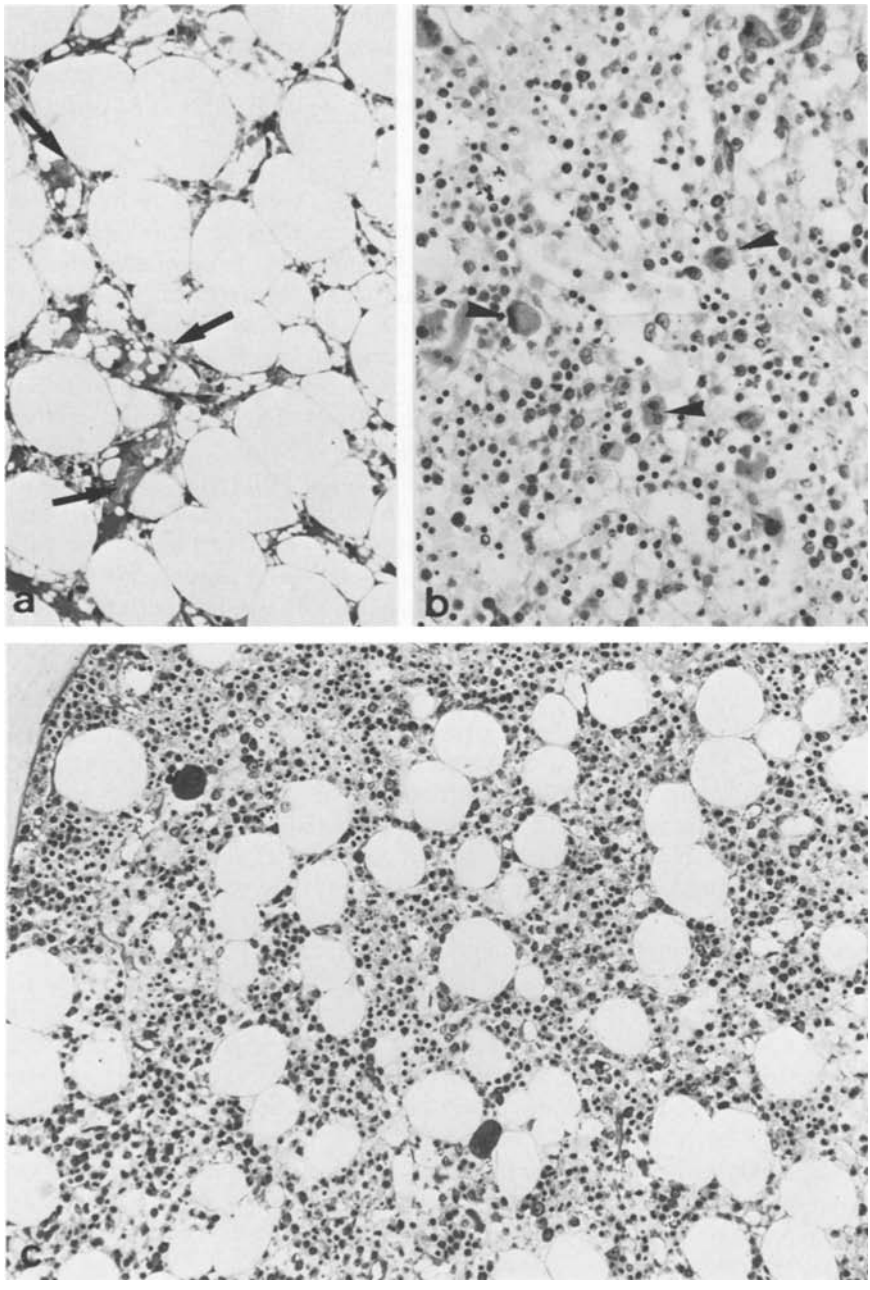

Fig. 3a. Total aplasia of haematopoiesis after ingestion of Phenylbutazone. Patchy oedema (arrow) is dispersed among the fat cells and the scarce remnants of haematopoiesis. **b** Hypocellularity of the bone marrow induced by Chloramphenicol. Noticeable are the microforms of megakaryocytes (arrow heads) which are thought to present early stages of maturation (12 year old boy). **c** Pronounced proliferation of haematopoiesis, particularly the erythropoiesis following drug-induced myelopathy (abuses of analgesics) consistent with a so called phase of regeneration (55 year old female). Giemsa **a** × 250; **b** × 250; **c** × 230

though alterations of both compartments generate the lesions regarded as toxic myelopathy. Changes in the mesenchymal compartment are usually most pronounced whereas the haematopoiesis may show various degrees of cellularity (total aplasia to regenerative hyperplasia) and very different compositions of cell lineages.

Haematopoiesis (parenchymal compartment). A pronounced reduction of the granulopoietic cell lineage is found in 16 of 57 cases and precursors are obviously reduced in number. Although remnants of the granulopoiesis are detectable along the spongy trabeculae, there seems to be an increase in the number of promyelocytes. Only a few residual mature polymorphonuclear granulocytes are observed in the central spaces of bone marrow around the vessels. The erythropoiesis exhibits relatively extended islets containing many erythro- and some proerythroblasts, but a reduced number of more mature normoblasts as "hot spots" (Figs. 2a and 3c). This feature is not evident in the total or partial aplasia of the bone marrow, but only in those cases with a hypocellular haematopoiesis. Megakaryocytes often display a remarkable pleomorphic appearance in addition to their hyperplasia. There is a prominence of microforms which are thought to present early stages of development or a left-shifting (Fig. 3b) and sometimes possibly due to disturbances of maturation, giant or so called overaged forms are present.

Myeloid stroma (mesenchymal compartment). The alterations of the interstitium – that is the soft tissue between the haematopoiesis – are marked by oedema (46 from 57 patients), necrobiosis or phagocytosis of cellular debris by histiocytic reticulum cells (23 from 57 patients) and a prominent perisinusoidal plasmacytosis (30 from 57 patients) (Table 2b). In only a few cases with a prolonged history of drug ingestion are some lymph nodules in the marrow seen, with large germinal centres containing many phagocytic histiocytes, in some instances. Patchy oedema which is rich in proteinaceous material is frequently dispersed among the fat cells and the scarce remnants of haematopoiesis (Figs. 1b, 2a and 3a). Occasionally a minimal increase in silver impregnated reticulin fibres occurs in the neighbourhood of the oedema compatible with the initiation of reticulin fibre sclerosis (scler-oedema). Besides the remarkable proliferation of histiocytic (phagocytic) reticulum cells with coarse of finely granulated deposits of haemosiderin, there is a striking appearance of phagocytosis of neutrophilic granulocytes and their nuclear residues (Fig. 1c). In the perivascular space around the sinusoidal vessels a deployment of plasma cells can be observed which becomes particularly evident following staining with methyl-green-pyronin (Fig. 2c). A clustering of eosinophilic cells or mast cells in the vicinity of sinuses is not very conspicuous. The various alterations of the haematopoietic and the mesenchymal compartment of the bone marrow following drug induced marrow insufficiency are summarized in the schematic presentation in Tables 2a and 2b.

Haematological data. A survey of the peripheral blood values in comparison with the major alterations of the bone marrow revealed some striking results. In 31 patients with a histological lesion of all 3 cell lineages of the haematopoiesis in the bone marrow (aplasia or hypoplasia), only 24 cases showed a corresponding pancytopenia in the peripheral blood. The remaining 7 patients displayed an alteration of one line in the peripheral blood count. In contrast to this discrepancy, concurrent findings were always encountered when only one lineage was affected, i.e. thrombocytes and neutrophilic granulocytes correlated in histopathology and the peripheral blood. However, 9 cases remained where this correlation between bone marrow and peripheral blood counts was not clearly evident. The temporal relationships of drug ingestion and the occurrence of bone marrow lesions are very difficult to assess exactly. When calculated grossly from the clinical data those patients with a total aplasia and particularly granulocytopenia (Table 2a) showed a period of manifestation ranging between 5 and 21 days. Regenerative hyperplasia and normoplasia was observed predominantly in cases with a history of drug intake about 3 and 18 weeks. However, in 10 patients with a severe aplastic anaemia the causative toxic agents were applied about 16 weeks before presentation without evidence of a haematopoietic recovery. It should also be mentioned that the temporal development of marrow lesions of clinical cytopenia was independent of the components of the ingested medicaments (Table 1).

Discussion

The clinical symptom of pancytopenia may be encountered in a variety of entities which can range from osteomyelofibrosis/-sclerosis and acute leukaemia without peripheral leukocytosis and sometimes be caused by an extensive metastasis to the bone marrow.

However, a significant proportion of the cases with severe bone marrow failure or so called hypoplastic panmyelopathy originates from variable aetiologies mostly of unknown pathogenesis (Gmür 1980). A clinically important group which represents the majority is caused by toxic agents (Heimpel and Kern 1976; Heimpel and Heit 1984). There are two main types of drugs which may be responsible for the disease: cytostatic drugs or immunodepressive agents are bound to cause an obligatory depression of the bone marrow. This type of drug however, never results in a sustained insufficiency, but rather in a transient and reversible lesion that is clinically controllable (Islam et al. 1980). Another group of drugs which generates a panmyelopathy independently of the applied doses and only in sensitive people. These agents include substances mainly from the large group of antirheumatics and analgesics (Siegmeth 1971; Wohlenberg 1972).

It can be concluded from our findings that the histopathology of bone marrow failures following the application of these facultative toxic substances shows uniform lesions which are independent of the suspected agent. In addition to the different degrees of cellularity or depression of the mar-

row, mesenchymal reactions with proteinaceous oedema, perivascular plasmacytosis and frequent necrobiosis are very peculiar and prominent features. This monotonous response to various exogenous lesions presents similar histopathological features to those that one may observe after application of cytostatics in acute leukaemias with complete remission (Islam et al. 1980; Krech et al. 1982). These cases with alterations generated by chemotherapy display merely quantitative not qualitative differences, when compared with those lesions induced by facultative myelotoxic agents. Further they offer the unique opportunity to study the pathodynamics of marrow changes which are difficult to follow closely by haematological data. The quantitative differences between facultative and obligatory myelotoxic drugs may be induced not only by a varying effect of the dosage. Cytotoxic drug regimens rarely cause irreversible changes, but these are more frequently seen after certain drugs i.e. chloramphenicol, analgesics. Analysis of the histopathology of marrow specimens in toxic myelopathy further displays that, in contrast to Burkhardt (1970 and 1975), we were not able to place our patients into precise categories, i.e. into cases with predominantly allergic reaction patterns (prominent eosinophilia) and into those with distinctive signs of a direct toxic lesion (complete depletion of bone marrow). Moreover, the histopathology of the bone marrow as described by us does not allow a specification of the kind of drug or group of drugs that might be causative without the knowledge of the clinical history. However, the morphological features permit the recognition of lesions caused by toxic agents. A valuable diagnostic aid is the characteristic mesenchymal alteration which can be easily assessed using the technique of methacrylate embedding and semithin sectioning (Burkhardt et al. 1982). A comparison of haematological data with the findings of histopathology demonstrates that there is good correlation between peripheral blood values and alterations in the bone marrow. The discrepancies which are encountered in some cases may probably be referable to the time lag of haematopoietic regeneration and release of cells into the circulation. However, preliminary results suggest that depression of the haematopoiesis and also regeneration may follow a focal or discontinuous pattern throughout the bone marrow space as revealed by postmortem findings from necropsies at various sites of the skeleton in such patients. Consequently even a large core of the iliac crest may not offer a representative insight into the state of haematopoiesis, which may also explain some of the disparate results between peripheral blood counts and histopathology. Our findings emphasize that a bone marrow biopsy should be included in the diagnostic procedures, in all cases of uncertain pancytopenia with a clinically suspected toxic origin.

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