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Erythromyelosis

(Morbus Di Guglielmo).

Review and Report of a Case in a Benzene (Benzol) Worker.

By

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While erythroblasts (*i.* e., immature, nucleated erythrocytes) are seen not infrequently in the blood of newborn children and infants, normally as well as even after mild infectious disease., their occurrence in adults in relatively large numbers is nearly always a sign of disfunction of erythropoiesis, a reaction to a serious toxic attack on the organism, or evidence of a reparative or compensatory measure on the part of the organism.

Table 1.

Survey of the More Important Diseases in Adults associated with an Increase in the Production or Occurrence of Erythroblasts in the Bone Marrow or Blood Stream.

I. With preponderant erythroblast production in the bone marrow:
- a. *Reparative or compensatory.*
  1. Hemolytic anemias (congenital or acquired forms, in infectious diseases or poisoning with benzene (benzol) and its derivatives, sulphonamide, acetanilide, etc.).
  2. Remission in simple acute or subacute anemias.
- b. *Disturbances in the maturation of erythrocytes.*
  1. Pernicious anemia (increasing in degree with decreasing hemoglobin percentage).
  2. Sprue.
- c. *Neoplastic.*
  1. Acute erythromyelosis (morbus Di Guglielmo).
  2. Chronic erythromyelosis (Di Guglielmo, Heilmeyer, Schöner).
  3. True erythroleukemia.
  4. Terminal erythroblastosis in polycythemia (partly due to extramedullary erythropoiesis).

II. With preponderantly extramedullary erythroblast production resulting from changes in erythropoiesis in the bone marrow.
1. Calcinosis of the bone marrow, myelomatosis, etc.
2. Symptomatic erythroleukemia, *i.* e., compensatory erythroblastosis in leukosis.
3. Osteosclerosis.
4. Panmyelophthisis, aplastic anemia.

Even in the absence of any sharp borderline, the morbid conditions with increased occurrence of erythroblasts in the blood stream may roughly be divided into two main groups according to whether the erythroblast production be mainly intramedullary or extramedullary. A thorough study and definition of these conditions has been possible only after the introduction of biopsy of the bone marrow. In hemolytic anemias and in remissions of simple, acute or subacute anemias the erythroblast production represents a reparative or compensatory measure on the part of the organism. Here, presumably, the production of the red blood cells proceeds so rapidly that full maturity of these cells is not attained. In infectious diseases or other toxic conditions erythropoiesis may conceivably take place in response to a stimulus, possibly in order to effect a compensation. In pernicious anemia and sprue the appearance of megaloblasts in the blood stream is due to disturbances of maturation leading to extramedullary erythropoiesis.

In [illegible], as a rule, the erythroblastosis is reversible once the toxic irritant is eliminated, the anemia abolished, or the specific anti-anemic factor provided. In the »neoplastic erythroblastoses» the position is quite different: Here we meet with acute or chronic erythromyelosis and erythroleukemia, sometimes also the terminal stage in polycythemia vera.

In 1917—1926 Giovanni Di Guglielmo was the first to try *to* elucidate the clinical picture he designated as erythemia, or erythromyelosis, as this morbid condition later has been called.

The principal symptom of this disease was a severe and progressive anemia terminating fatally.

The blood stream presented a great number of erythroblasts, originating from a primary, isolated, proliferative change in the erythropoietic system with very slight tendency to maturation of the cells, and in which the leukopoietic system did not take part. The bone marrow was filled with cells belonging to the erythropoietic system, and other medullary elements were suppressed, partly or completely. Further, proliferating erythropoietic tissue was found in the liver, spleen and lymph nodes and other organs. In spite of the enormous activity of the erythropoietic tissue, the erythrocytes matured only sparsely, and the new-formed erythrocytes were imperfect and had a shorter life-span than ordinary erythrocytes. The destruction of these was increased and the production lowered. A resemblance can thus be noted to megaloblastic anemias. The megalocytes have also a shortened lifetime.

Besides the anemia the clinical findings consisted in leukopenia, thrombocytopenia, moderate enlargement of the liver and spleen, intermittent fever, slight jaundice and a hemorrhagic diathesis. The acute form might terminate fatally within a few weeks.

In 1940 Moeschlin published a critical review of the cases reported up *to* that time and came to the conclusion that only 5 cases conformed *to* the criteria set up by Di Guglielmo, namely: besides the two cases reported by Guglielmo, 3 cases reported by Lazarro, Benedetti & Paradiso. Later, 2 cases were described by Lüdin and by Israëls. In addition, Heilmeyer and Schöner, and Lüdin have reported cases having a more chronic course. Whether the disease map be classified under

one or other form will depend me think on the maturing tendency in the proliferating erythropoietic tissue. In addition to the acute »pure» erythromyelosis cases of so-called »true erythroleukemia» have been described by Guglielmo and other Italian hematologists and also by others e. g., Blackburn and Lajtha, Moeschlin, and Lüdin. In these cases the bone marrow presents a combined proliferation of both the erythropoietic and leukopoietic system leading to erythroblastosis as well as myeloblastosis. This condition should not be mistaken for *symptomatic erythroleukemia* in which the erythroblastosis is mainly due to compensatory extramedullary production of red blood cells because the medullary erythropoiesis has been suppressed or inhibited by the leukopoietic tissue. Tho conclusive evidence of true erythroleukemia is claimed to Le the much higher erythroblast percentage in the bone marrow than in the blood stream whereas the opposite applies to eymptomatic erythroleukemia.

Guglielmo considered erythromyelosis analogous to leukosis — something Papperheim bad been looking for as early as in 1911. Also Guglielmo mentioned that Ellermann in his studies on transferable chicken leukosis had succeeded in producing such a type. Malignant erythromyelosis occurs but seldom, for which reason it has been described ouly exceptionally in the textbooks and this may perhaps be one of the reasons why the diagnosis is not made frequently.' In this connection it will be appropriate to refer to Handbuch der Inneren Medizin (Bergmann and Staehelin) in which Heilmeyer recognizes erythromyelosis as a malignant lesion.

As to the differential diagnosis, hemolytic anemia has to be taken into consideration and — before the introduction of liver therapy — also pernicious anemia. Perhaps cases of erythromyelosis may have been included among the vague clinical pictures as Jaksch-Hayem's anemia. leukemia. aleukemia hemorrhagica Franck, and others. Like leukosis. malignant erythromyelosis is also taken to be a neoplastic lesion, the eliciting factor of which has remained obscure to the above-mentioned authors. So it is of considerable interest that in benzene (benzol) poisoning it has been possible to demonstrate pronounced hyperplasia of the erythropoietic system with clinical features corresponding to those of acute erythromyelosis (Mallory, Gall and Brickley).

Such a case has been admitted to the Medical Department E of Frederiksberg hospital, Copenhagen, apparently the first case of this kind described in Denmark.

Case Record.

The patient was a gas-worker 60 ~ears old (Rec. So. 753/51). Parents did of old age, 8 sib, all well.

The patient had always felt well until December 1950. when he started to feel constantly tired, lost appetite, lost weight. and became readily dyspnoeic, and also dizzy.

On admission 10/2 51 he was very pale and slightly cyanotic. So definite abnormality could be demonstrated on examination of the heart and lungs, no enlargement oi the liver, spleen or lymph nodes. So petechiae seen.

16/2 51: percentage hemoglobin about 52; red blood count 2.6 millions. Colour index about 1. White blood count about 3.700; thrombocyte count about 18,000. Icterus index: 12.

8/3 51: 1st sternal puncture which gave the striking result shown in table 2. The marrow showed an enormous increase in the erythropoietic tissue which by far exceeded anything we had previously seen even in severe hemolytic anemia. On comparison of the graphic presentation (Fig. 1) with the numerical values for the normal erythropoietic system obtained by counting 400 cells of the »white system« and at the same time counting elements of the erythropoietic system (showing the distribution of the latter to be a few proerythroblasts, somewhat more basophil erythroblasts, with eosinophil erythroblasts in the majority) the red blood picture presented by our patient was completely reversed, with an enormous tendency towards proliferation, especially in the number of proerythroblasts.

The blood stream showed a pronounced degree of erythroblastosis. (Fig. 2.) Our first impression was that this might perhaps be a case of severe hemolytic anemia, and hence efforts were made by further examination to prove or refute this possibility. The osmotic resistance of the erythrocytes was found to be normal. The icterus index was slightly increased (Table 3). Prothrombin index 64. Bleeding time 5 min. Göthlin's capillary resistance test: 5 petechiae. No irregular antibody was demonstrated; and no Rh subtype antibody. Blood group: 0. Rh neg. Coombs test negative. Liver functional test: thymol 0.0%0. Takata-Ara test normal. Urine: + urobilinogen.

Table 2.

Differential count of smears from sternal puncture. (400 cells counted.)

	16/2 51	8/3 51
Myeloblasts	[illegible] %	12.25 %
Promyelocytes	3.50 %	5.75 %
Neutrophil myelocytes	12.25 %	19.50 %
Eosinophil myelocytes	3.25 %	6.25 %
Basophil myelocytes	0	0
Metamyelocytes and stab cells	13.75 %	12.50 %
Polymorphonuclear leucocytes	7.75 %	5.50 %
Eosinophil leucocytes	2.25 %	2.75 %
Basophil leucocytes	0	0
Lymphoblasts	0	0
Lymphocytes	47.25 %	23.25 %
Monocytes	0	0
Plasmacells	0.25 %	3.25 %
Megakaryocytes		0.25 %
Reticulum cells	5.50 %	6.75 %
Per 400 cells of »the white system« were found:		
Proerythroblasts (mitoses: 16/2 = 66, 8/3 = 174)	1,040	1,853
Early basophil erythroblasts (mitoses: 16/2 = 21, 8/3 = 65)	565	1,075
Late eosinophil erythroblasts	80	102

The reticulocyte values were at first from low to slightly increased; later they were quite low.

The diameter of the erythrocytes, however, measured between 2—3 and 9—10 microns, and they often differed greatly from the normal by the occurrence of oval forms and pronounced anisochromia.

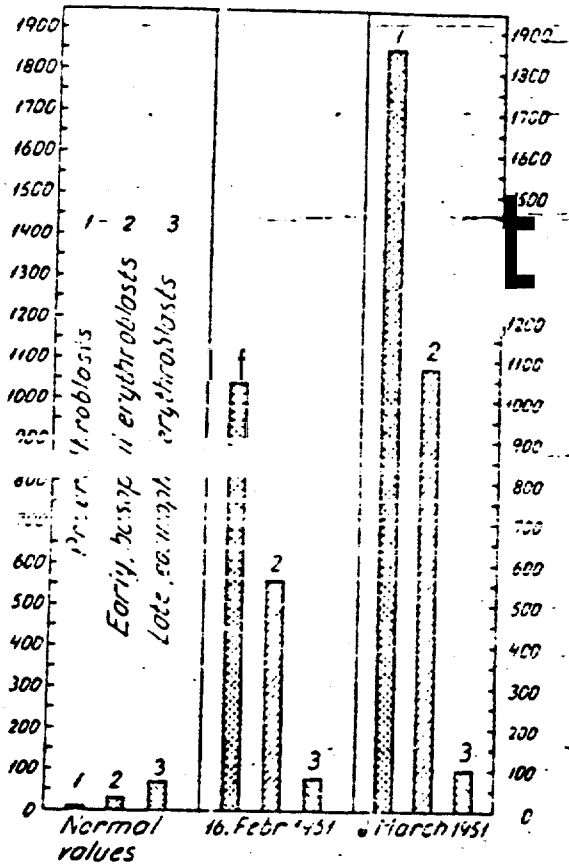

Fig. 1. Sternal puncture countings diagrammatically in relation to normal counting.

Table 3.

	Quantitative fragility test.						
	17/2	20/2	7/3	12/3	20/3	27/3	3/4
Beg. Hem.	0.46	0.50	0.48	0.46	0.46	0.44	
Tot. Hem.	0.34	0.34	0.34	0.34	0.32	0.32	
	Icterus Index						
	12	12	12	10	15	10	10
	Serum iron						
	0.151						

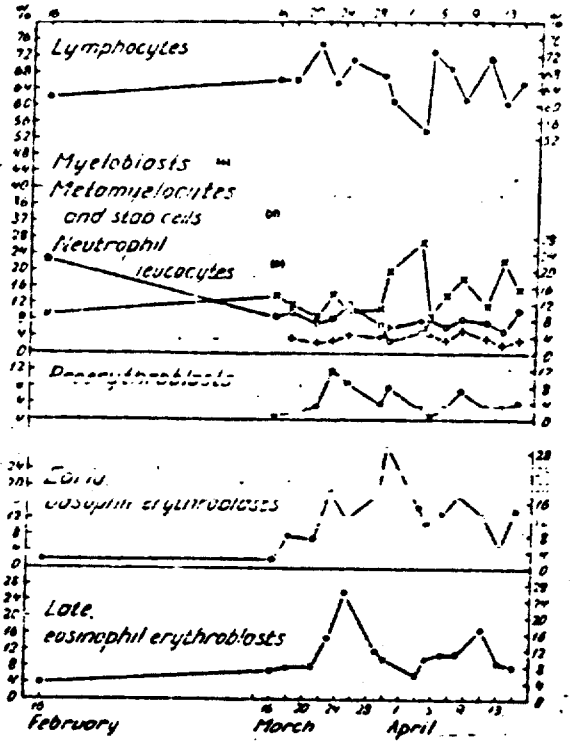

Fig. 2. Percentage of nucleated cellular elements in the peripheral blood during the disease.

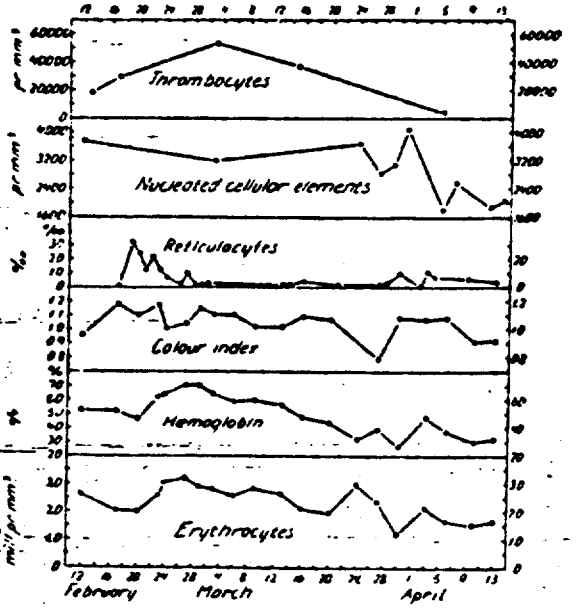

Fig. 3. Hemoglobin, index colour and corpuscular elements during the disease.

Having discussed the clinical picture of the lesion we realized that here we were faced by a condition we had not seen before and we considered the possibility of erythromyelosis.

[illegible] 2nd sternal puncture, which gave similar findings as the first, only more pronounced. In particular the proerythroblasts, varying in size between 12 and 22 microns, were a dominant feature showing many mitoses and also polynuclear forms (paraerythroblasts).

Furthermore the proliferating tendency and cell atypia were most marked among the proerythroblasts — a feature also mentioned by Guglielmo and by Ludin. On com-

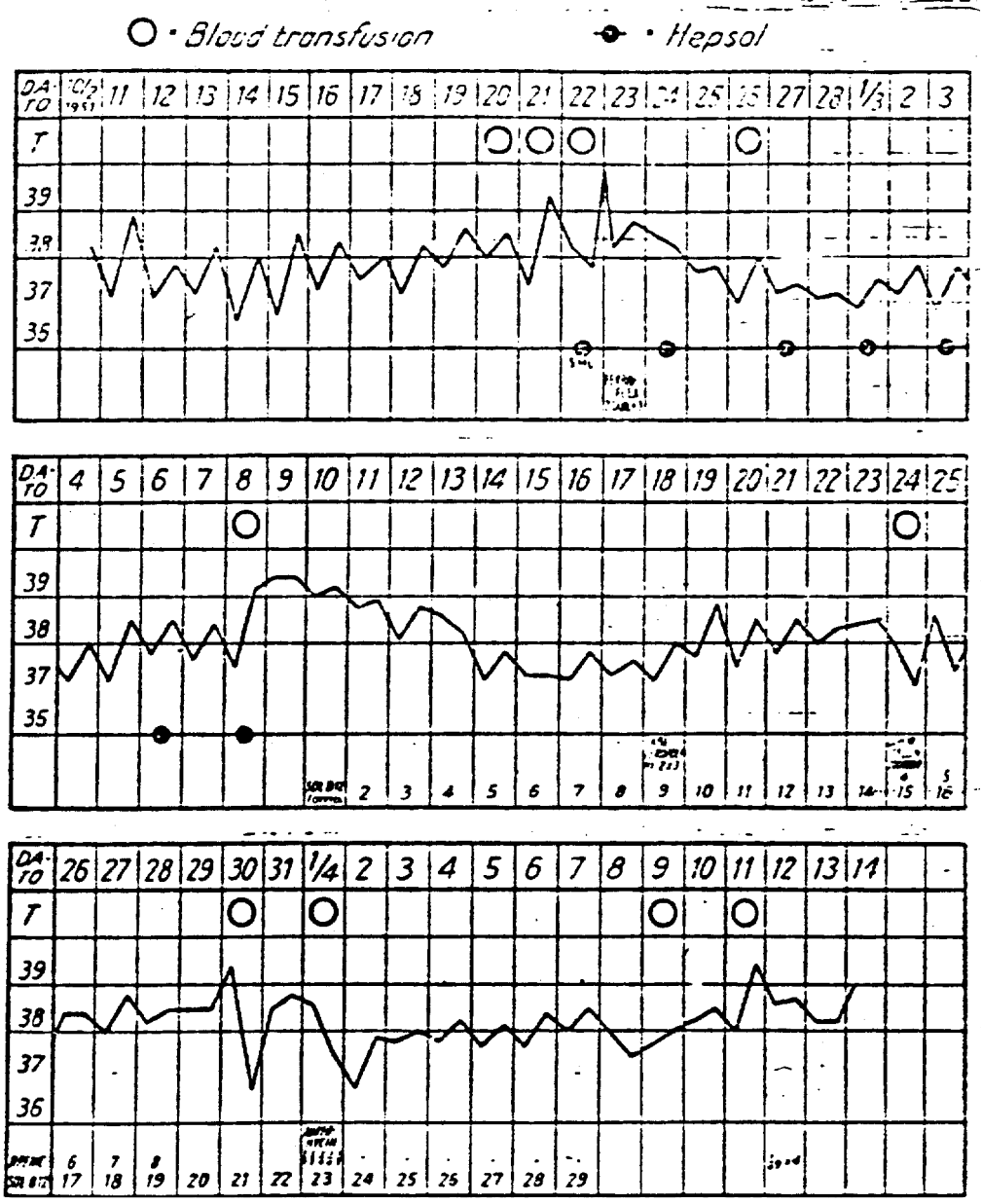

Fig. 4. The temperature curve and treatment.

parison of this type of bone marrow with the marrow found in megaloblastic anemia with a low hemoglobin percentage, the latter is also found to present an increase in the number of cells but the hyperplasia involves both the megaloblastic erythropoiesis and the myelocytic system. In the present case, however, the erythropoietic system made up nearly the entire marrow. In hemolytic anemia, too, the myelocytic cells constitute a relatively greater part of the total — as is evident from the cell count.

In our case the anemia persisted in spite of treatment with Hepsol Meo., vitamin B 12 and terofolin. A further 9 blood transfusions were given with only transitory effect.

The temperature was slightly elevated throughout the course of the disease — as shown in Fig. 4.

Antibiotics as Dipenicillin Leo and Aureomycin End no particular effect.

A replacement transfusion was planned but a considerable aggravation of the patient's condition now occurred in the form of severe hemorrhagic diathesis, and before the replacement transfusion could be carried out the patient died after about three months ill.

Autopsy. Among the autopsy findings should be mentioned in particular that the spleen weighed 440 G, was deep red and very soft.

The liver was considerably enlarged. There was no enlargement of lymph nodes. The hemorrhagic diathesis was found in many organs. The bone marrow was red and hyperplastic. *Microscopy* showed the enormous hyperplasia of the bone marrow already observed, *with* marked preponderance of the proliferating erythroblastic tissue. Further, the splenic pulp showed a very pronounced hyperplastic proliferative erythropoiesis. The liver showed moderate erythropoiesis.

The spleen, liver and lymph nodes showed also small numbers of myeloblasts and myelocytes explaining the occurrence of these cell-types in the peripheral blood.

The clinical diagnosis was thus verified by the autopsy findings.

We thank dr. L. Heerup for the kind permission to use the material.

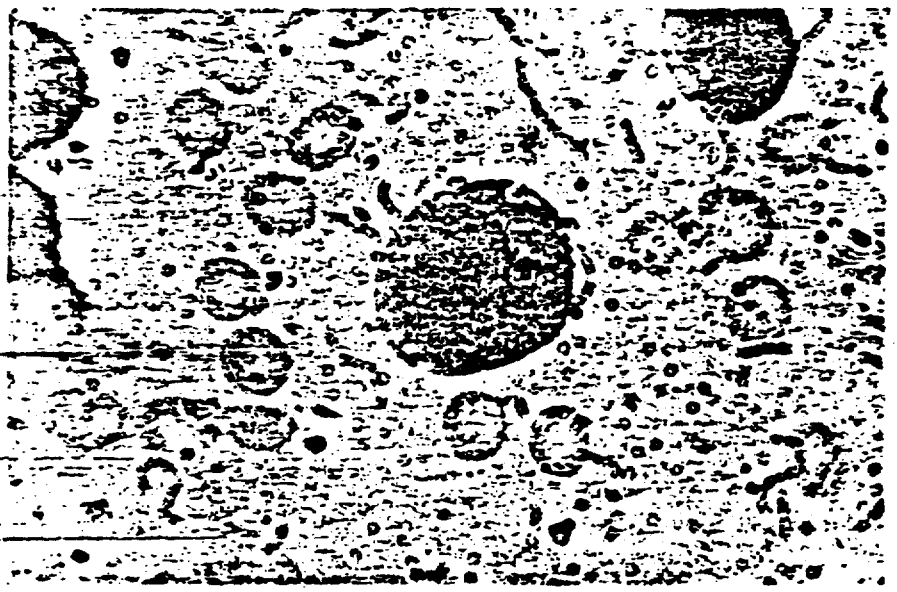

Fig. 5. Paraerythroblast × 1,000.

Fig. 6. Paraerythroblast and proerythroblasts × 1,000.

Fig. 7. Paraerythroblast in atypical mitosis × 1,000.

Fig. 8. Paraerythroblast and proerythroblasts × 1,000.

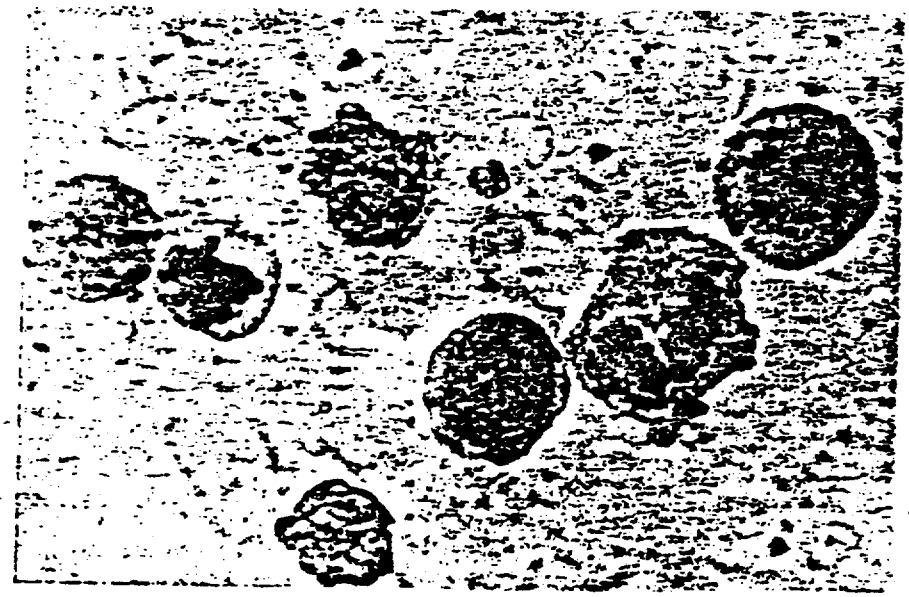

Fig. 9. Proerythroblasts and paraerythroblast in mitosis × 1,000.

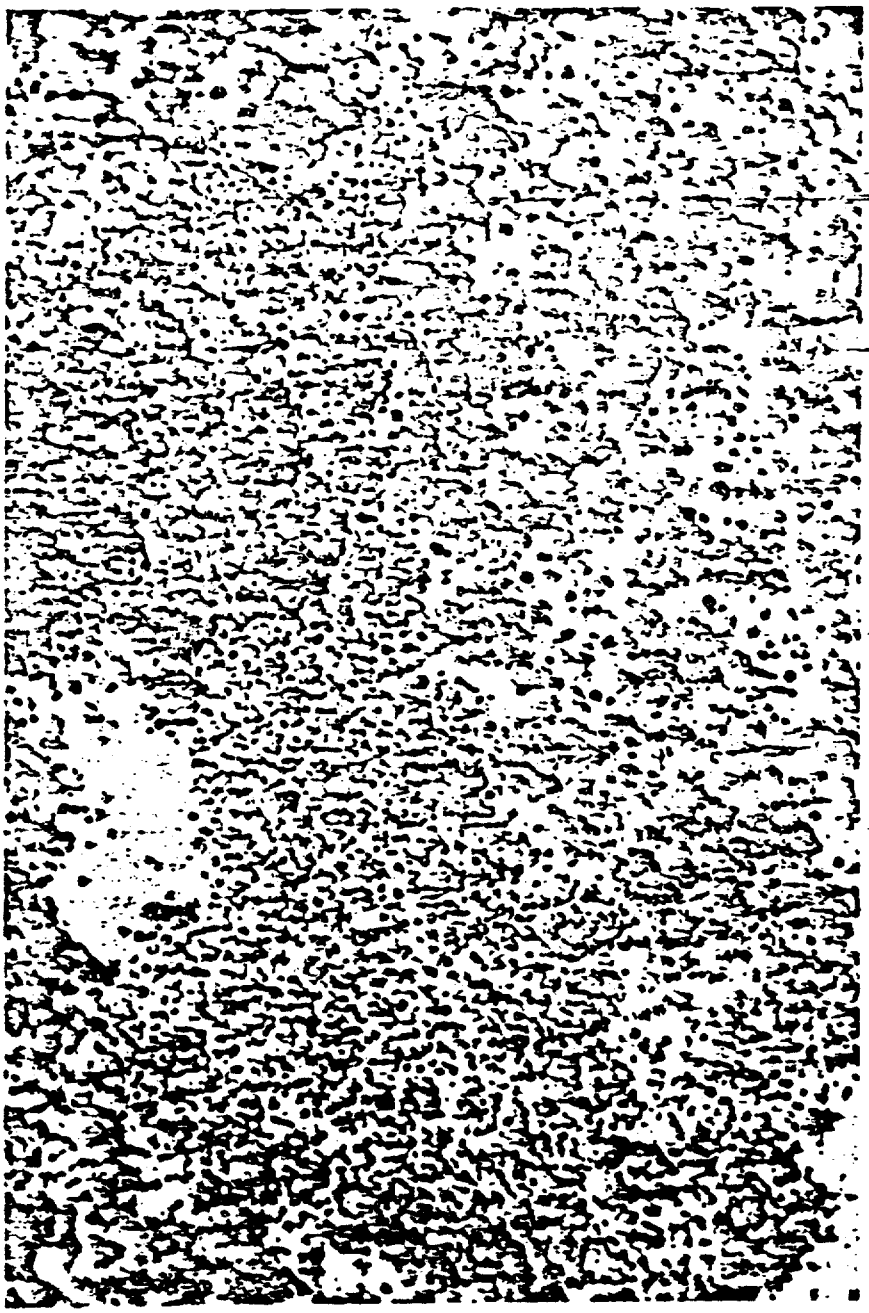

Fig. 10. Marrow particles solely consisting of cells, preponderantly erythropoetic tissue × 100.

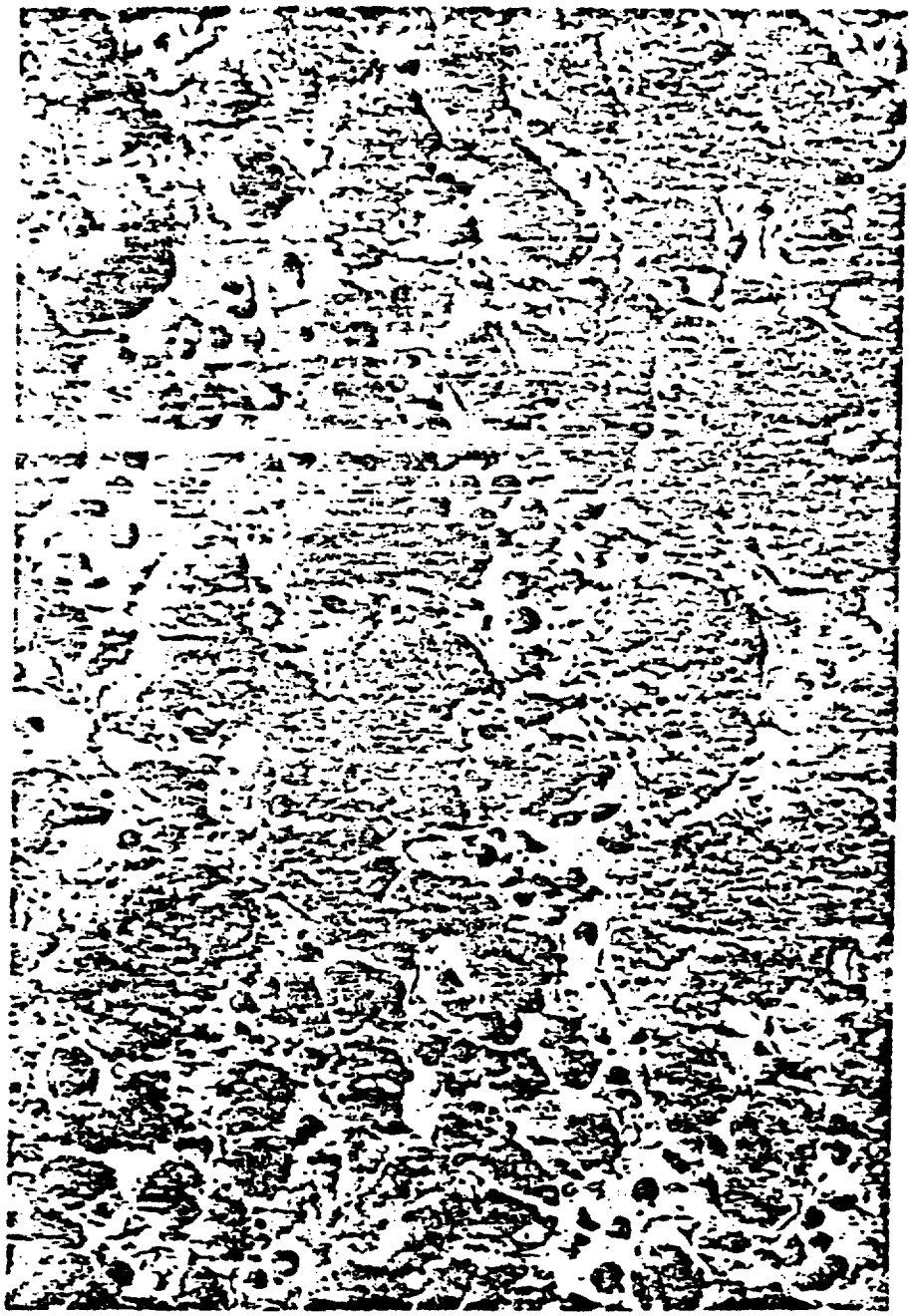

Fig. 11. Hematopoietic infiltration in liver X 400.

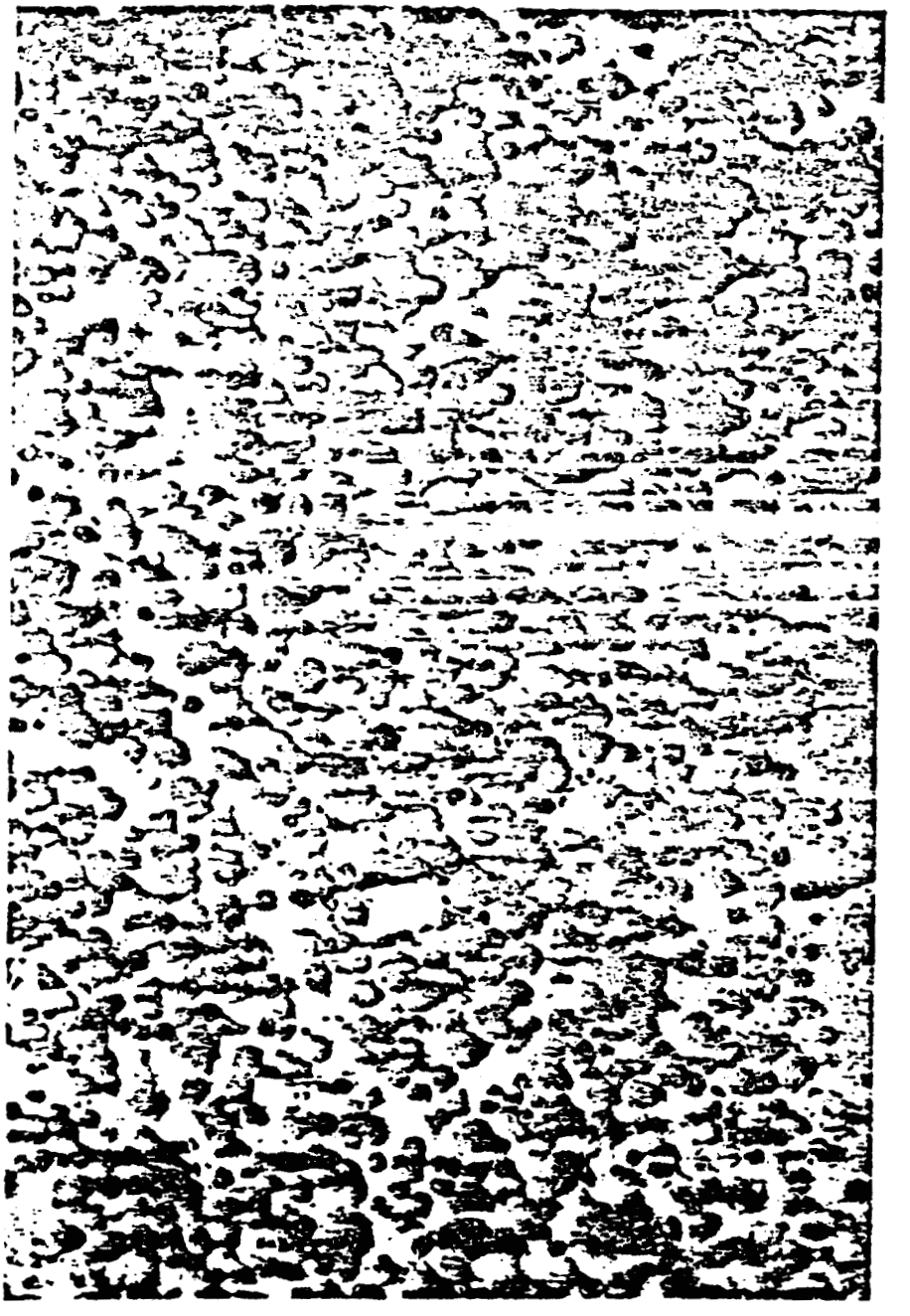

Fig. 12. Hematopoietic infiltration in splenic tissue x 400.

Recapitulation of the Symptoms.

1. Severe progressive anemia.
2. Erythroblasts present in the peripheral blood.
3. Hyperplastic proliferative erythropoiesis with slight tendency to maturation in the bone marrow, and also in the spleen, liver and lymph nodes.
4. Continuous elevation of the temperature.
5. Leukopenia.
6. Progressive reticulocytopenia.
7. Thrombocytopenia.
8. Icterus index slightly increased.

Etiology, Pathogenesis and Discussion.

Our patient had been employed at the Eastern Gasworks, Copenhagen from $^{24}/_{5}$—$^{15}/_{8}$ 47, from $^{8}/_{9}$ 47—$^{31}/_{3}$ 48, from $^{4}/_{4}$—$^{11}/_{4}$ 48 and from $^{13}/_{4}$—$^{8}/_{9}$ 48; at Valby Gasworks from $^{29}/_{9}$—$^{5}/_{10}$ 49 and finally, from $^{29}/_{3}$ 49 to the onset of illness $^{5}/_{2}$ 51. For about six months before the onuet of his illness he had been working at the benzene (benzol) plant — thoughnot in it — occupied with transporting »tar acid« from the plant to a pool. This was done by means of a wagon with a tank holding about two hundred litres. The wagon was hauled by a motor truck and at the pool two men tipped the tank, standing on the wagon, and emptied it rapidly. This transport took about one hour, twice a day. Under certain weather conditions the patient was greatly inconvenienced by the fumes from tbe »tar acid«, with imitation of the nose and throat and coughing spells. He had often to wear rubber clothes to avoid corrosion of the skin. Sometimes he felt ill during this work. The »tar acid« was a byproduct of benzene (benzol), for which 92 % sulphuric acid was used; it was said to consist of sulphonated, unsaturated hydrocarbons, sulphuric acid and presumably sulphurous acid. Its benzene @ea-zol) *content* was assumed to be about 1 %. The development *of* intense heat when the »tar acido was poured into the pool must be taken into consideration.

In *the* past 20 years clinical observations and experimental research have now fully established that benzene (benzol) and its derivatives can not only produce the classical picture of aplastic anemia but also act as a cancerogenic irritant on the bone marrow and produce not only reversible leukemoid conditions but also irreversible features of leukemia, erythroleukemia rad — probably most infrequently — an attack upon the erythropoietic t h e *alone*, resulting in erythromyelosis. For information on *this* matter, see W. C. Hueper: Occupational tumors and allied diseases 1942, p. 552—602, J. P. Greenstein: Biochemistry of Cancer 1947, p. 52 and A. Hamilton and H. L. Hardy: Industrial Toxicology 1943, p. 268. We will not here enter further into this comprehensive literature but merely mention a work from Massachusetts General Hospital by Mallory, Gall and Brickley, who emphasize that Santesson's and Selling's classical experimental and clinical observations on benzene (benzol) poisoning as an aplastic-

anemia have been interpreted erroneously as necessarily dependent upon aplasia of the bone marrow: »that such a picture in the peripheral blood does not, however, necessarily indicate an aplastic marrow ha3 been recognized by numerous observers in recent years. Blumer, Thompson, Richeter and Edsall, Rhodes and Miller have presented abundant evidence that the presumption of an aplastic marrow is not always warranted under such conditions. In fact relatively few cases cited by these authors showed any diminution of bone marrow activity, whereas the majority exhibited marked medullary hyperplasia.o

Mallory, Gall and Brickley further report 19 cases of benzene (benzol) poisoning, with a fatal course in 14 which were examined and followed closely. Of these patients 6 showed the clinical picture usually described with aplasia of the bono marrow, whereas 5 presented a picture exactly corresponding to that of acute erythromyelosis, and one resembled myeloid leukemia and one lymphogenous leukemia. These authors — and also Hunter — emphasize as a significant point that [illegible] cumulative factors and the duration of exposure to the action of benzene (benzol) the sensitivity also of the given individual *to* this action *must* be highly variable just as the sensitivity to the toxic effect of other compounds upon the bone marrow (*e. g.* amidopyrin, arid methyl thiouracil). Furthermore, Hunter who observed 89 individuals exposed to benzene (beutol; fumes has pointed out that it may take some length of time before the first symptoms of poisoning manifest themselves.

Finally the hypothesis was advanced by Mallory, Gall anil Brickley that prognostically the hyperplastic reaction of the marrow is the more favourable form, allowing continuous exposure of the individual to the benzene (benzol) fumes for many years whereas the aplastic form is far more serious unless the patient is removed from contact with the toxic agent. The hyperplastic reaction may conceivably represent an overcompensation *of* the bone marrow as a means of defence against the toxic agent. Something analogous is assumed to apply to chronic radium intoxication (Martland).

According to recent research, the polymorphous pathologic-anatomical picture of *benzene (benzol) poisoning has io be looked* upon *as* an *established fact, and* thw *it cannot be excluded that benzene (benzol) — together with individual hypersensitiveness — must have played a rôle in the development of acute erythromyelosis* in *our patient.* The possibility of benzene intoxication being the causa of the illness was not admitted by the insurance board.

Summary.

A brief survey of erythroblastosis is given together Kith the report of a case of acute erythromyelosis (morbus Di Guglielmo) that appeared in a gasworker employed in the benzene (benzol) plant.

The toxic effect of benzene (benzol) on the bone marrow is discussed, with particular emphasis on the point that hyperplastic reaction of the erythropoietic system has to be looked upon as more frequent than usually assumed, and sometimes leading to erythromyelosis.

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