remissions in five out of thirteen patients, of various ages, with acute leukaemia, and partial remissions in two others. The remissions were only temporary, and resistance to further therapy with 6-MP eventually resulted.

Six patients with chronic myeloid leukaemia showed a varying response. One patient in the acute terminal phase had a remission lasting four and a half months.

Two patients with chronic lymphatic leukaemia, two with multiple myeloma, and one with reticulosis of the skin did not respond, while one patient with mycosis fungoides obtained some improvement.

6-MP is of low toxicity and no serious complications have followed its use.

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ERYTHRAEMIC MYELOSIS TERMINATING IN ERYTHROLEUKAEMIA

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Malignant hyperplasia of the erythron, analogous to leucoblastic proliferation in leukaemia, was first described by Copelli (1912) and later defined as a pathological entity by Di Guglielmo (1923, 1926, 1937) when he recorded three cases as examples of true "erythraemic myelosis." These cases, with others published on the Continent, have been exhaustively reviewed by Di Guglielmo (1945, 1946) and Leitner (1949).

As with leukaemias, acute and chronic forms are recognized. Acute erythraemic myelosis (Di Guglielmo, 1945), pursuing a fatal course of one or two months, presents with severe anaemia, irregular fever, splenomegaly, slight hepatomegaly, and erythroid hyperplasia, with atypical erythroblasts in the blood, many of which

fail to mature. The chronic form (Duesberg, 1940; Heilmeyer and Schöner, 1941; Di Guglielmo and Quattrin, 1942) runs a longer course, up to two years, and the circulating erythroblasts are orthochromatic and less atypical.

In this country four examples of the chronic form appear to have been recognized, three of which have been published in Britain (Israëls, 1939; Neumark, 1948; Emery, 1951; Mackenzie and Stephenson, in *Blood*, 1952). A subacute form, terminating in acute granulocytic leukaemia, has also been recorded (Discombe and Nickol, 1954).

If in the case described below the patient had died within the first two months a diagnosis of acute erythraemic myelosis would have been accepted, but repeated blood transfusions sustained life for a further four months, during which the erythroleukaemic nature of the disease became manifest. In this respect our case closely resembles those of Verloop, Deenstra, and van der Hoeven (1952) and Discombe and Nickol (1954), lending support to the theory that erythraemic myelosis and erythroleukaemia are probably unusual variants in the onset of acute leukaemia.

Case Report

A single woman aged 30 gave up work in a soda-water factory early in August, 1953, because she felt very tired and breathless on the slightest exertion. Two weeks later she developed lumbar pain, headache, and nausea with vomiting.

On admission on August 25 she was very pale, had a temperature of 102° F. (38.9° C.) and fetid breath but no ulceration of the gums or fauces. The liver was palpable and the spleen descended five fingerbreadths in inspiration. There was no relevant personal or family history. Clinically she was considered to be a case of leukaemia, but subsequent blood and marrow pictures (see below) indicated erythraemic myelosis.

Owing to the severe anaemia she was given repeated blood transfusions, 26 pints (14.8 litres) in all, over a period of six months, the highest haemoglobin achieved being 78% (12.4 g.). Transient improvement followed each transfusion; vomiting ceased, the appetite returned, and the temperature subsided.

As her condition could not be maintained despite transfusions, liver, cyanocobalamin ("cytamen"), iron, vitamins, folic antagonists, and corticotrophin, it was decided to remove her spleen. This was done without incident on December 18. Improvement followed splenectomy, the haemoglobin remaining at 66% (10.5 g.), and in January, 1954, she was sent home on corticotrophin. She was now apyrexial, eating well, and gaining weight.

She was readmitted on February 19, 1954, with recurrent vomiting and pyrexia and the haemoglobin had now fallen to 42% (5.7 g.). Further transfusions had little effect and she continued to go downhill. Early in March a large gluteal abscess, following an injection of corticotrophin, was evacuated and 11 oz. (320 ml.) of pus obtained. The wound continued to discharge, and shortly before death on March 23 the haemoglobin had fallen to 16% (2.5 g.). Transfusions were now withheld, as she was obviously in the terminal stages of her illness.

Investigations

General.—Histamine-fast achlorhydria. Urobilinogen excess in urine but no haemosiderin in centrifuged deposit. Bile pigments scanty. Serum bilirubin, 1.2 mg. per 100 ml.

Blood.—Three representative blood counts are set out in the Table. Red cells showed marked anisocytosis, poikilocytosis, and moderate polychromasia. Platelets were scanty

Peripheral Blood

	Week of Admission	Week after Splenectomy	Week before Death
Haemoglobin	5.4 g. (34%)	10.5 g. (66%)	2.5 g. (16%)
Erythroblasts	15,370	21,000	100,600
Leucocytes	2,400	18,800	117,000
Myelocytes	1%	8%	5%
Metamyelocytes ..	4%	11%	7%
Polymorphs	29%	51%	19%
Eosinophils	1%	2%	1%
Lymphocytes	53%	20%	2%
Monocytes	12%	3%	23%
Fromonocytes	—	—	34%
Stem cells	—	5%	9%

at all times. Reticulocytes 5.5% during cyanocobalamin therapy. Red-cell fragility was not significantly increased and tests for underlying haemolytic mechanisms were negative. Cold agglutinins were absent.

Sternal Marrow Punctures.—September 11, 1953 :—Easily aspirated, densely cellular, hyperplastic marrow—over 95% of the nucleated cells being erythrocyte precursors in which megal-, macronormo-, and normo-blastic erythropoiesis were evenly represented. Multipolar mitoses and nuclear-cytoplasmic “ripening” dissociation were present in minor degree. November 22 :—Same dense cellularity, but granulocytes now numbered 24.5% and red-cell precursors had fallen to 60%. As before, megakaryocytes were very scanty. Erythroid mitoses were still plentiful, but there appeared to be fewer mitotic abnormalities. An increase in megaloblasts was attributed to antifolic therapy. February 23, 1954 :—A hypocellular marrow aspirated with difficulty. Monocytes and their precursors now predominated. Some of the mature forms contained red cells.

Splenectomy.—December 18, 1953 :—The spleen weighed 41 oz. (1,120 g.). It was flabby, bright red in colour, and contained three recent infarcts. Histologically the Malpighian bodies were small and widely separated. The sinuses were filled with erythroblasts, but the reticulo-endothelial lining appeared to be normal and unproliferative. A few iron-laden macrophages and small foci of granulopoiesis were present.

Liver Biopsy.—December 18, 1953 :—Small centres of granulopoiesis, normoblasts in the portal tracts, and a sprinkling of haemosiderin in the periphery of the lobules.

Necropsy Report

Necropsy performed 16 hours after death. Several greyish macules on trunk and a few petechiae on forearms. The heart was slightly enlarged, very pale and flabby, and contained greyish-pink creamy blood. The liver (2,621 g.) was pale and yellowish grey. Two enlarged, soft, greyish lymph nodes were found at the hilum. The kidneys were enlarged and showed scattered wedges of homogeneous yellowish-grey colour with little demarcation between cortex and medulla. The marrow of sternum, ribs, vertebral bodies, and left femoral shaft was uniformly grey in colour. Several pea-sized cherry-red nodules were found in the dura over the left cerebral vertex but the brain was normal. Apart from bloodlessness the other organs appeared normal.

Histology.—The bone marrow showed a dense uniform cellularity with a few widely scattered islands of erythroblasts. The predominating cell had a round or oval vesicular nucleus with a thin rim of cytoplasm. Mitoses were scanty. Lymph-node architecture was partially disorganized, the surviving follicles at the periphery being small and devoid of germinal centres. The invading cells were a mixture of those seen in the marrow and normoblasts. The liver cells were compressed and loaded with haemosiderin in the outer and middle zones of the lobules and there were numerous monocytoïd cells and normoblasts in the portal tracts.

The dural nodules, skin, stomach, intestines, heart, kidney, adrenals, thyroid, pituitary, uterus, and ovaries all showed infiltration in varying degree by cells indistinguishable from those in the marrow.

Discussion

In the evaluation of this and other cases presented as acute erythraemic myelosis the greatest difficulty lies in excluding various forms of haemolytic anaemia. The presence of atypical erythroblasts with abnormal nuclei is among the features characteristic of the disease (Di Guglielmo, 1946), the typical failure of maturation in the erythroblasts of our cases being evidenced by the low reticulocyte counts.

Although deaths from erythraemic myelosis still occur (Emery, 1951; Schwartz and Critchlow, 1952) evidence accumulates to suggest that the longer the patient lives the more likely is acute leukaemia to develop. Gradations and transitions between erythraemic myelosis, erythroleukaemia, and myeloid leukaemia have been noted by Blackburn and Lajtha (1951) and by Martin and Bayrd (1954). Our case, in developing a monocytic element, constitutes a departure from the usual myeloblastic finale, but this may have been of Naegeli type, the so-called “monocytic phase of myeloid leukaemia.” However, in describing the Schilling type, Wintrobe (1951) states that some of the cases have shown a widespread hyperplasia of monocytic cells in the connective tissue, especially about the blood vessels. It is of interest that the same perivascular reticulo-endothelial hyperplasia has been noted in several cases of erythraemic myelosis, Di Guglielmo himself describing transitional forms between reticulo-cellular and erythroblasts as a feature of the disease. Moreover, many cases, critically reviewed and accepted as erythraemic myelosis, have shown a frank monocytosis.

If we accept Dameshek's view that marrow reaction may be non-specific and provoke response along multiple channels, or Downey's modification of the neo-unitarian theory, ascribing toti-potentiality to the reticulo-endothelial cell, then we may conveniently regard erythraemic myelosis, erythroleukaemias, and leukaemias as manifestations of a fundamental “stem-cell” derangement and satisfactorily group them together as a reticulo-endotheliosis.

Summary

A woman aged 30 died six months after the onset of a profound resistant anaemia characterized, in the early stages, by erythroblastaemia, leucopenia, and erythroblastic hyperplasia in the marrow. A diagnosis of acute erythraemic myelosis (Di Guglielmo's disease) was made.

Following splenectomy the picture changed to one of erythroleukaemia, the leukaemic element being monocytic and probably of Naegeli type.

The relationship between erythraemic myelosis, erythroleukaemia, and leukaemia is briefly discussed.

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