Ingram, 1960; Muller and Jonxis, 1960). These three haemoglobins can therefore be designated as follows:

It seems that the infant changes progressively on maturing from γ -chain production to β -chain production, so producing more and more haemoglobin A and less and less haemoglobin F. In the normal child virtually no haemoglobin F is formed after the first year of life. Thus the characteristic feature of the adult environment is the formation of $\alpha_2\beta_2$ globin molecules as in haemoglobin A and the inability to form $\alpha_2\gamma_2$ units as in haemoglobin F. If there is any impairment of haemoglobin A formation, the production of foetal haemoglobin may continue in later life. Once a break occurs in γ_2 -sub-unit formation, however, it appears to be irreversible, and if anaemia appears at an age at which foetal haemoglobin formation has ceased the impairment in haemoglobin A production will not be compensated by formation of haemoglobin F. This could explain the fact that in our patients transfused with foetal cells there was no formation of haemoglobin F in spite of immunological and haematological evidence that the transfused cells were multiplying in the recipient adults.

The transfused foetal cells have, however, a relatively lower capacity for haemoglobin A formation, and their tendency would be to produce more F and A_2 as occurs in β -chain thalassaemia. In this classical thalassaemia haemoglobin A ($\alpha_2\beta_2$) formation is suppressed and there is a compensatory increase in F ($\alpha_2\gamma_2$) and A_2 ($\alpha_2\delta_2$). In our patients the situation is, however, different from that obtaining in this congenital disease, since the foetal cells are introduced into the new environment after $\alpha_2\gamma_2$ (haemoglobin F) formation has long ceased there. Thus, with haemoglobin A production decreased and haemoglobin F formation blocked the transfused cells will tend to increase the $\alpha_2\delta_2$ formation—the haemoglobin A_2 detected by electrophoresis.

Should our observations be confirmed in subsequent cases then the demonstration of excess haemoglobin A_2 would serve as a convenient indicator of the survival and maturation of transfused foetal erythropoietic cells. This method would have the advantage that the fate of the transfused erythropoietic cells could be followed in every case and not only in those in which dissimilarity in the blood groups of donor and host was present.

Summary

Eight patients suffering from some form of malignant disease and who developed severe toxic marrow failure after anti-cancer chemotherapy were given transfusions of haemopoietic cells as contained in foetal liver suspension. Three eventually recovered normal marrow function but the remaining five died within a short period of the transfusion. In all those who recovered, besides haemoglobin A, a "slow"-moving band of haemoglobin became visible on starch electrophoresis of the haemoglobin for a time after the foetal cell transfusion. In two cases this haemoglobin was identified as haemoglobin A_2 and in the remaining case it is felt that it is most likely that excess haemoglobin A_2 was also present.

It is postulated that the haemoglobin A_2 arose from transfused erythropoietic cells and a theoretical explanation is offered. It is suggested that the presence or

absence of haemoglobin A_2 would serve as a useful method of determining if transfused foetal erythropoietic cells had survived and matured in the recipient adult.

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PRIMARY MYELOID METAPLASIA

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The disorderly proliferation of haemopoietic cells beyond the physiological demands is the principal concept relating a group of conditions which collectively have become known as the "myeloproliferative disorders." Certain common forms, such as polycythaemia vera, myeloid leukaemia, and essential thrombocythaemia, are named and usually recognized from the characteristics of the peripheral blood; they represent the classical diseases of the group. Dameshek (1951) focused attention on the variety of intermediate forms which may occur, and it is now widely accepted that a blood spectrum of overlapping clinicopathological patterns is embraced by the term. That this is so appears to derive from the proliferative process affecting several cell lineages at various stages of their development, and involving them to differing degrees.

The peripheral blood picture has been strongly emphasized in the descriptions of these conditions, but it is really of importance only in so far as it may reflect the underlying abnormality of proliferation in the tissues, for which histology provides more direct, if less quantitative, evidence. Since little is known at present of the factors governing the release of cells from sites of haemopoiesis the histological evidence must take precedence.

The condition commonly known as "myelosclerosis" is one of the most problematical in the group, and the many synonyms which have been summarized by Heller *et al.* (1947) reflect the wide divergence of views regarding its significant features. In this condition it is

common to find sclerosis of the bone-marrow associated with myeloid metaplasia of the spleen and liver and sometimes of other organs. The view was enunciated by Donhauser (1908) that the marrow was first replaced by fibrous tissue or bone, the myeloid metaplasia arising in compensation by a process analogous to the development of extramedullary erythropoiesis in pernicious anaemia, haemolytic anaemias, myelomatosis, and other myelophthisic diseases. This hypothesis still attracts support (Wyatt and Sommers, 1950; Leonard *et al.*, 1957; Whitby and Britton, 1957; *British Medical Journal*, 1960) despite certain difficulties.

One alternative view is that a proliferative stimulus affects various cell lines all derived from the "primitive mesenchymal cell," including the fibroblast and osteoblast as well as the haemopoietic cells (Vaughan and Harrison, 1939; Carpenter and Flory, 1941; Rosenthal and Erf, 1943; Heller *et al.*, 1947; Beattie and Withey, 1953). According to this concept, the marrow and extramedullary changes proceed simultaneously and are perhaps more readily recognized at an early stage in the extramedullary sites, where the presence of the proliferating cells is the more conspicuous in their abnormal site. This change in emphasis led to the revised clinical approach of Jackson *et al.* (1940), who described cases under the title of "agnogenic myeloid metaplasia of the spleen."

In the present study, 16 patients showing histological evidence of myeloid metaplasia of unknown origin have been reviewed to examine the usefulness of regarding them together as a single clinical condition. An attempt has been made to separate these cases into useful clinical groups illustrated by selected case histories. The radioisotope studies made on many of these patients are reported elsewhere (Bowdler, 1961).

As already stressed, the wide variation in the clinical and haematological features of these cases stems from the variable degree to which the individual cell lines are involved. From an essentially clinical aspect it is possible to discern certain clinical patterns which differ in problems of diagnosis and management, and the cases described here are considered under their salient presenting features.

1. Bone-marrow Failure with Hepatosplenomegaly (5 Cases)

Case 1A

A wholesale provisions merchant aged 54 was first seen in June, 1957, complaining of pallor, abdominal discomfort, and dyspnoea on exertion. Liver and spleen were enlarged about 3 cm. A blood count showed haemoglobin 6.6 g./100 ml. and white cells 3,950/c.mm., with occasional myelocytes and nucleated red cells. No marrow was obtained from the sternal puncture. A biopsy specimen taken from the iliac crest showed active haemopoiesis and a slight increase in the fibrous stroma. Splenic puncture demonstrated normoblasts and myelocytes. Skeletal x-ray films showed no abnormalities. Isotope studies showed normal red-cell survival and impaired haemopoiesis.

Blood transfusion raised the haemoglobin to 8.8 g./100 ml., and on prednisone 15 mg. daily this rose to 13.9 g./100 ml. after six months. He remained well until July, 1959, when he was readmitted with lobar pneumonia, the blood count showing haemoglobin 9.1 g./100 ml. and white cells 450/c.mm. He died on the second day, and necropsy revealed extensive fibrosis of the marrow in the lumbar vertebrae and the upper thirds of the femora, and conspicuous haemopoiesis in the spleen, in the sinusoids of the liver, and in para-aortic lymph nodes.

Case 1B

A business man aged 61 was first investigated in March, 1951, for complaints of epigastric discomfort, lassitude, and malaise which had arisen two months previously. Investigations showed: haemoglobin, 9 g./100 ml.; total white-cell count, 1,400/c.mm., with 1% myelocytes and 2% immature cells; 4 nucleated erythroid cells per 100 white cells; reticulocyte count 2.5%; platelet count, 310,000/c.mm.

Sternal marrow proved difficult to obtain on puncture, but no abnormal cells were seen. Iliac crest biopsy showed a hyperplastic marrow with numerous megakaryocytes and eosinophils. There was no excess of myeloblasts or any evidence of fibrosis. Skeletal radiographs showed no abnormality.

Treatment with prednisolone 30 mg. daily was continued for 28 months. At the end of three months the spleen had decreased in size, the white-cell count was 4,200/c.mm., and the haemoglobin level 12.3 g./100 ml. The immature cells disappeared from the peripheral blood and were not detected again for 18 months. Diabetes mellitus developed shortly after the beginning of steroid therapy and peripheral neuropathy was later detected. After 26 months of treatment there was an episode of purpura and the haemoglobin fell to 7.8 g./100 ml., but control was regained with a slightly increased dose of steroid. The white cells fluctuated between 2,600 and 6,700/c.mm., the variations becoming more marked with time; there was no close correlation with the haemoglobin level.

In April, 1960, he was admitted to hospital with a severe leucoerythroblastic anaemia (haemoglobin 5.8 g./100 ml.). The platelet counts were variable, but there was no persistent thrombocytopenia. Isotope studies showed a marked diminution in Cr-51 red-cell survival, and splenectomy was carried out. This resulted in a reduction in the number of transfusions required but no significant change in the white-cell count or platelets. Marked anisocytosis and leucoerythroblastosis persisted after splenectomy. He died four months after splenectomy, after a myocardial infarction. Necropsy showed extensive myeloid metaplasia involving liver, lymph nodes, adrenals, and kidneys, with an increase in marrow reticulum and fibroblast proliferation.

Case 1C

A maintenance engineer aged 64 was referred for investigation of an abnormal shadow demonstrated by miniature radiography. He had no symptoms. On examination there were no clinical findings in the chest, but the liver and spleen were enlarged and palpable at 6 cm. and 3 cm. below the costal margins respectively. Tomography of the lung showed an irregular mass anterior to the right hilum, and bronchoscopy showed no intraluminal growth. Blood examination revealed: haemoglobin, 12.6 g./100 ml.; white-cell count, 11,200/c.mm., with one normoblast per 200 white cells; reticulocyte count, 1.5%; platelets, 440,000/c.mm. The sternal marrow was extremely hypocellular, but no abnormal cells were found. Percutaneous liver biopsy showed islands of erythropoiesis in the sinusoids with scattered megakaryocytes. Radioisotope studies showed a virtually inactive bone-marrow with red-cell production in the spleen.

Radiotherapy was given to the right lung on the presumptive diagnosis of carcinoma of the bronchus. Seven months later the patient was readmitted, having had a haematemesis. Conservative treatment was followed by a satisfactory recovery. The white-cell count at this time was 10,000/c.mm., with 7% myelocytes and 4 nucleated erythroid cells per 100 white cells. Bleeding and clotting times were normal. A barium-meal examination showed no abnormality.

Thirteen months after the first admission the patient was admitted with a second gastro-intestinal haemorrhage, and a barium-meal examination disclosed a large gastric ulcer. Blood examination showed: haemoglobin, 14.6 g./100 ml.; white cells, 7,000/c.mm., with 1% myelocytes, and 3 eryth-

roid precursors per 100 white cells; platelets, 650,000/c.mm. One month later he died after a further massive haemorrhage.

At necropsy the lungs showed patchy emphysema and bronchopneumonia with no evidence of neoplasm in the right lung. No macroscopic evidence of fibrosis was found in the lumbar spine or femora. The liver and spleen showed microscopical evidence of massive myeloid metaplasia. The bone-marrow showed moderate infiltration with fibrous tissue and patchy centres of haemopoiesis with a considerable increase in megakaryocytes.

2. The Polycythaemic Type (3 Cases)

Case 2A

A housewife aged 64 was referred to a dermatologist in February, 1957, complaining of recurrent attacks of pruritus for six years. At this time the haemoglobin level was 16.4 g./100 ml. In November she was observed to have splenomegaly 6 cm. and hepatomegaly 3 cm. below the costal margins. There was no lymphadenopathy. The blood count showed haemoglobin, 16.4 g./100 ml.; haematocrit, 52%; platelet count, 560,000/c.mm.; and white-cell count, 9,600/c.mm., with 0.5% myelocytes. Marrow aspiration showed a hypercellular marrow with increased numbers of megakaryocytes. In the course of the next year the haemoglobin varied between 15 and 15.9 g./100 ml.

FIG. 1.—Photomicrograph of marrow trephine biopsy from Case 2A, showing a highly cellular marrow without significant fibrosis.

FIG. 2.—Splenic aspiration smear from Case 2A, showing normoblasts and pronormoblasts.

FIG. 3.—Marrow trephine biopsy from Case 2A taken 10 months after that shown in Fig. 1. Fibrosis is well marked.

In May, 1958, sternal trephine biopsy showed a cellular normoblastic bone-marrow and no evidence of fibrosis (Fig. 1), and splenic aspiration showed many normoblasts and myelocytes (Fig. 2). Ten months later the haemoglobin had fallen to 11.5 g./100 ml., and in June, 1959, the patient was readmitted with advancing breathlessness on exertion and abdominal distension. The liver and spleen had enlarged further and the blood count showed: haemoglobin, 7.9 g./100 ml.; platelets, 146,000/c.mm.; white cells, 6,800/c.mm., 1% myelocytes and 0.5% immature cells. Marrow aspiration produced scanty numbers of cells, but there was no morphological abnormality. Marrow trephine biopsy now showed evidence of myelofibrosis (Fig. 3). Blood transfusion raised the haemoglobin to 11.1 g./100 ml., and this level was maintained during the next nine months, treatment with prednisone 20 mg. daily being continued throughout this time.

In June, 1960, she was readmitted with severe anaemia (haemoglobin 6.4 g./100 ml.), and has since been requiring frequent transfusions, her red-cell survival being slightly reduced. Three months later red-cell survival was greatly reduced and isotope studies indicated splenic destruction of red cells. Splenectomy was carried out and no further transfusions were required, but she died following pulmonary embolism six months later. Necropsy showed myeloid metaplasia in the liver with megakaryocytic hyperplasia in the marrow and patchy fibrosis.

Case 2B

A housewife aged 75 was admitted to hospital in April, 1958, complaining of irritation of the legs for five years and prominence of the abdomen for two years. Three months previously she had been examined elsewhere. The haemoglobin was 16.1 g./100 ml., and the white-cell count showed a polymorphonuclear leucocytosis of 34,700, with 5% myelocytes. Extensive skeletal radiography had shown no abnormalities.

On examination she showed widespread scattered bruising, the spleen was palpable at the umbilicus, and the liver was enlarged by 3 cm. Investigations showed: haemoglobin, 18 g./100 ml.; red cells, 7,240,000/c.mm.; haematocrit, 62%, normocytic, normochromic cells; platelet count, 470,000/c.mm.; white-cell count, 24,000/c.mm., with no immature cells. Aspiration biopsy showed the sternal marrow to be morphologically normal and skeletal radiographs showed nothing abnormal. Splenic puncture revealed the presence of myelocytes and many normoblasts. Treatment with 5 mc of radiophosphorus led to a reduction in the size of the spleen and liver and some fall in the haemoglobin level, but she has since needed venesection and further treatment with 5 mc of P-32. There has been con-

siderable reduction in splenomegaly with this treatment, but the haemoglobin, after falling satisfactorily for five months, rose again to polycythaemic levels. After more than two years from the initial treatment with radiophosphorus there has been no evidence of marrow failure.

3. Presentation With Leucocytosis (1 Case)

Case 3A

A housewife aged 62 complained in September, 1956, of "fullness in the abdomen" present for nearly 20 years, and increasing fatigue and breathlessness on exertion for three months. She appeared pale, the spleen was palpable at the umbilicus, and the liver was felt 6 cm. below the costal margin. The blood count showed: haemoglobin 9.9 g./100 ml.; platelet count, 550,000/c.mm.; white cells, 30,000/c.mm. (75.5% polymorphs, 6% lymphocytes, 2.5% monocytes, 2.5% eosinophils, 3.5% basophils, 9.5% myelocytes, 0.5% blast cells); there was one normoblast per 100 white cells. Sternal marrow aspiration showed a hypocellular marrow with 64.5% polymorphonuclear leucocytes, 17.5% myelocytes, and 4% blast cells; the megakaryocytes were reduced in numbers. Splenic aspiration showed myelocytes and many normoblasts, and isotope studies revealed a normal red-cell life and a high rising splenic Fe-59 curve. No radiographic changes were seen in the pelvis; the femora showed slight patchy osteoporosis.

No treatment was given at this time, but in May, 1957, when the white cell count had risen to 60,000/c.mm., a course of busulphan lasting 10 weeks was started, resulting in a fall to 11,000 within five weeks. At this time she was also given prednisone, the haemoglobin rising from 8.3 to 11.5 g./100 ml. in six weeks (Fig. 4). She remained well until shortly before her final admission in June, 1958, when she was admitted stuporous and hemiplegic. The haemoglobin was 12.3 g./100 ml., and the white-cell count 18,400/c.mm. She died shortly after and necropsy could not be obtained.

Fig. 4 outlines the treatment of this patient. The effect of busulphan in producing a fall in the white-cell and myelocyte counts is easily apparent. The mean haemoglobin in the absence of treatment was 10.81 ± 0.96 g./100 ml., and it was reduced to 8.92 ± 0.73 g./100 ml., while the patient was taking busulphan alone. This was significant to a level of over 0.0001. The mean haemoglobin when the patient was taking prednisone was 12.33 ± 0.58 g./100 ml., the difference from the untreated levels being again highly significant. It appears that the simultaneous use of prednisone will compensate for the fall induced by busulphan, since the mean level on the combined therapy (11.34 ± 2.58 g./100 ml.) does not differ significantly from that found with prednisone alone. It should be emphasized that the red-cell life in this patient was normal, and therefore the effect of prednisone probably resulted from an increase in red-cell production.

Summary of Clinical Findings in Cases of Myeloid Metaplasia

Case	Age and Sex	Initial Investigations			Pelvis, %	Presenting Signs		Method of Diagnosis	Haemolysis	Haemorrhage	Other Conditions	Plasma Proteins	Notes
		Hb (g./100 ml.)	W.B.C.	Platelets		Spleen (cm.)	Liver (cm.)						
1A	54 M	6.6	3,950	160,000	—	3	3	Splenic puncture. Necropsy. Isotope study	Nil	Nil	Terminal pneumonia	Increased α_1 -globulin. Slightly reduced albumin	Skeletal x-ray films normal
1B	61 M	9.0	1,400	310,000	2.5	6	1.5	Liver biopsy. Bone biopsy. Isotope study	Developed after 3 yrs.	Purpura	Diabetes. Neuropathy. D.U.	Increased γ -globulin	" "
1C	64 M	12.6	11,200	440,000	1.5	3	6	Liver biopsy. Necropsy. Isotope study	Present from onset	Duodenal	D.U.	—	Bleeding and clotting times normal
1D	59 F	9.5	2,000	450,000	1.6	18	3	Isotope study	Nil	Purpura on busulphan	Recurrent urinary infection	Normal	Prothrombin 70%. Translucencies in pelvic x-ray film
1E	55 F	11.7	2,000	190,000	0.7	12	3	Splenic puncture. Isotope study	"	Nil	Pyelitis. Steatorrhoea	Diffusely increased γ -globulin	—
2A	64 F	16.4	9,600	560,000	—	3	6	Splenic puncture. Bone biopsy. Isotope study	Developed after 3 yrs.	"	—	—	—
2B	75 F	18.0	24,000	470,000	3.6	12	3	Splenic puncture. Isotope study	Nil	Ecchymosis	—	—	Skeletal x-ray films normal
2C	54 F	21.2	10,000	740,000	—	3	3	Histology after splenectomy	"	Post-operative	Oesophageal stricture	Normal	Oesophago-gastrostomy for benign stricture
3A	62 F	9.9	30,000	550,000	—	12	6	Splenic puncture. Isotope study	"	Nil	Cerebral thrombosis	Markedly increased γ -globulin. No macro-globulins	Patchy porosis in both femora. Blood uric acid, 11.7 mg. 100 ml.
4A	75 F	14.5	11,600	700,000	1.6	9	6	Necropsy. Isotope study	"	Ecchymosis. Purpura	Broncho-pneumonia	Normal	Skeletal x-ray films normal. Prothrombin 70%
4B	40 F	18.1	18,700	2,500,000	—	18	3	Splenic puncture. Isotope study	"	Tooth extraction. Menorrhagia. Haematemesis and melaena	Haemorrhages for 17 yrs.	—	Thromboplastin-generation impaired. Bleeding and clotting prolonged. Skeletal x-ray films normal
4C	26 F	14.7	13,500	860,000	—	6	4.5	Splenic puncture. Lymph-node biopsy	"	Nil	—	—	Patchy porosis of femora and tibiae
4D	41 M	14.0	28,800	1,900,000	—	—	3	Histology after splenectomy	"	Spontaneous ecchymoses	Angina pectoris	—	Bleeding time 1 hr. Thromboplastin-generation normal. Skeletal x-ray films normal
5A	66 F	10.0	7,000	280,000	2.2	T ₀ RIF	4.5	Necropsy. Isotope study	Very marked	Nil	—	—	Sclerosis of ribs and femora
5B	50 F	9.3	9,500	—	5.6	12	2.5	Liver biopsy	Marked	"	—	Increased γ -globulin	Prothrombin 60%. Coombs negative
5C	72 F	11.5	16,700	36,000	1.2	10.5	0	Necropsy. Isotope study	Moderate	"	Cerebral thrombosis	Raised α_1 and γ -globulin	Coombs negative. Skeletal x-ray films normal

FIG. 4.—Case 3A. Haemoglobin level, white-cell count, and myelocyte count, while under treatment with busulphan and prednisone.

4. Presentation with Thrombocythaemia or Megakaryocytosis (4 Cases)

Case 4A

A housewife of 75 years was admitted to hospital in November, 1959, in cardiac failure with mitral incompetence. She complained of recurrent bruising on minimal injury for the previous three years. On examination there were purpuric spots on all the limbs, and the liver was enlarged to 6 cm. and the spleen to 9 cm. Hess's test was negative. The blood count showed: haemoglobin, 14.5 g./100 ml.; white cells, 11,600/c.mm. with a normal differential count; platelets, 700,000/c.mm. No abnormality was found in the bleeding and clotting times, the thromboplastin generation test, plasma proteins, or in radiography of the abbreviated skeleton. The prothrombin concentration was 80% of normal by the one-stage method.

In January, 1960, the haemoglobin was 14.5 g./100 ml., and the platelet count had risen to 2,000,000/c.mm. Shortly after this the patient developed bronchopneumonia and died. Necropsy showed the liver to be enlarged (2,300 g.), and on microscopy fairly numerous haemopoietic cells were seen in the sinusoids. The spleen weighed 1,060 g., and on microscopy there was generalized fibrosis and hyperplasia of the red pulp with active haemopoiesis. The bone-marrow of the femora was uniformly red, very soft, and hyperplastic, and it extended throughout the shafts; microscopically, the marrow showed normal formation of erythroid and myeloid cells with an excessive number of megakaryocytes.

5. Presentation with Haemolytic Anaemia (3 Cases)

Case 5C

A housewife aged 72 was seen in February, 1957, when she had been weak and intermittently confused and incontinent for eight months. Examination revealed pallor and splenomegaly to 10.5 cm. A blood count showed: haemoglobin, 11.5 g./100 ml.; white cells, 16,700/c.mm. with 4% metamyelocytes, 1% myelocytes, and two nucleated erythroid cells per 100 white cells. Sternal puncture

showed the bone to be very firm in consistency and the marrow to be scanty. A few normal myelocytes and normoblasts were seen.

During the next five months the patient required five blood transfusions (shown in Fig. 5). Further investigation during this time showed myelocytes and normoblasts on splenic puncture, and a trephine biopsy of the iliac crest showed active haemopoiesis, mainly leucoblastic, with large

FIG. 5.—Case 5C. Haemoglobin level, white-cell counts, and reticulocyte count while under treatment with prednisone.

numbers of megakaryocytes. There was no evidence of myelosclerosis. The direct Coombs test was negative; serum bilirubin 1.2 to 1.5 mg./100 ml., with no bile pigment in the urine; the reticulocyte count 1.2 to 1.5/100 ml.; and the platelet count 36,000/c.mm. Isotope studies showed a moderately reduced red-cell survival ($T_{1/2}Cr=17$ days), impaired iron utilization, a high rising curve of iron uptake in the spleen, and a depressed lumbar marrow.

In view of the transient effect of the blood transfusions, treatment with prednisone was started, which produced a brisk reticulocyte response, and the haemoglobin and white-cell count rose. The patient was subsequently maintained on steroid therapy without need of transfusion, and was in good health for about one year, after which the haemoglobin fell again. Shortly after this the dose of prednisone was raised, with a prompt haemoglobin response, but the patient died a few days later with a cerebral thrombosis.

Necropsy revealed extension of pale red marrow with active haemopoiesis into the shafts of both femora, and

FIG. 6.—Case 5C. Relationship of the white-cell count to the haemoglobin level. ● = Before treatment; x = treatment with prednisone. Regression of haemoglobin on white cell count.

microscopy showed that there were large numbers of megakaryocytes. Microscopy of the spleen showed many immature leucocytes, numerous megakaryocytes, and some erythroid cells. Myeloid metaplasia was seen in the sinusoids of the liver. A heavy reticulin pattern was seen in the bone-marrow and spleen, and there was some excess of collagen.

It was possible in this patient to follow the course of the condition with numerous blood counts, both before and during prednisone therapy. These are plotted in Fig. 6. There is a highly significant positive correlation between the haemoglobin and white-cell counts ($r=0.70$). Thus the response of the blood was one simultaneously affecting leucocytic and erythroid elements.

Discussion

The pathological aspects of primary myeloid metaplasia have been summarized by Marshall (1956), who gives reasons for regarding the process as a form of benign multifocal neoplasia. The process affects mainly the spleen, less intensively the liver, occasionally lymph nodes, and rarely the perivascular tissues of the lung. In addition to myelocytes, normoblasts, and erythroblasts, there are usually prominent numbers of mature and immature megakaryocytes, some showing abnormal nuclear patterns, and many cells with pale oval nuclei resembling primitive reticular cells. This picture does not suggest a simple compensatory extra-medullary haemopoiesis, and, in cases showing the latter, massive enlargement of the affected organs is not expected.

As has been seen, myelofibrosis and myelosclerosis are common accompaniments of this picture, but, as in Case 2A, the myeloid metaplasia may precede the marrow fibrosis, an observation that has also been recorded previously (Taylor and Simpson, 1950). Secondly, the proliferation of fibrous tissue may be well developed in the spleen and lymph nodes and not confined to the marrow, suggesting the presence of a generalized fibroproliferative tendency (Jordan and Scott, 1941). Hewer (1937) observed that myelosclerosis was sometimes partial and irregular, and could scarcely have affected the marrow volume in some cases. Further, the frequent occurrence of myeloid metaplasia with excessive production of red cells, white cells, or platelets does not suggest that it is arising in response to a deficiency of cell formation. The significance of such observations in relation to the compensatory hypothesis of the origin of this condition have been discussed by McMichael and McNee (1936), Carpenter and Flory (1941), Taylor and Simpson (1950), Dameshek (1951), and Beattie and Withey (1953). The proliferative hypothesis suggested by Vaughan and Harrison (1939) provides a more acceptable explanation in keeping with these observations. For this reason, the term "primary myeloid metaplasia" is to be preferred to "myelosclerosis" in describing such cases.

The problems of classification of the myeloproliferative disorders have increased with the recognition of the many intermediate forms which lie between the classical syndromes. One tendency has been to use the term "myeloproliferative disease" to cover any condition of this type, but this would appear to be so broad as to deny any specific clinical connotations. The usefulness of a classification in clinical work depends on the reliability of the references in distinguishing patterns of presentation, in predicting the course of the disease, and in suggesting the probable response to therapeutic measures. In general, these requirements are best met

when aetiology is sufficiently understood to provide a basis for the classification, and, failing this, tissue pathology may provide a useful substitute. Little is known at present with regard to the aetiology of these conditions, although there is some evidence that there are chromosomal abnormalities in the marrow cells of cases showing myeloid metaplasia (Pranker, 1960), which perhaps suggests that the origin of the proliferative process lies in a somatic mutation affecting primitive mesenchymal cells, which restricts the ability of these cells to respond to the normal limiting factors governing cellular proliferation. It may be that the potentialities of the particular cell strain affected by the mutation determine the types of cell predominating in the individual clinical picture. At the present time, however, this offers no simple criterion for recasting the accepted classification of this group of disorders.

A vexed question related to those cases showing high red-cell or white-cell counts is whether these are properly to be regarded as aberrant forms of polycythaemia vera or chronic myeloid leukaemia. With regard to the former, the study published by Lawrence *et al.* (1953) is of great interest; in their Fig. 2 they show clearly the tendency of the white-cell count and the incidence of leucoerythroblastic anaemia to rise in cases of polycythaemia in parallel with increasing size of the spleen. Large as this series is, however, there are insufficient cases with moderate or considerable splenomegaly to know whether there is, in fact, one population with a skew distribution of these characteristics, or whether a true discontinuity exists, indicating two populations. From a clinical aspect, there is a clear advantage in distinguishing the cases with demonstrable primary myeloid metaplasia, since these differ in having marked splenomegaly and larger numbers of immature cells in the blood, in showing a tendency to marrow failure and occasionally to haemolytic anaemia, and in having a poorer prognosis.

It is of interest that Berlin *et al.* (1950) found a direct correlation between the red- and white-cell counts in cases of polycythaemia vera, similar to the correlation between haemoglobin levels and white-cell count in our Case 5C with primary myeloid metaplasia under treatment with steroids. This emphasizes the similarity between the proliferative processes in the two conditions. In fact, it may be that polycythaemia rubra vera is merely one expression of the disease primary myeloid metaplasia, in which there is exaggerated normoblastic proliferation and in which undue attention has been paid to the peripheral blood picture.

The differences between cases of primary myeloid metaplasia and chronic myeloid leukaemia are usually well marked. The white-cell counts are generally lower, histology shows the proliferation to affect more than one cell line, the destruction of splenic and lymph-node architecture is minimal, and the diffuse infiltration of tissues by abnormal cells is not seen (Black-Schaffer and Stoddard, 1953). Jackson *et al.* (1940) emphasized the longer survival of some of their patients, but it is doubtful whether this is a helpful distinguishing feature, since Koler (1957) found the mean survival of 143 cases from the literature, and from his own series, to lie between 4 and 4.2 years, which compares with a mean survival of 32 to 36 months in chronic myeloid leukaemia (Scott, 1957).

Whatever the criteria of classification of the myeloproliferative disorders it is to be expected that intermediate forms will be found (Hutt *et al.*, 1953).

However, the usefulness of distinguishing as a clinical reference those cases showing primary myeloid metaplasia is considerable. Firstly, the diagnosis rests on a clear pathological basis and may be made without difficulty by splenic puncture, liver biopsy, and occasionally lymph-node biopsy. In cases where a haemorrhagic tendency precludes needle puncture of the liver or spleen, isotope investigations provide an alternative method (Bowdler, 1961). Secondly, in this group of conditions, diagnoses defined in terms of the blood count may need frequent revision during the course of a single case, while the underlying tissue changes have not significantly altered. Thirdly, such a diagnosis will draw attention to the possible sequelae which may follow the establishment of these tissue changes, notably haemolytic anaemia, marrow failure, marrow unresponsiveness to haemorrhagic stress or haemolysis, and the consequences of unrestricted cellular proliferation of one or more lines of haemopoietic cells.

With regard to the treatment of this condition, most discussions in the past have centred principally on the advisability of splenectomy (Hickling, 1937; Green *et al.*, 1953; *Blood*, 1955). Briefly, in only one of our patients with haemolytic anaemia was the spleen found to play such a predominant part in the haemolytic process that this course was thought advisable. One patient (Case 4B) was recommended for irradiation to the spleen, but this was abandoned early in the course of the treatment owing to excessive nausea and malaise. In general, the two most useful agents have proved to be corticosteroids and radiophosphorus. The effect of steroid therapy in ameliorating the haemolytic anaemia of this condition is seen in Fig. 5, which shows a close correlation of the dosage with haemoglobin level. Of special interest is the brisk reticulocyte response which followed the start of therapy, suggesting that part at least of its effect was in altering the degree of marrow responsiveness to the haemolytic process. The effects of treatment in Case 3A have already been discussed; busulphan was found effective in correcting the leucocytosis but resulted in a slight depression of the haemoglobin level. Steroid therapy corrected the anaemia and controlled the depression of the haemoglobin induced by busulphan.

Four patients have had short courses of busulphan, but all proved to be remarkably sensitive to this drug and showed profound falls of white-cell and platelet counts on doses as small as 2 mg. daily for five days. No patients appeared clinically better, and therefore we do not regard this drug as having any great value in treatment.

Radiophosphorus may well be indicated for patients in hazard from polycythaemia or thrombocythaemia, in whom it may produce an effective reduction of the peripheral blood count to normal. Its use in patients already showing evidence of marrow failure would seem undesirable; in those patients of the present series seen to have polycythaemia and thrombocythaemia marrow failure has not been a feature.

Summary

A series of cases is described, all of which showed evidence of myeloid metaplasia. These have been grouped according to their most prominent presenting features, but this did not provide an exclusive differentiation owing to the degree to which the different cases overlapped.

The cases have been used to illustrate features of the clinical course, complications, presentation, and treatment of the condition.

The use of the term "primary myeloid metaplasia" in preference to that of "myelosclerosis" has been discussed, and the occurrence of the former before evidence of the latter invalidates the concept that the metaplasia is part of a compensatory mechanism.

The features of cases showing this condition are compared with other myeloproliferative disorders, and it is maintained that the term provides a useful clinical reference despite the wide spectrum of cases covered by its use.

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