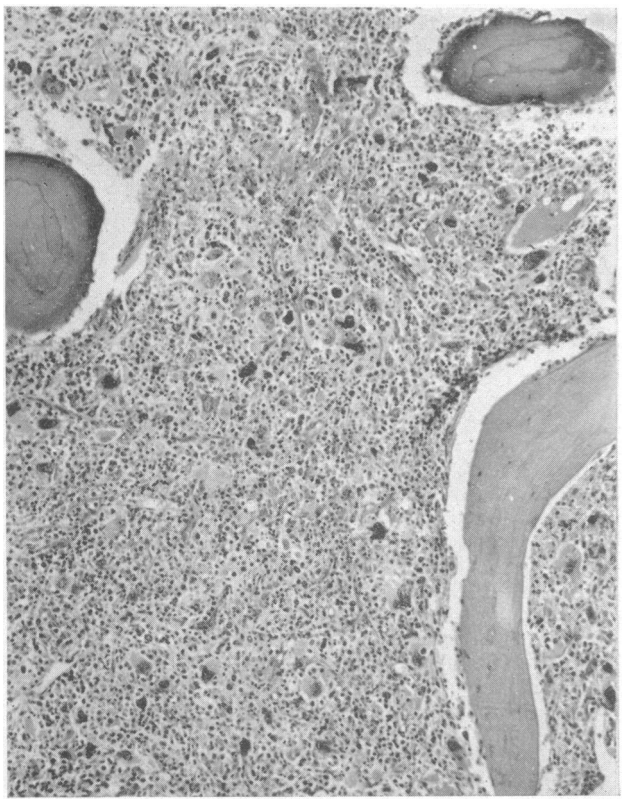

FIG. 1.—Photomicrograph of a section of bone marrow from Case 4. Iliac crest biopsy. (H. and E. ×100.)

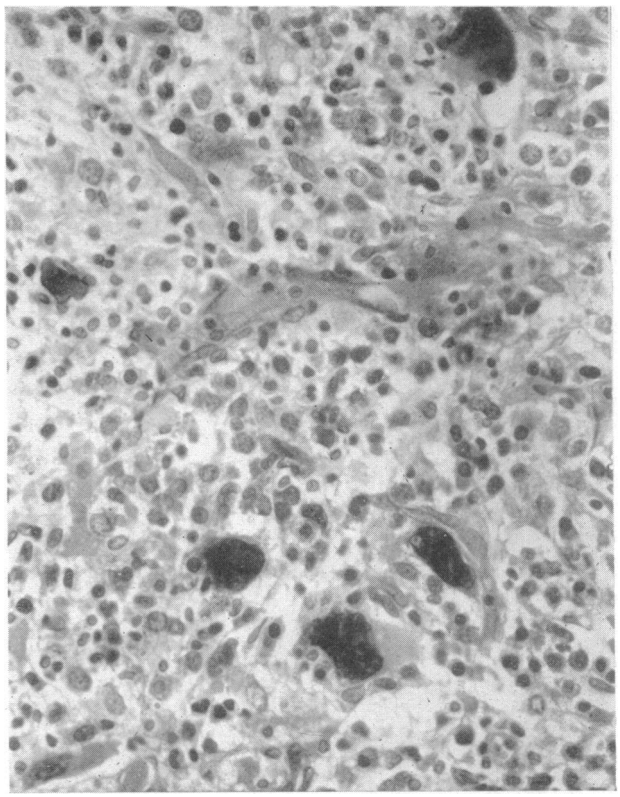

FIG. 2.—High-power view of portion of section illustrated in Fig. 1. (×360.)

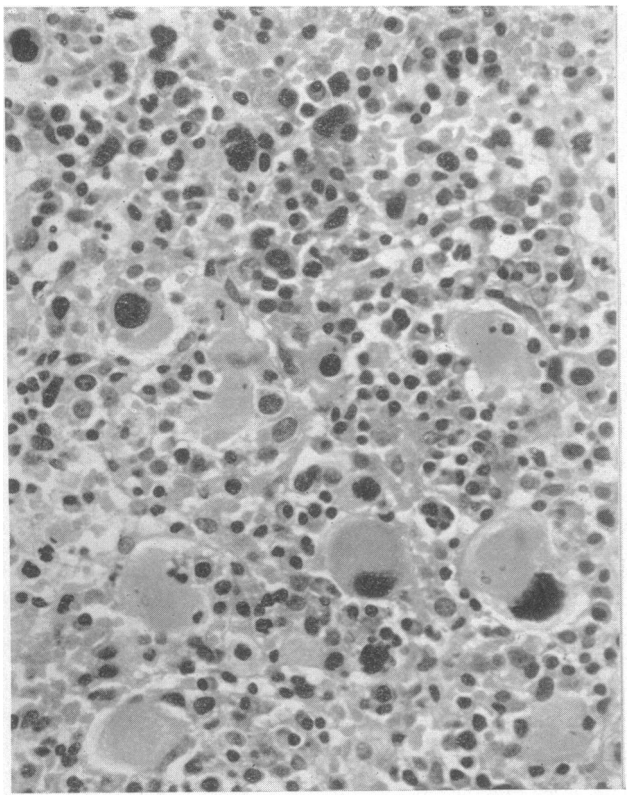

FIG. 3.—Photomicrograph of a section of bone marrow from Case 5. Iliac crest biopsy. (H. and E. ×360.)

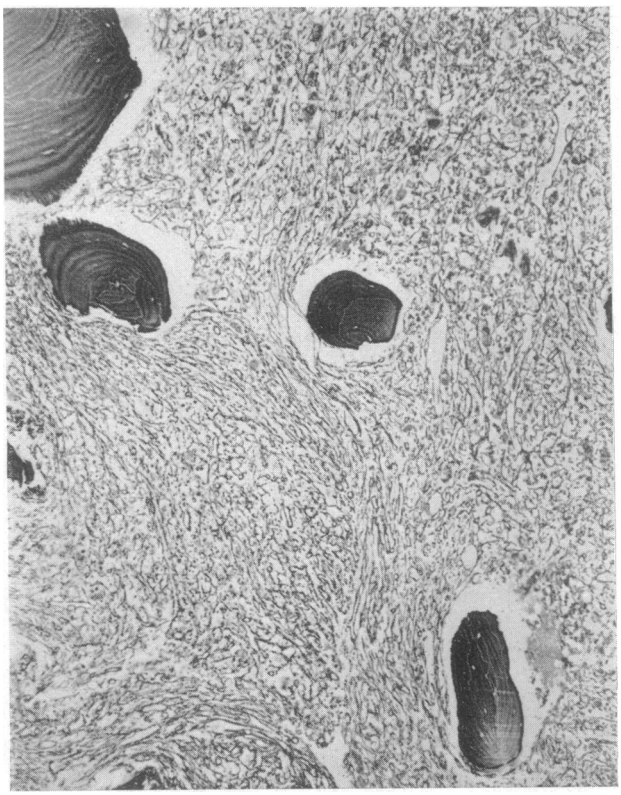

FIG. 4.—Photomicrograph of a section of bone marrow from Case 4. Iliac crest biopsy. Stained for reticulin by silver impregnation method. (×100.)

in the decision whether or not to advise surgery in the patients with unilateral lesions.

In most previously reported cases of polycythaemia associated with a renal lesion the polycythaemia has not been accompanied by splenomegaly, leucocytosis, or thrombocytosis. As mentioned in the introduction, however, a number of cases have been described in which one or more of these features were present, and in a few such cases a remission of polycythaemia has been reported after nephrectomy. Our own survey of a group of patients with apparent polycythaemia vera adds to those already described seven more examples of associated renal lesions and polycythaemia accompanied by splenomegaly, leucocytosis, or thrombocytosis. More information is required about the incidence of renal lesions, especially cysts, in patients with apparent polycythaemia vera, and the relationship of these lesions to the polycythaemia still needs to be clarified. At present we believe that the idea that polycythaemia due to a renal lesion can be clearly separated from polycythaemia vera with a coincidental renal lesion by the absence of splenomegaly, leucocytosis, and thrombocytosis may prove difficult to sustain. Such a division seems to have limited practical value in any case, as patients with apparent polycythaemia vera may occasionally have normal leucocyte and platelet counts in the absence of any demonstrable lesion known to cause an increase in the red-cell mass. Until further information is available, we suggest that intravenous pyelography should become part of the routine investigation of all patients with polycythaemia vera.

Summary and Conclusions

The incidence of renal lesions in 91 patients who had been previously diagnosed as suffering from polycythaemia vera by exacting criteria was determined by routine radiological investigation.

Some unusual deformities of the left kidney caused by splenic enlargement are described.

The total incidence of renal lesions discovered was 21% (19 cases).

The incidence of renal lesions which have been described as causing polycythaemia was 9% (8 cases).

Seven of the eight patients with this type of lesion showed one or more of the features splenomegaly, leucocytosis, thrombocytosis.

It is suggested that the idea that polycythaemia due to a renal lesion can be clearly separated from polycythaemia vera by the absence of splenomegaly, leucocytosis, and thrombocytosis may prove difficult to sustain.

Renal investigation should be included in the routine examination of all patients with apparent polycythaemia vera.

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MALIGNANT MYELOSCLEROSIS

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[WITH SPECIAL PLATE]

The term " myeloproliferative disorders " has been used to stress the close relationship which exists between several diseases characterized by the proliferation of one component, or more, of the bone-marrow (Dameshek, 1951 ; Wasserman, 1954). These diseases are of unknown aetiology and include a number of more or less clearly defined syndromes, of which the best-recognized are acute and chronic granulocytic leukaemia, polycythaemia vera, erythroleukaemia (Di Guglielmo's disease), and myelosclerosis. It is, however, generally accepted that these conditions may merge into one another.

Myelosclerosis is a chronic but progressive and eventually fatal disease in which there is replacement of the bone-marrow by connective tissue and, at times, cancellous bone. The marrow is characterized by an increase in argyrophil reticulin and myeloid proliferation with an increase in reticulum cells and often numerous megakaryocytes. The haematological features vary. There is usually a leuco-erythroblastic anaemia, at times with a large number of circulating nucleated red cells and a moderate rise in the reticulocyte count ; marked variation

occurs in the shape of the red cells, tear-drop poikilocytes being especially prominent. The total leucocyte count may be normal, reduced, or increased, and there are usually a variable number of myelocytes although only an occasional myeloblast. The platelet count, too, may be reduced, but is usually normal or increased.

Extramedullary haemopoiesis usually occurs in myelosclerosis, predominantly in the liver and spleen, although other organs—for example, kidney, lymph nodes—may also be involved. Splenomegaly is almost invariably present and may be the dominant clinical feature. The liver is also often enlarged. The hepatosplenomegaly is thought to be due to extramedullary haemopoiesis. The average survival after diagnosis is probably longer than two to three years (Bouroncle and Doan, 1962) and many patients survive for ten years or more. Death is usually due to complications caused by anaemia, thrombocytopenia, or intercurrent infections. At the end of a relatively chronic course some patients may develop a terminal acute phase, often with a pancytopenia and myeloblasts in the peripheral blood.

In recent years several patients have been observed who presented with an acute rapidly progressive illness and who showed the histological features of myelosclerosis but had unusual haematological and clinical features. The existence of a variant of myelosclerosis which presents in an acute form *ab initio* has not previously been clearly recognized. In order to distinguish this syndrome from the terminal (" acute ") phase of chronic myelosclerosis it might be called " malignant myelosclerosis."

Clinical and Haematological Features

During the past seven years five patients who appear to belong to this group have been seen at Hammersmith Hospital. The clinical features are summarized in Table I and detailed in the case reports. It will be noted that there were three men and two women, and that all were older than 40 years. They presented with symptoms due to rapidly developing anaemia and thrombocytopenia. The clinical examination was essentially negative and, significantly, in no patients was there enlargement of spleen or lymph nodes.

The dominant features of the blood counts were anaemia and leucopenia (Table II). The anaemia was associated with the presence of variable numbers of circulating normoblasts, but the reticulocyte count was persistently low. The red cells showed a moderate variation in shape, but while poikilocytosis was present it was not prominent. The striking feature of the low leucocyte count was a neutropenia. Blasts were present in all cases, usually 1–2% on presentation. Leucocyte alkaline phosphatase was studied in only one patient (Case 2), in whom it was found to be high. The platelet count was low in all cases, but it fluctuated during the course of the illness (Figs. I–V).

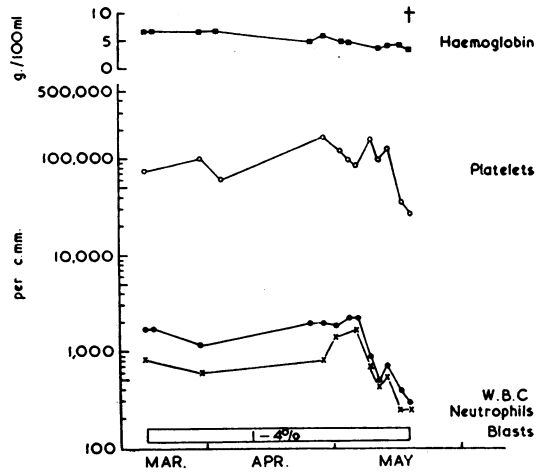

FIG. I.—Haematological observations on Case 1.

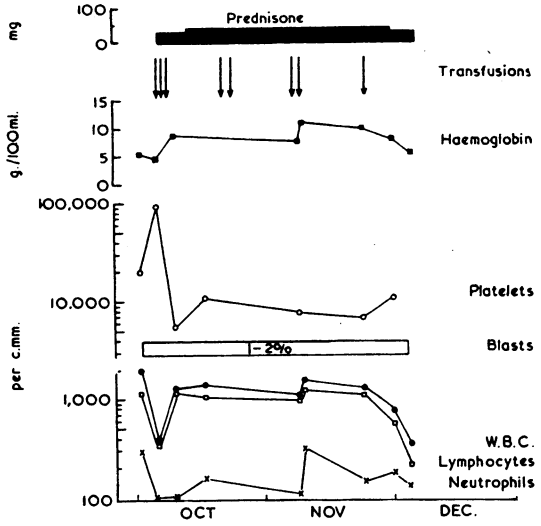

FIG. II.—Haematological observations on Case 2.

TABLE I.—*Clinical Features of Patients with Malignant Myelosclerosis*

Case No.	Age	Sex	Initial Diagnosis	Spleen	Liver	Lymph Nodes	Main Clinical Features	Duration (From Onset of Symptoms)	
								Until Admission to Hammersmith Hospital (Months)	Until Death (Months)
1	68	F	Acute leukaemia	0	0	0	Anaemia	1	3
2	55	M	Erythroleukaemia	0	0	0	Thrombocytopenia and anaemia	6	8
3	53	F	Lymphosarcoma	0	0	0	Anaemia	3	15
4	43	M	? Aplastic anaemia/acute leukaemia	0	0	0	,,	8	11
5	56	M	Acute leukaemia	0	3 cm.	0	,,	6	6

TABLE II.—*Initial Blood Counts at Hammersmith Hospital*

Case No.	Hb (g./100 ml.)	P.C.V. (%)	Retic. (%)	Circulating Normoblasts (/c.mm.)	Platelets (/c.mm.)	W.B.C. (/c.mm.)	Differential Count (%)						
							Blasts	Myel.	N.	E.	B.	Ly.	Mono.
1	6·6	20	2·1	54	80,000	1,800	1	11	49	3	1	34	1
2	7·8	23	1·8	400	6,000	1,300	2	0	4	0	0	94	0
3	4·5	16	0·2	Occasional	60,000	1,000	7	0	7	0	0	84	2
4	3·8	11	0·8	15	24,000	1,500	2	11	23	0	0	61	3
5	5·4	17	0·1	Occasional	98,000	1,500	2	0	8	0	0	90	0

Marrow Aspiration.—Attempts to obtain marrow by aspiration were made in all cases. In Cases 3 and 4 no marrow was obtained from either sternum or ilium. In the other cases the material obtained included few or no fragments, and the cells present were predominantly blasts (myeloblasts, erythroblasts); a few reticulum cells and megakaryocytes were also seen.

Bone Biopsy.—This was obtained from the iliac crest in four of the patients by means of a Sacker-Nordin trephine, and in the fifth (Case 3) by means of surgical trephine of a rib. A characteristic histological picture was seen. There was an alteration in the normal architecture with an increase in collagen tissue. The fat spaces and normal haemopoietic tissue were reduced. Round and oval mononuclear cells (probably primitive reticulum cells) were present, and giant cells similar to megakaryocytes were a prominent feature. Mitosis was increased, but not markedly so (Special Plate, Figs. 1–3). Staining by silver impregnation showed a pronounced increase in argyrophil reticulin, which was present as coarse fibres surrounding groups of cells (Special Plate, Fig. 4).

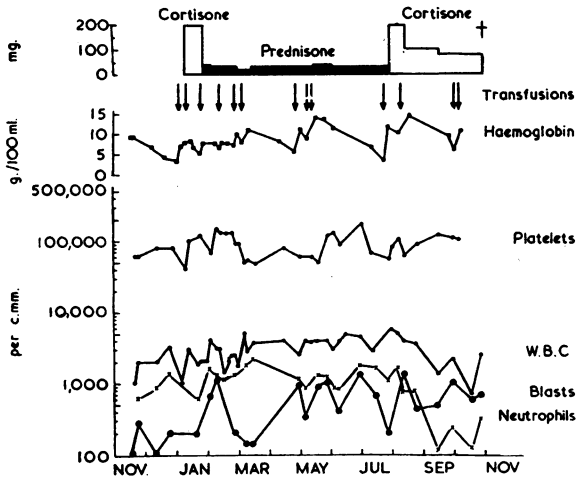

FIG. III.—Haematological observations on Case 3.

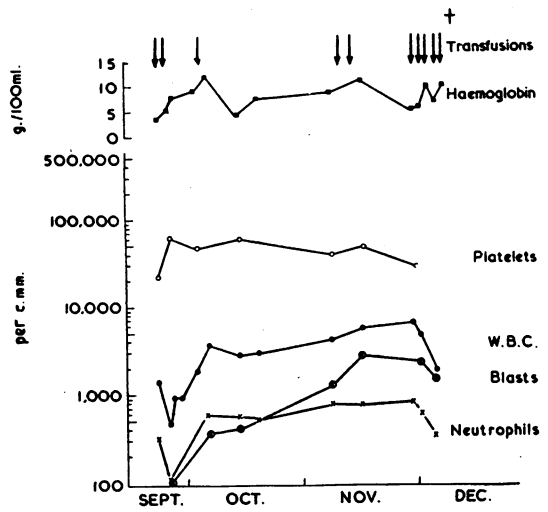

FIG. IV.—Haematological observations on Case 4.

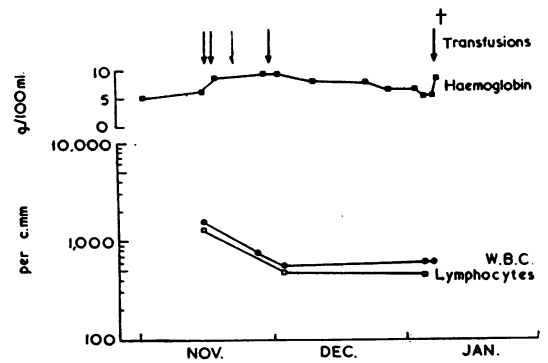

FIG. V.—Haematological observations on Case 5.

Course.—There was a rapid downhill course without any evidence of even a temporary remission (Figs. I–V). The survival time from first admission to hospital until death varied between 2 and 12 months, while four of the patients died within three months. The patients required frequent blood transfusions, and the patient who survived for 12 months did so only with the help of massive transfusions. It is, of course, impossible to determine an exact date of onset, especially as the presenting symptoms were caused by the anaemia. So far as could be ascertained, the total duration was also short, and varied between 3 and 15 months.

Necropsy.—A similar picture was seen in all cases. There was considerable replacement of marrow throughout the skeleton by an abnormal cellular tissue in which reticulin fibres were conspicuous, the appearances being identical with those in the bone biopsies (see above). A variable amount of developing haemopoietic tissue was found in scattered foci. The proliferative process was not confined to the marrow but occasionally infiltrated outside the bone, and there was also, to a greater or less extent, infiltration of haemopoietic tissue of the same general character in other organs, especially the spleen, liver, and renal cortex. Lymph nodes and testes were involved in one case. The spleen was only slightly enlarged in three of the cases, weighing 300, 400, and 550 g. The liver was not enlarged and in most cases showed fatty changes. Extramedullary haemopoiesis was found in the spleen only in Case 1 and in the liver only in Case 2. The immediate cause of death was anaemia or haemorrhage.

Case Reports

Case 1

A woman, aged 68 when admitted to Hammersmith Hospital on March 15, 1955, stated that about one month previously she had had "flu" (coryza, headache, and muscular aches). She improved after a few days, but two weeks prior to admission developed epigastric and substernal discomfort with nausea and periodic vomiting, and she also felt weak generally.

On admission to hospital she was pale and had retinal exudates and haemorrhages. The lymph nodes were not enlarged and the liver and spleen were not palpable. The *x*-ray picture of the chest was normal and a barium-meal examination showed a large irreducible hiatus hernia. *X*-ray films of the spine and femora were normal but the skull showed some translucent areas. The initial blood picture is shown in Table II. Other investigations showed proteins 7.5 g./100 ml. (albumin 3.5 g., globulin 4 g.) and bilirubin 0.6 mg./100 ml. It was suspected that she had acute leukaemia. She was transfused, and on April 29 treatment with 6-mercaptopurine (150 mg. daily) was begun. On May 15 she developed epistaxes, her platelet count fell to 34,000/c.mm., and the mercaptopurine was stopped. Her condition rapidly deteriorated and she died on May 20.

Case 2

The patient was aged 55 when he was admitted to Hammersmith Hospital on October 14, 1961. In 1953 he had right apical tuberculosis, which was treated by thoracoplasty. He was seen regularly thereafter. In March, 1961, he had a number of epistaxes and developed lassitude and increasing

dyspnoea on exertion. He was seen at another hospital on September 1, and was found to be anaemic and leucopenic. Other investigations were essentially normal. He was transfused and placed on prednisone, 30 mg. daily. His haemoglobin continued to fall and he was transferred to Hammersmith Hospital for further investigation.

On admission he was pale; there were petechiae on the legs and feet; the lymph nodes were not enlarged; the liver was just palpable but the spleen was not felt. The initial blood picture is shown in Table II. The leucocyte alkaline phosphatase was high. In view of the severe pancytopenia he was given blood transfusions only. He was readmitted on November 7 because of marked dyspnoea and general weakness. He was given a further transfusion of 8 pints (4.5 litres) of blood and was discharged four days later. He had to be admitted again on November 23 because of recurrence of lassitude, nausea, and severe post-nasal haemorrhage. On this occasion widespread purpura was found on the arms, legs, and trunk. He was transfused and treated with prednisone, 40 mg. daily, but his condition deteriorated and he died on December 5.

Case 3

This patient was aged 53 when first seen in November, 1955. Three months previously she noted that she was getting easily tired. Towards the end of August she had severe haemorrhage after dental extraction. On September 8 she was admitted to another hospital with pyrexia (104° F.—40° C.). She was found to be anaemic, and an *x*-ray examination of the chest suggested a tumour at the left hilum. A bronchoscopy showed no abnormality, and the temperature settled with antibiotics. A rib biopsy was performed and lymphosarcoma was suggested. The patient was referred to Hammersmith Hospital. When first seen here the liver and spleen were not felt and no glands were palpable. The initial blood picture is shown in Table II. It was thought that she had an acute myeloblastic leukaemia. *X*-ray examination of the chest suggested that the lesion in the left lung was due to segmental deflation and there was no real evidence of hilar enlargement. In December her anaemia again became severe and she developed lassitude, dyspnoea, and weakness. She was treated with steroids (see Fig. III). At first there was a suggestion of clinical and haematological improvement, but this was not maintained. In February and April, 1956, she received further transfusions and the dose of prednisone was increased. Throughout the period the spleen remained impalpable. A number of other investigations were performed, and these were essentially negative. During October she received 9 pints (5.1 litres) of blood. She was discharged from hospital on November 3, 1956, but one week later she suddenly developed upper abdominal pain and died on November 11.

Case 4

The patient was aged 43 when admitted to Hammersmith Hospital on September 22, 1955, with symptoms of his terminal illness. In 1940 he complained of backache, which was diagnosed as being due to ankylosing spondylitis. In 1949 he had a course of *x*-ray treatment to the spine at another hospital. The symptoms recurred in 1953 and he had a further course of radiotherapy at Hammersmith Hospital. Towards the end of 1954 he began to feel unwell, with nausea and lack of energy. In August, 1955, he noticed that his tiredness increased; he became dyspnoeic on exertion and had cramps in the legs on walking.

On admission in September he was very anaemic (see Table II). The liver and spleen were not palpable and no lymph nodes were found to be enlarged. *X*-ray examination of the spine confirmed ankylosing spondylitis. He was transfused with 7 pints (4 litres) of blood and discharged on October 6. He was readmitted on November 7 because he had become severely anaemic and had palpitations and dyspnoea on exertion. A total of 8 pints (4.5 litres) of blood was given and he was discharged on November 16. He had to be readmitted on November 29 with severe anaemia, epigastric discomfort, and dark stools. The liver and spleen remained impalpable. He was given further blood transfusions (13 pints; 7.4 litres), but in spite of this he continued to deteriorate, dying on December 11, 1955.

Case 5

This man was aged 56 when admitted to Hammersmith Hospital on January 4, 1956. About six months previously he had noted that he was getting easily tired and was short of breath on exertion. This became more pronounced after a few months and he also developed precordial pain on exertion, anorexia, and paraesthesiae in the hands and feet. He had lost considerably in weight. He had been admitted to another hospital on October 28, 1955, and was found to be grossly anaemic. A histamine-fast achlorhydria was diagnosed and he was at first treated with vitamin B_{12} injections and supplementary iron therapy. He required a number of blood transfusions and folic acid was also given. During December, 1955, his condition deteriorated, he developed a swinging pyrexia and was then transferred to Hammersmith Hospital for further investigations.

On admission he was moderately pale; there was a suggestion of an icteric tinge and he had purpuric spots on neck, both arms, and soft palate. The liver was palpable 3 cm. below the costal margin, but the spleen was not felt. The initial blood picture is shown in Table II. Other investigations showed proteins 5.1 g./100 ml. (albumin 1.4 g., globulin 3.7 g.), bilirubin 1.2 mg./100 ml., and blood urea 91 mg./100 ml. He was transfused. Next day he developed pain on the left side of the chest and haemoptysis. Further purpuric spots and ecchymoses occurred. He deteriorated rapidly, and died on January 8, 1956.

Discussion

The five cases described above appear to have in common a number of features which justify their inclusion in a distinctive group. The patients presented with symptoms of a rapidly developing anaemia with a lack of physical findings. Notably, there was no clinical evidence of enlargement of spleen or lymph nodes. The peripheral blood picture was suggestive of acute leukaemia, but the bone-marrow appearances were similar to that of chronic myelosclerosis. The disease was invariably fatal after a rapid course. Because of these features we think that the condition is most clearly defined by the term "malignant myelosclerosis." This also serves to distinguish it from the well-recognized acute terminal phase of chronic myelosclerosis.

In three of the patients no possible aetiological factors could be discovered. In Case 2 there was a history of pulmonary tuberculosis, but at the time of onset of the final illness the lung lesions appeared to be quiescent and at necropsy there was no evidence of active tuberculosis. It is improbable that the pulmonary tuberculosis played a part in the causation. One patient (Case 4) had ankylosing spondylitis, for which he had received spinal irradiation two and six years previously. The leukaemogenic effects of irradiation are well recognized, and it has also been suggested as a possible factor in the development of myelosclerosis. It is, of course, not possible to be certain about the association in the present case, but it cannot be excluded.

The disease may be confused with a number of conditions, as is shown by the fact that the patients were initially referred with a diagnosis of acute leukaemia (2), erythroleukaemia (1), lymphosarcoma (1), and ? aplastic anaemia/? acute leukaemia (1). On the basis of the clinical and haematological findings, malignant myelosclerosis must be distinguished from acute leukaemia, chronic myelosclerosis, and reticulum-cell sarcoma, as it has some characteristics of each.

Acute Leukaemia.—It is difficult to distinguish malignant myelosclerosis from cases of acute leukaemia by the history

and clinical features alone, although in leukaemia splenic enlargement is frequent and the lymph nodes may be palpable. In a typical case of leukaemia the peripheral blood picture is usually diagnostic. However, cases presenting in an aleukaemic phase may be almost indistinguishable from malignant myelosclerosis, although in the latter condition the leucopenia is usually more profound and there are few blasts. The diagnosis is elucidated by the bone-marrow findings. The aspiration of hypercellular fragments of marrow with numerous primitive cells in leukaemia contrasts with the inability to obtain marrow in malignant myelosclerosis, where the failure of aspiration suggests an alteration in the texture of the marrow rather than marrow-cell proliferation. To obtain marrow material in the latter condition may require a bone biopsy, by means of which the differentiation of the two conditions becomes apparent.

Chronic Myelosclerosis.—The bone-biopsy appearances of malignant myelosclerosis may be indistinguishable from those of chronic myelosclerosis. In both conditions the picture is dominated by a diffuse increase in reticulin fibres and the presence of giant cells and reticulum cells. There does not appear to be greater mitotic activity in the malignant myelosclerosis as compared with the chronic form, and there are no clear features indicative of its rapidly progressive nature. The conditions can be differentiated by the history and clinical features and the peripheral blood picture. Patients with chronic myelosclerosis usually have a long history, the spleen and liver are usually markedly enlarged, the anaemia is generally less severe, and there may be a characteristic peripheral blood picture of tear-drop poikilocytes, reticulocytosis, and relatively large numbers of normoblasts. The leucocyte count may be normal although at times it may be increased or decreased. The platelet count is often increased, but it may be normal or occasionally decreased. Extramedullary haemopoiesis, usually in spleen or liver, may be a dominant feature (Szur and Smith, 1961). As a rule the course of the disease from the time of diagnosis is a prolonged one, and while it may terminate in an acute phase, this will develop only after a lengthy period.

Reticulum-cell Sarcoma.—In its classical form reticulum-cell sarcoma presents with local or generalized adenopathy and there may be splenic and hepatic enlargement. This should not be confused with malignant myelosclerosis. Bone deposits may occur as a late manifestation, but, unlike the diffuse infiltration of malignant myelosclerosis, they remain well defined. Primary reticulum-cell sarcoma of bone has been described (Parker and Jackson, 1939; Ivins and Dahlin, 1953; Francis *et al.*, 1954), but this presents normally as a solitary lesion in a long bone. Even when the lesions are multiple the clinical and histological findings are those of a localized bone tumour. The presenting feature is a painful swelling. The tumour responds well to radiotherapy and the prognosis is relatively good. The histological picture is a uniform one of primitive reticulum cells with fine reticulin fibrils between individual cells as well as coarse fibres surrounding clumps of cells. Megakaryocyte-like giant cells are not present. A diffuse variant of reticulum-cell sarcoma confined to bone might well result in a similar clinical picture to that of malignant myelosclerosis. Such a condition might represent a less well differentiated form of malignant myelosclerosis, and the problem of differentiation would then be a semantic one.

Therapy.—Various forms of treatment were attempted in the five patients. These included steroids, 6-mercaptopurine, and various haematinics. None appeared to be of any benefit. The patients required frequent transfusions for prolongation of life. While androgens have been reported of value in chronic myelosclerosis they were not tried in the present group.

Relationship to Myeloproliferative Disorders

The concept of myeloproliferative disorders as described by Dameshek (1951) and by Wasserman (1954) is a useful one as it affords an understanding of the way in which a number of neoplastic diseases may arise from a common stem cell, the marrow reticulum cell, and the relationship of the diseases to each other. The various conditions may arise *de novo* or may develop during the course of one of the others of the group. Furthermore, the diseases merge with each other and not infrequently there may be borderline cases which cannot be distinctly classified.

Chronic myelosclerosis is well recognized as a member of the group. Malignant myelosclerosis fits into the general concept of the myeloproliferative disorders, and its relationship both to chronic myelosclerosis and to the other more common diseases is illustrated in Fig. VI. Reticulum-cell sarcoma has not generally been considered to belong to this group, but a possible link may be provided by malignant myelosclerosis.

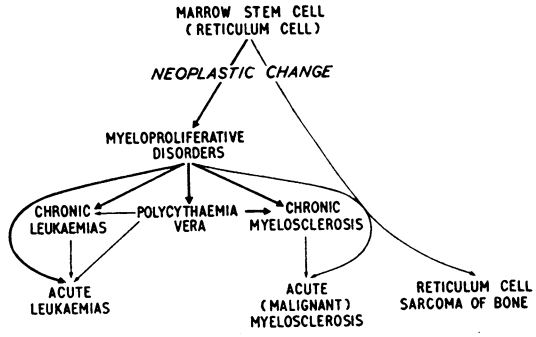

FIG. VI.—Schema of interrelationship of acute and malignant myelosclerosis with the commoner myeloproliferative diseases and with reticulum-cell sarcoma.

As discussed above and suggested in Fig. VI, it has been considered that the relationship of malignant myelosclerosis and chronic myelosclerosis is similar to that of acute granulocytic leukaemia and chronic granulocytic leukaemia.

Although malignant myelosclerosis is a rare and invariably fatal disorder for which no useful therapy is at present available, its recognition is of theoretical and prognostic importance.

Summary

Five cases of an unusual form of myelosclerosis are described. There was an acute onset, with symptoms due to anaemia and thrombocytopenia, and a rapid downhill course. The spleen and the lymph nodes were not palpable in any of the patients.

The term "malignant myelosclerosis" has been used to describe the condition, which is thought to be an acute variant of myelosclerosis.

Malignant myelosclerosis has some features of chronic myelosclerosis, acute leukaemia, and reticulum-cell sarcoma, but it can be distinguished from each by a combination of the characteristic clinical findings, blood counts, and bone-biopsy histology.

It differs from the acute terminal phase of chronic myelosclerosis as it presents acutely *ab initio*. Its relation-

ship to chronic myelosclerosis is probably similar to that of acute granulocytic leukaemia to chronic granulocytic leukaemia, and it may provide a link between reticulum-cell sarcoma and the myeloproliferative disorders.

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MALARIAL ANTIBODY TITRES OF WEST AFRICANS IN BRITAIN

BY

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In the past it has been almost impossible to know the status or duration of immunity to malaria in endemic malaria zones, owing to the difficulty in not being able to differentiate a relapse from reinfection, and owing to the fact that, where malaria is prevalent, sometimes two, if not three, of the human-malaria parasite species may be present, appearing consecutively in the same individual (Coggeshall, 1943). Acquired immunity to malaria is manifested only gradually in some malarial infections but more suddenly in others, and frequently results in the suppression and elimination of the infection and in refractiveness to super-infection and reinfection (Boyd, 1949).

Little is known about malarial immunity in individuals previously immune who have left their environment of repeated exposure to malaria for one where none exists. Coggeshall (1938) and Maier and Coggeshall (1944) found that immunity to reinfection with *Plasmodium knowlesi* lasts from three to fourteen months after complete sterilization of the blood with sulpha drugs. Boyd *et al.* (1936, 1939) found immunity to the homologous strain of *P. vivax* three and seven years after the primary attack of malaria. Coggeshall (1943) has demonstrated that latent malaria in experimental animals can be destroyed by chemotherapy and that the duration of immunity is brief, usually a matter of months, while the eradication of an acute infection in its earlier stages leaves the host with no immunity whatsoever. More recently, Kuvin *et al.* (1962a, 1962b) followed the course of malarial antibody production in normal volunteers, utilizing the indirect method of immunofluorescence. They found detectable malarial antibody for as long as 335 days after sporozoite infection. In addition, all the infected volunteers demonstrated an increase in their serum gamma-globulin levels.

Schofield (1957) investigated the serum protein patterns of West Africans resident in Britain. He demonstrated by electrophoretic methods that when healthy adult Africans enter a European environment the serum proteins change steadily but very slowly from a typical "African" pattern with low serum albumin and high gamma-globulin values, toward a typical "European" pattern, with a marked fall in the gamma-globulin fraction. He concluded that these changes in gamma-globulin levels reflected a recovery from pathological effects induced by the previous African environment of malaria and malnutrition. The belief that *protective* malarial antibodies were present at some time after infection was given support when Coggeshall and Kumm (1937) demonstrated that the serum of rhesus monkeys with chronic *P. knowlesi* infections conferred passive immunity upon monkeys with acute infections with this parasite. Cohen *et al.* (1961) clinically correlated the high serum gamma-globulin levels in Gambian Africans infected with malaria with the production of protective antibodies.

Previously, attempts have been made to follow the course of malarial-antibody production with specific complement fixation and precipitation reactions with sera from patients infected with malaria, but these efforts have met with only limited success (Coggeshall and Eaton, 1938; Lippincott *et al.*, 1945; Mayer and Heidelberger, 1946). The fluorescent antibody technique has been used in the specific staining of malaria parasites (Ingram *et al.*, 1961; Tobie and Coatney, 1961; Voller, 1962), and previous investigations employed the indirect method of immunofluorescence to follow the course of antibody production in man (Kuvin *et al.*, 1962a, 1962b; Voller and Bray, 1962; Tobie *et al.*, 1962). These studies suggested that the fluorescent antibody technique provides a specific and sensitive method for titrating malarial-antibody production in man.

The object of the present investigation was to determine whether malarial antibody production and serum gamma-globulin levels were altered in individuals from endemic malarial areas by residence outside these zones. We were also interested in evaluating the suitability of the simian parasite *P. cynomolgi bastianellii* as a diagnostic and investigative antigen for use in studying the immune response in human malaria, utilizing the fluorescent antibody technique. This parasite can be readily maintained in rhesus monkeys as a laboratory infection, whereas human-malaria parasites cannot be grown in culture, will not readily infect animals, and are obtained only from patients with clinical malaria.

Material and Methods

Serum was obtained from 26 West Africans between the ages of 19 and 46 years admitted to the Hospital for Tropical Diseases. All were of the African race and native to West Africa where *P. falciparum* is endemic. They left West Africa to reside in Britain for reasons of employment or study. In addition to taking a malarial history, physical examination was performed, special attention being paid