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II. ANÄMIA WITH HYPOCellular, NORMOBlastic Marrows

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In a previous communication (1943) we proposed a classification for refractory anaemias based mainly on sternal puncture findings. The present paper is concerned with the clinical and haematological features of cases falling into the group characterised by hypocellular, normoblastic sternal marrows. These cases are further divisible into two main sub-groups according to aetiology:

(a) secondary to exposure to toxic substances; (b) idiopathic.

(a) Secondary to exposure to toxic substances

Included in this group are four cases in which the onset of the anaemia was known to follow exposure to well-recognised haemotoxic substances. In two of the cases the noxious agents were administered therapeutically—arsenical compounds in the treatment of syphilis and gold salts in the treatment of rheumatoid arthritis. It will be seen that both of these cases eventually made a complete recovery. In the other two cases the toxic substances were benzol and trinitrotoluol, the exposure being occupational. Both of these cases were fatal.

Case 1.—Male, æt. 30, bookbinder.

The patient was employed in an occupation involving exposure to benzol fumes for 6 years until September 1939. He had periodical medical examinations and was passed fit for the Army in September 1939. Two months later he began to complain of weakness, tiredness and anorexia. He was admitted to hospital in Newcastle on 4.12.39. His blood picture at that time was: Hb., 45% ; R.B.C., 1,729,000; W.B.C., 3400 per c.mm.; C.I., 1.3; and reticulocytes, 1.3%. Sternal marrow examination was stated to reveal "an increase of megaloblasts." He received intensive parenteral liver therapy with "Anaheimin" and "Campolon," but there was no response and he was accordingly transfused with blood. He left Newcastle in March 1940 and, after a short stay in a Ministry of Pensions hospital, was invalidated out of the Army

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one month later. He became progressively weaker and was admitted
to Edinburgh Royal Infirmary on 7.5.40.

Physical examination.—Temperature 103°F. Pulse 120. The
patient appeared rather poorly nourished and very pale. No oedema
or petechiae and no enlargement of liver, spleen or lymph glands detected.

Laboratory findings.—Hb., 36%; R.B.C., 1,050,000; W.B.C.,
5,200 per c.mm.; C.I., 1.43; reticulocytes, less than 1%; platelets,
85,000 per c.mm.; M.C.V., 123.8 cu.µ; M.C.H.C., 36%. Film showed
anisocytosis and poikilocytosis of the red cells which were well filled,
many oval macrocytes being present. Differential white count: poly-
morphs, 91%; lymphocytes, 9%. Toxic granulation and shift to the
left of the polymorphs. An occasional myelocyte was seen. Icteric
index, 8. Van den Bergh, indirect positive. Urobilinuria was present.

Gastric analysis.—Histamine-fast achlorhydria.

Sternal puncture.—The marrow tissue was scanty, but as no excess
of fat was observed, no assessment could be made of the actual degree
of marrow cellularity. The cells appeared to be present in approxi-
mately normal proportions and maturation to be proceeding normally
in both the red and white series. Erythropoiesis was normoblastic.
The granulocytes showed a somewhat high proportion of polymorphs,
some of which were of the macrocyte type.

Progress.—Haematinic treatment with "Pernämon Forte" and iron
resulted in no erythropoietic response. Eight pints of blood were trans-
fused during the patient’s nine weeks’ stay in hospital. A second sternal
puncture on 25.5.40, eighteen days after his admission, revealed a marrow
picture similar to the first one. Four weeks after admission he developed
lobar pneumonia which responded to treatment with sulphapyridine.
This infection was accompanied by a leucocytosis which persisted after
recovery from the pneumonia, the white cell count rising to 26,000 per
c.mm. A third sternal puncture on 28.6.40 showed that, while the
marrow tissue was still scanty, there was a significant increase in the
granulocytes, myelocytes and polymorphs being abundant.

A striking feature of the later peripheral blood films was the presence
of myelocytes and myeloblasts which increased in frequency until eventu-
ally they formed 14% and 8% respectively of the total white cells.

Following his recovery from pneumonia the patient’s condition
continued to deteriorate and his hemoglobin fell to 23% with 940,000
red cells, 26,600 white cells and 50,000 platelets per c.mm. The high
white cell counts and the presence of the primitive white cells referred
to were thought to indicate the onset of a leukaemic condition. The
patient was allowed to leave hospital at his own request and died a few
days later.

An autopsy was performed, the full details of which are unfortunately
not available, but it is known that myeloid infiltration was found in the
liver and spleen and that the general findings were held to be consistent
with a diagnosis of myeloid leukaemia.

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Case 2.—Unmarried female, æt. 21.

The patient had worked in a munition factory for 12 months with liquid trinitrotoluene. She stated that the fumes caused a gripping sensation in her throat and that she had complained repeatedly of abdominal pain of a colicky nature accompanied by nausea and vomiting. Her clothes, skin and hair became yellow-red in colour. For four months before admission to hospital on 16.1.42 she had noticed that she was becoming paler and more easily tired at work. During the twelve days before admission she had had profuse menorrhagia.

Physical examination.—Temperature 99° F. Pulse 108. The patient was well nourished but very pale and tired, with a lemon tinge on the skin but no oedema or petechiae. No enlargement of liver, spleen or lymph glands was noted.

Laboratory findings.—Hb., 23%; R.B.C., 835,000; W.B.C., 1800 per c.mm.; C.I., 1.35; platelets, 50,000 per c.mm. Film showed anisocytosis but the cells were well stained and appeared to be of normal mean diameter. Icteric index, 10. Webster’s test for T.N.T., positive.

Sternal marrow films showed a marked decrease in all the marrow elements, with a corresponding increase of the fatty tissue. Of the cells present reticulum cells, plasma cells and lymphocytes showed an increased frequency. Red cell precursors were infrequent and were normoblasts. The scanty granulocytes were mainly promyelocytes and myelocytes. Megakaryocytes and platelets were not seen.

Progress.—Following admission the patient continued to bleed profusely per vaginam. Five blood transfusions were given during a period of three weeks totalling 19½ pints of blood. In addition she was given "Anahæmin" and "Pernaemon"—as well as iron, ascorbic acid, calcium, stilbestrol and hemoplatin. The vaginal bleeding continued and uterine packs were employed on two occasions. The haemoglobin level was raised by transfusion to 64% but at no time was there any reticulocytosis in the peripheral blood. As a terminal event infection supervened in the genital tract, and a culture of haemolytic streptococci and bacterium coli was obtained from the blood. The patient died on 7.2.42.

At autopsy, a septic endometritis was present, with multiple haemorrhages and widespread toxic changes in all organs, but especially in the liver, which showed much fatty change. The bone marrow in the long bones and sternum showed marked fatty replacement with only very little haemopoietic tissue remaining.

Case 3.—Married female, æt. 42, housewife.

The patient had a history of progressive weakness for two months before admission to hospital on 30.10.41. During the previous year she had received anti-syphilitic treatment with repeated courses of nearsphenamine and bismuth. Amenorrhœa had been present since 1932.
Physical examination.—Temperature normal, pulse 100. Appearance somewhat under-nourished and very pale. The tongue appeared normal. There was no evidence of jaundice, petechiae or oedema. No enlargement of liver, spleen or lymph glands was noted.

Laboratory findings.—Hb., 26%; R.B.C., 1,160,000; W.B.C., 2600 per c.mm.; C.I., 10; reticulocytes, less than 1%; platelets, 70,000 per c.mm. The red cells showed marked anisocytosis and poikilocytosis with many fully stained macrocytes present, but ovality of outline was not evident. M.C.V., 120 cu.μ.; M.C.H.C., 31.2%. Icteric index, 8. Gastric analysis revealed free hydrochloric acid. Wassermann reaction was negative.

Sternal puncture (31.10.41).—The marrow picture was hypoplastic with abundant fatty material and scanty cells. The few red cell precursors present were normoblastic. The white cell series showed a reduction in polymorphs with a maturation arrest at the myelocyte stage. Lymphocytes were relatively increased.

Progress.—The patient was given intensive treatment with injections of Anaehæmin, but no reticulocyte response or sustained increase in red cell counts resulted. In addition she received iron, ascorbic acid, nicotinic acid and yeast in full doses. Five transfusions of one pint each were given during a period of 25 days.

She was discharged from hospital on 4.12.41 with a haemoglobin level of 60%. Throughout her stay in hospital there was no evidence of active blood regeneration. On her discharge she was instructed to continue taking iron and yeast tablets.

The patient was re-admitted on 2.1.42 with Hb., 34%; R.B.C., 1,640,000; and W.B.C., 2600 per c.mm. Platelets were scanty in cover-slip films. The colour index was 1.06. Sternal puncture again revealed a hypoplastic fatty marrow. The cells present showed a relative increase of reticulum cells, myeloblasts and lymphocytes. Erythropoiesis was seen to be normoblastic, but red cell precursors and granulocytes were scanty. She was treated as before, receiving three blood transfusions, and was discharged with 75% haemoglobin, and advised to continue taking iron and yeast.

Subsequent follow-up revealed evidence of restoration of haematopoiesis. Sternal puncture on 16.4.42 showed that the marrow was still hypocellular but distinctly more cellular than on the previous occasion. Normoblastic proliferation was now prominent, with mature myelocytes and polymorphs in evidence. Reference to Fig. 1 will show that her recovery was maintained. When last seen on 21.1.43, 443 days after admission to hospital, her blood count was as follows: Hb., 92%; R.B.C., 4,420,000 per c.mm.; C.I., 104; M.C.V., 91.6; M.C.D., 7.6μ.

Case 4.—Married female, æt. 49, housewife.

When first seen on 23.2.39, the patient was a pale thin woman with advanced rheumatoid arthritis affecting many joints. She was obviously
Fig. 1.—Showing the blood counts and treatment of an example of secondary toxic hypoplastic anaemia with recovery (Case 3).
severely anaemic. There were no signs of jaundice or oedema or of enlargement of the liver, spleen or lymphatic glands. Petechiae were present in many situations and a history was obtained of uterine bleeding which had been treated with radium. This metrorrhagia had been diagnosed as menopausal on account of the patient’s age, but it is highly probable that it was in fact a toxic effect of gold injections which the patient had received over a period of fifteen months, a total of 2.6 G. having been given.

It is of interest to note that the patient’s sister had likewise suffered from rheumatoid arthritis, which had been treated with injections of gold salts, and had subsequently developed aplastic anaemia from which she succumbed.

Laboratory findings.—Hb., 30%; R.B.C., 1,700,000; W.B.C., 3400 per c.mm.; C.I., 0.85; reticulocytes, 5%. Film showed well-stained red cells of average size with little anisocytosis or poikilocytosis. Differential count, neutrophils, 43%; lymphocytes, 29%; eosinophils, 19%; monocytes, 9%. Platelets very scanty in films.

No sternal puncture could be performed in this case.

Progress.—It was advised that intensive haematogenic therapy should be continued along with further blood transfusions for at least another six months. Accordingly the patient was given liver extract injections, whole liver orally, iron and yeast. There was little response for one month, but thereafter there was a slow, steady improvement and further transfusion was unnecessary. On 7.4.39 the blood picture was: Hb., 50%; R.B.C., 3,290,000; W.B.C., 4700 per c.mm.; C.I., 0.75; and reticulocytes, 8%.

Subsequent follow-up in June 1942 showed that the patient ultimately made a complete recovery as regards her blood condition.

Discussion of the toxic group

The cases described in this group call for little general comment. The danger of aplastic anaemia developing in individuals exposed to potentially haemotoxic agencies, as a result of occupational hazards or of certain therapeutic measures, should be sufficiently widely appreciated to require no stressing. Nevertheless, the fatal outcome in two of these cases and the recovery of the other two may serve as a reminder of the need for constant vigilance in scrutinising the blood pictures of individuals exposed to such contingencies and for prompt preventive measures when any signs of deterioration of the haemopoietic tissues are observed.

Case 1 presents features of considerable interest in that following pneumonia a progressive leucocytosis developed which culminated in myeloid leukaemia. It is of interest to note that
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the development of leukæmia has previously been observed to follow exposure to benzol (Bowditch et al., 1939).

The familial history in Case 4 is also remarkable. We are unaware of any previous record of aplastic anaemia developing after injection of gold in two siblings.

(b) Refractory Anaemias with Hypocellular, Normoblastic Marrow of Unknown Origin. (Cases 5-16.)

The cases included in this group comprise nine with fatal termination within a year of the onset of symptoms of anaemia (Nos. 5-13), two in which the anaemic state has pursued a chronic more or less stationary course over periods of four and two years respectively (Nos. 14, 15), the patients still surviving at the time of writing. Finally, we include one case (No. 16) which has survived for over two years and differs from the other by its relapsing character.

In consideration of the desirability of economising in space, we have displayed the essential clinical and haematological features of the cases in this group in tabular form (Fig. 2) and have given detailed case histories of only two examples (Nos. 6 and 16).

For the proper understanding of the data set forth in the table on p. 362, it is necessary that the following points should be appreciated.

In all cases the medical histories of the patients provided no indication of any anaemic manifestations previous to the onset of the present anaemia, nor was there any history of extrinsic or intrinsic factors that could be considered to play any aetiological rôle in the production of the anaemia. The only possible exception to this statement is that in Case 8 there was a history of jaundice in childhood forty-nine years before the present illness.

The general nutritional state of the patients when first seen was good. Only one patient was underweight. The clinical manifestations which were essentially those of anaemia, and in some cases those of thrombocytopenic purpura, developed insidiously. Clinical evidence of enlargement of spleen, liver or lymph glands was absent in all cases. Clinical jaundice was apparent in only one case (No. 8).

The haematological data in the table were those noted on the patients’ admission to hospital. With the exception of Cases 14, 15 and 16, not only was no subsequent improvement in


Cases of Refractory Anaemia of Idiopathic Origin with Hypocellular Normoblastic Marrows

| Age | 5 | 6* | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16* |
|-----|---|----|---|---|---|----|----|----|----|----|----|-----|
| Sex | M | M | M | M | F | F | F | F | F | M | F | M |
| Signs of purpura | + | 0 | 0 | + | + | + | 0 | + | + | + | + | + |
| Icteric index | 8 | 9 | 25 | 15 | ... | 17 | 12 | ... | 15 | 8 | ... | ... |
| Hb. % | 47 | 30 | 30 | 25 | 45 | 24 | 26 | 66 | 60 | 34 | 44 | ... |
| Red cells (millions) | 1.96 | 1.41 | 1.12 | 1.12 | 1.75 | 1.06 | 1.07 | 1.23 | 3.48 | 2.46 | 1.31 | 1.86 |
| Colour index | 1.19 | 1.07 | 1.34 | 1.13 | 1.28 | 1.14 | 1.22 | 1.05 | 0.95 | 1.22 | 1.30 | 1.18 |
| Reticulocytes % | <1 | <1 | <1 | 4 | 3 | 1 | 1 | <1 | <1 | 1.5 | 5 | <1 |
| Macrocytosis | + | + | + | + | + | + | 0 | 0 | + | + | + | + |
| Fragility | ... | Normal | ... | Normal | Normal | Normal | Normal | ... | Normal | Normal | Normal | Normal |
| White cells | 1000 | 2600 | 800 | 3600 | 4800 | 2200 | 2800 | 2400 | 2200 | 1000 | 4400 | 1800 |
| Platelets | Scanty | Scanty | Scanty | Scanty | 20,000 | 15,000 | 70,000 | 77,000 | 20,000 | Scanty | 15,000 | 70,000 |
| Gastric juice. Free HCl present | ... | 0 | 0 | 0 | + | ... | + | + | ... | + | 0 | 0 |
| Duration of symptoms before hospitalisation in months | 6 | 2 | 5 | 4 | 5 | 4 | 3 | 7 | 2 | 4 | 24 | 15 | 2 |
| Duration of subsequent survival in months | 6 | 5 | 2 | 4 | 3 | 1 | 4 | 2 | 1 | 27 | 12 | 26 | ... |

* Case histories appended.

Fig. 2.—Table showing essential clinical and haematological data of 12 cases of refractory anaemia with hypocellular, normoblastic marrows.
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red-cell counts noted but the anæmic state displayed a progressive advance except for the temporary effects of blood transfusions. The same statement applies to the white-cell counts. All patients displayed a granulopenia which showed no remission, with the exception of Cases 6 and 16. The former case displayed a transient leucocytosis of 13,600 white cells per c.mm. during the course of a streptococcal septicæmia shortly before death. Examination of blood films revealed that varying degrees of anisocytosis and poikilocytosis were general, and the appearance of well-filled cells constituted a constant feature. Price-Jones' curves were not done, but visual inspection of the films showed a moderate degree of macrocytosis in all cases except Nos. 12 and 13.

Sternal puncture was performed in all cases, as soon as possible after admission to hospital. In several cases it was repeated on one or more occasions during the patients' stay in hospital. Although in many instances the aspirated marrow flecks were large and abundant, examination of the marrow films revealed in all cases marked hypocellularity with abundant fat spaces. In two cases the aspirated sternal material consisted of blood containing droplets of fluid fat. In general the white-cell precursors showed a maturation arrest, the proportion of polymorph leucocytes being considerably reduced with a relative increase of myelocytes or promyelocytes and myeloblasts. A relative increase in lymphocytes and reticulum cells was a fairly constant feature, and in some cases "Q-cells" were prominent. In all the marrows erythropoiesis was indubitably normoblastic. In general the erythroblasts were relatively scanty. Of the various types present those with basophil and polychrome cytoplasm having nuclei with dense, lumpy chromatin were relatively the most frequent. Megakaryocytes and platelets were very scanty, without exception.

Treatment was throughout along the same general lines, and consisted of numerous injections of large doses of liver extract of known potency at frequent intervals, massive doses of iron, vitamins B and C, and in most cases yeast by mouth. In no instance was any erythropoietic response to such treatment indicated by the reticulocyte or blood counts. All the patients received transfusions of citrated blood. The average amount given to each of the eight fatal cases was ten pints.

Reference to the table will show the period during which symptoms of anaemia had been present in each patient. The
duration of survival after the institution of energetic treatment is also indicated. Patients 14 and 15 are still alive and, apart from the temporary benefits of blood transfusions, their haematological condition remains stationary. Case 16 is described in detail.

Autopsy was obtained in three of the fatal cases (Nos. 6, 7, 8) in which examination of the various bones revealed a state of generalised myeloid aplasia with a few small patchy areas of reactive marrow.

(i) **Progressive Hypoplastic Anaemia with Fatal Termination**

Case 6.—Male, æt. 67, motor-driver retired.

The patient gave a history of breathlessness, tinnitus and increasing pallor of some two months' duration. There had been no loss of weight and his appetite was good. His previous health had been very good except for osteo-arthritis of the hip four years previously. He had been treated with parenteral liver extract and iron by mouth during the two weeks before admission to hospital on 24.3.41.

**Physical examination.**—Temperature normal, pulse 90. The patient was well nourished but displayed a marked pallor. The tongue showed some atrophy of the mucosal papillae. Koilonychia was absent. No signs of jaundice, oedema or purpura were detected. The liver, spleen and lymph glands were not enlarged. Reflexes were present and equal. No diminution in the vibration sense was noted.

**Laboratory findings.**—Hb., 30%; R.B.C., 1,410,000 per c.mm.; C.I., 1.07; reticulocytes less than 1%; W.B.C., 2600 per c.mm. Platelets were very scanty in cover-slip films. The red cells were fully stained, moderately macrocytic and displayed poikilocytosis and anisocytosis, but the degree of anisocytosis and macrocytosis appeared to be less than that seen in classical pernicious anaemia of equivalent severity. No abnormal white cells were seen, but a granulopenia was apparent. The mean cell diameter by halometer reading was 8.1 μ. The fragility of the red cells in hypotonic saline was within normal limits. Icteric index, 8. No excess of urobilin was noted in the urine. Gastric analysis; histamine-fast achlorhydria. Wassermann reaction, negative. Stool examination for occult blood, negative. Radiological examination by barium meal, negative.

**Sternal puncture** (19.4.41).—Marrow flecks were abundant in the aspirated sternal fluid, but examination of the films showed a hypoplastic marrow picture with numerous large fat spaces. Marrow cells occurred in scattered groups. Erythropoiesis was normoblastic, most of the red cell precursors consisting of smallish basophil and polychromic cells with dense, lumpy nuclei. Fully haemoglobinised normoblasts
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were scanty. The white cell precursors showed a striking maturation arrest, polymorphs being infrequent but promyelocytes and myeloblasts were relatively increased. "Q-cells" and reticulum cells were frequent. Megakaryocytes and platelets were very infrequent.

Progress.—The essential features concerning treatment and the haematological data are displayed in Fig. 3. Ferrous sulphate, 18 gr. daily, was given for a month, and parenteral liver totalling 36 c.c. of "Neo-hepatex" and 84 c.c. of "Hepatex-T" was given during the seventy days of the patient's first sojourn in hospital. In addition, ascorbic and nicotinic acid were each given in daily doses of 300 mgm. by mouth. On no occasion was a reticulocyte response noted, nor was there any rise in haemoglobin that could be interpreted as an erythropoietic response. By means of blood transfusions in which 17 pints of blood were given, the patient's haemoglobin was eventually raised to 80% when he was discharged from hospital.

A month later he was re-admitted for the purpose of a further transfusion and was given the cells from 3 pints of blood, but this was followed by a reaction consisting of rigor, epistaxis, petechiae, haemoglobinuria and a pyrexia of 103° F. The pyrexia persisted, and two days later a blood culture yielded a haemolytic streptococcus. This infection resulted in a leucocytosis of 13,600 per c.mm., of which 70% were polymorphs with a marked shift to the left. A sternal puncture done at this time revealed that although the red-cell precursors were still scanty, the white-cell series displayed maturation. Compared with the previous marrow film myeloblasts were scanty, but myelocytes and polymorphs were relatively numerous.

The infection was treated with blood transfusions and a course of sulphathiazole which resulted in remission of the pyrexia, which was accompanied by a rapid fall in the leucocyte count. For a few days the patient felt remarkably well, but his condition then deteriorated in spite of a further transfusion. It was eventually decided that no further treatment was warranted. The haemoglobin fell to 10% and death ensued.

Autopsy findings.—The lungs were congested and oedematous at the bases; the myocardium showed fatty changes, the liver was normal in size but showed marked fatty change; the spleen was small, pale, and firm. Examination of the femur, tibia, fibula, small bones of the foot, humerus, radius, ulna, ribs and sternum revealed small patchy areas of reactive marrow in the upper halves of femur, humerus and sternum. Elsewhere only fatty tissue was found, including the ribs.

(iii) Relapsing Hypoplastic Anaemia

Case 16.—Male, â©. 49, motor mechanic.

The patient served in the 1914-18 war, during which he contracted sandfly fever in the Near East, but has no history of other illnesses;
Fig. 3.—Showing the hematological course of an example of idiopathic hypoplastic anemia with fatal termination (Case 6).
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he admits, however, to having been a fairly heavy whisky drinker. He rejoined the Army at the outbreak of the present war, and was quite fit until November 1940, when increasing breathlessness was noted. After medical examination he was admitted to a hospital with a diagnosis of pernicious anaemia. Treatment with iron and liver extract was ineffectual, his red cells falling to 1,480,000 per c.mm., with a colour index of 1·27 and his white cells fell to 875 per c.mm. Three blood transfusions were given and he was discharged from the Army with a red and white count of 3,690,000 and 4000 per c.mm. respectively. He was seen by us two weeks later, in January 1941.

Physical examination.—The patient was of spare build but well-nourished, with a sallow but not jaundiced complexion. The tongue was healthy in appearance, and no enlargement of liver, spleen or lymph glands was noted. An old retinal hæmorrhage was present in the right eye.

Laboratory findings.—When first seen by us the blood count was as follows: Hb., 92%; R.B.C., 4,180,000 per c.mm.; C.I., 11.1; reticulocytes, 1·2%; M.C.V., 103 cu.μ.; M.C.H.C., 33·4%; M.C.D. (halometer), 8·1 μ; W.B.C., 7200 per c.mm. The film showed anisocytosis and macrocytosis but only a moderate degree of poikilocytes. The red cells were fully stained. No primitive cells were seen and platelets were numerous. The icterus index was 8. A test-meal revealed no free hydrochloric acid but this was detected following injection of histamine.

Sternal puncture revealed a hypoplastic marrow picture with abundant fat spaces. Erythropoiesis was normoblastic, and leucocyte maturation appeared to be proceeding normally. Numbers of "Q-cells," however, were evident, and lymphocytes were relatively increased.

Progress.—The patient was instructed to report back but did not do so until after some months. Since then he has been under constant observation over a period of nearly two years and has received regular treatment with liver extract, iron, yeast and ascorbic acid. He has had two relapses necessitating hospitalisation, during which haematinic treatment was intensified and blood transfusions given when necessary. During his last period in hospital a course of pentnucleotide injections were given which resulted in an abscess developing in the buttock accompanied by a temporary but marked increase in the leucocyte count.

The essential features of his blood count and treatment are displayed graphically in Fig. 4. Films of the peripheral blood have consistently shown well-filled red cells with an average diameter larger than normal, but poikilocytosis and ovality of outline have never been prominent. A reticulocyte count above 1% was observed on only one occasion, when it was 2·4%.

It will be noted that an important feature of this case is the severe granulopenia which accompanied the anæmic phases. The platelet count was also low during phases of relapse, but apart from a retinal
Fig. 4.—Showing the relapsing character of the anaemia and leucopenia in Case 16.
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Haemorrhage no purpuric manifestations developed, and the Hess test was repeatedly negative. Jaundice was never a feature. On the whole the patient's general condition was surprisingly good even during the most severe phases.

A blood volume estimation was made by the Evans blue method (Davis, 1942) on 11.12.41. The data obtained are as follows: total blood volume, 4261 c.c.; total blood volume per kg. body weight, 66.4 c.c.; total blood volume per sq. metre, 2477 c.c.; plasma volume, 3580 c.c.; and cell volume, 681 c.c. These figures indicate a considerable reduction in cell volume with a partial compensatory increase in plasma volume.

Sternal puncture was performed on eight occasions, and on each occasion erythropoiesis was normoblastic; the differential counts are set forth in Fig. 5. Examination of this with reference to Fig. 4 shows that the leucoblastic activity of the sternal marrow is related to the leucocyte count of the peripheral blood. The large proportion of "Q-cells"

|    | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    |
|----|------|------|------|------|------|------|------|------|
|    | 27.1.41. | 2.6.41. | 27.11.41. | 6.1.42. | 30.1.42. | 19.5.42. | 11.6.42. | 7.7.42. |
| Reticulum cell | 1.0 | 0.6 | 2.0 | 2.0 | 0.8 | 4.8 | 5.2 | 1.2 |
| Myeloblast | 5.4 | 4.6 | 8.6 | 8.6 | 12.0 | 14.8 | 21.6 | 14.6 |
| "Q-cell" | 13.0 | 26.2 | 27.2 | 30.2 | 16.4 | 4.0 | 4.0 | 4.0 |
| Promyelocyte | 11.2 | 10.0 | 11.2 | 15.0 | 2.8 | 5.0 | 6.2 | 4.2 |
| Myelocyte | 6.2 | 3.6 | 1.4 | 8.0 | 11.8 | 8.8 | 12.8 | 13.2 |
| Leucocyte— | | | | | | | | |
| "Juvenile" | 8.2 | 1.2 | 1.0 | 5.6 | 6.2 | 1.4 | 5.2 | 10.6 |
| Segmented | 15.0 | 1.6 | 0.6 | 3.6 | 12.0 | 0.4 | 3.0 | 19.4 |
| Lymphocyte | 12.4 | 23.6 | 19.4 | 17.0 | 18.2 | 21.0 | 28.2 | 20.2 |
| Plasma cell | 1.6 | 1.0 | 1.2 | 1.4 | 0.4 | 2.4 | 5.4 | 0.6 |
| Monocyte | 3.2 | 0.4 | 0.6 | 1.6 | 0.6 | 0.4 | 0.4 | 1.0 |
| Erythroblast— | | | | | | | | |
| Type I | | | | | | | | |
| "II" | 2.8 | 1.2 | 1.2 | 4.8 | 1.8 | 1.6 | 4.8 | 3.2 |
| "III" | 14.8 | 15.0 | 12.4 | 28.2 | 13.0 | 21.2 | 14.0 | 16.2 |
| "IV" | 2.8 | 6.6 | 5.6 | 4.2 | 4.6 | 2.0 | 2.4 | 2.8 |
| Megakaryocyte | 0.4 | | | | 0.4 | 0.4 | 0.4 | 0.2 |
| Undetermined | 1.2 | 3.4 | 7.6 | 1.6 | 5.0 | 2.4 | 2.4 | 2.4 |
| Peripheral blood— | | | | | | | | |
| R.B.C. per c.mm. | 4.18 | 4.01 | 1.86 | 2.00 | 3.71 | 1.83 | 2.00 | 3.96 |
| Colour index | 1.11 | 1.05 | 1.18 | 1.25 | 1.13 | 1.39 | 1.25 | 1.13 |
| W.B.C. per c.mm. | 6400 | 3800 | 1800 | 3600 | 4800 | 1700 | 2900 | 7250 |
| Polymorphs per cent. | 62 | 14 | 8 | 55 | 55 | 20 | 25 | 57 |

Fig. 5—Showing differential cell counts on marrow films on the occasion of each sternal puncture, together with the corresponding peripheral blood counts (Case 16).
in the films during the leucopenic phases constituted a prominent feature. In Fig. 6 the percentage of primitive cells, myeloblasts, promyelocytes and "Q-cells" counted at each sternal puncture are plotted against the percentage of granulocytes, myelocytes and polymorphs found on each corresponding occasion. In the same graph is recorded the actual number per c.mm. of granulocytes in the peripheral blood at the time of each sternal puncture. It will be noted that this displays a close correlation with the curve for the granulocytes in the marrow, while the curve for the primitive white cells in the marrow exhibits a definite negative correlation with the other two curves.

**Comment**

The relapsing character of this case is well displayed in the graph, which shows three well-defined remissions and relapses involving all the formed elements of the blood during a period of observation of over 700 days. Several questions deserving discussion emerge from consideration of this case.
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(1) Diagnosis and prognosis.—When he was first seen by us the state of the patient’s general and haematological condition was superficially satisfactory, and it is accordingly of interest to examine closely any features of his case which might at that time have facilitated an understanding of his true condition. The history of severe anaemia with gross leucopenia resistant to liver therapy obviously suggested that this was not an ordinary case of pernicious anaemia. However, the earlier treatment was not under our observation and accordingly it was felt undesirable to lay undue stress on the poor response, as it might have been due to the use of impotent liver extract or to other factors.

As regards the peripheral blood when first examined, the only abnormal feature was the degree of macrocytosis as observed in dried films and indicated by the mean cell volume. This was more marked than one would expect in a case of pernicious anaemia under treatment with a red-cell count of over four million.

Another feature of diagnostic significance was the presence of free hydrochloric acid in the stomach contents following injection of histamine.

The diagnostic value of sternal puncture in this case obviously requires consideration. While many of the marrow films obtained during the course of the observation of this patient leave little room for doubt as to the hypoplastic nature of the sternal marrow, it may well be asked whether the sternal puncture performed when the patient first came under our notice provided data of diagnostic significance. Was the marrow picture then compatible with a diagnosis of pernicious anaemia in a phase of remission? We are of the opinion that the answer is “no.” The marrow picture as a whole was hypoplastic, the proportion of red-cell precursors was too scanty. Furthermore, the relative immaturity of the white cells with undue proportions of myeloblasts and promyelocytes and the presence of large numbers of the “Q-cells” were all points against the case being one of pernicious anaemia in remission. It was therefore considered that while the precise clinical significance of these findings could not at that time be assessed accurately, they certainly warranted a guarded prognosis and continued observation of the patient. The significance of the association of a macrocytic blood picture with a normoblastic marrow will be discussed later.

(2) Cause for relapses.—The history of the patient’s progress may now be examined more closely with a view to seeking any
possible clues leading to an explanation of his relapses. During a period of some three months after he was first seen, the patient ceased receiving liver injections or any other form of treatment, but during this time his blood level was maintained. He then recommenced treatment with regular injections of "Pernämon Forte" and received the other haematinic substances indicated on the graph, but in spite of this, during the next few months his red and white cells fell to low levels. During the whole of the time he was under observation, apart from the period of three months when he defaulted, the patient received at least one weekly injection of "Pernämon Forte" 4 c.c., which in our experience is well in excess of the dosage required to maintain cases of pernicious anaemia in a satisfactory state of remission. Close enquiry into the habits of the patient revealed only one factor seemingly of significance in contributing to his relapses, and that was addiction to alcohol. Although warned against it, he left us with little doubt that his indulgence in this respect continued to be excessive. His general dietary appeared to be satisfactory and he made a point of augmenting his meat ration with liver whenever possible. During the periods of better health the patient obtained work as a fitter in a light engineering shop, which apparently did not overtax his strength. No evidence of exposure to toxic substances was obtained. In short, then, apart from the tendency to alcoholism, no extrinsic cause was discovered for his relapses.

(3) Cause for remission.—The patient was admitted to hospital under our observation on two occasions when his general and haematological condition had considerably deteriorated. These two periods of hospitalization, as well as that prior to his coming under our observation, resulted in remissions of varying duration, but in each case of considerable magnitude when assessed in terms of the general condition of the patient and of his red and white blood cell and platelet counts. During these periods in hospital the general haematinic therapy was intensified; but it would seem unlikely that such treatment alone would be effective in a patient who was already receiving these substances in dosages presumably adequate for the correction of any existing deficiency. Cursory examination of the graph might lead to the conclusion that the rises in the blood counts were the direct result of the blood transfusions. More detailed examination, however, will dispel this view, since when the time intervals are taken into consideration it will be seen that the rises continued
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over periods longer than can be accounted for by the physical effect of the transfusions. This is particularly apparent in the case of the white-cell count, which displays a strikingly consistent parallelism with the red-cell count. Furthermore, the phases of remission are accompanied by cytological evidence of increased bone-marrow activity. It is accordingly possible to postulate a stimulating effect of the transfusions upon the bone marrow, but we are not aware of any convincing evidence that such an effect does in fact take place.

During the last period in hospital a course of pentnucleotide injections was administered which resulted in a gluteal abscess. This coincided with a sharp rise in the red and white blood cell counts, especially of the latter, but it is impossible to draw any valid conclusions that this leucocyte increase was caused by the pentnucleotide, since a similar rise was previously observed in the absence of pentnucleotide.

A feature deserving notice is the absence of a reticulocyte response at any time. The highest reticulocyte count observed on any occasion was 2.4 per cent.

It will be apparent, then, that the cause of this patient's remissions remains a matter for conjecture. Presumably the cumulative benefits of hospital treatment—rest, high intake of protein food and various hæmatinics, stoppage of alcohol, tiding over of periods of bone marrow exhaustion by blood transfusions—all contributed to sustaining the patient during his relapse phases. This presumption is compatible with the theory advanced by Bomford and Rhoads (1941) that refractory anæmias are due to a conditioned susceptibility to toxic substances associated with hepatic dysfunction. To decide whether they contributed to the resuscitation of the bone marrow, or whether this was quite spontaneous, is obviously beyond the scope of our present knowledge.

(4) The nature of the case.—The clinical course of this case, the bone marrow cytology during the periods of relapse, and the degree of the accompanying granulopenia and thrombocytopenia should serve to prevent its being confused with pernicious anæmia. On the other hand, the duration of the condition removes it from the classical type of aplastic anæmia. On the basis of the sternal marrow cytology we conclude that it should be regarded as an example of refractory anæmia of a hypoplastic relapsing variety.
Discussion of Idiopathic Hypoplastic Group

Aetiology.—The histories of the cases reviewed under this heading reveal no evidence of any previous disorders of blood formation, and neither, with the possible exception of Case 8, in which there was a history of attacks of jaundice in childhood, was there any indication of a possible aetiological factor. None of the patients had been engaged in occupations entailing exposure to haemotoxic substances.

The average age at which symptoms of anaemia were first noted was high, namely sixty-one years. In this connection it is of interest to note that it is generally stated that idiopathic aplastic anaemia is most common in young adults. Whitby and Britton (1942) and Bomford and Rhoads (1941) record that the average age of their series of cases of anaemia with partly cellular and hypocellular marrows was under forty years.

Haematological features.—In all the cases the anaemia was macrocytic or normocytic in character. In only two cases, Nos. 5 and 14, however, were the morphological features seen in the blood films such as anisocytosis, poikilocytosis, ovality of outline and macrocytosis sufficiently marked to present the appearance of classical pernicious anaemia in the stage of relapse. In the remaining cases the films were less characteristic, although anisocytosis and a variable number of well-filled macrocytes were present, except in Cases 12 and 13 which presented a normocytic picture.

Without exception the hypoplastic process affected all the cells formed in the marrow: red cells, granulocytes and platelets. Case 6, in which a granulopenia was succeeded by a leucocytosis of 13,600 cells per c.mm. during the course of a streptococcal septicaemia, exemplifies the ability of a hypoplastic marrow to produce a leucocytosis in the presence of sepsis. Case 16 may also be regarded as another example of the same phenomenon.

A reticulocyte count persistently higher than 1% was present in only three of the cases, Nos. 8, 9 and 15, in which counts around 5% were frequently encountered. Persistently elevated reticulocyte counts are obviously suggestive of a haemolytic factor being operative. In severe grades of anaemia, however, we do not consider a reticulocyte count of the order of 5% necessarily diagnostic of haemolytic anaemia, because reticulocytes of this frequency may well result from the premature liberation of young red cells by the remaining areas of reactive bone marrow.
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The autopsy findings in Case 8, in fact, proved that the underlying condition was essentially bone marrow aplasia.

One of the most pertinent questions arising from this study concerns the validity of accepting a hypoplastic normoblastic sternal marrow film as pathognomonic of hypoplastic refractory anæmia. The answer to this question obviously depends upon whether similar appearances are to be encountered in healthy subjects or in those suffering from other types of anæmia. It must be admitted that we have occasionally encountered normal individuals whose sternal marrow films have displayed moderate degrees of hypoplasia. Such findings are presumably due to irregular distribution of erythropoietic activity, since a second sternal puncture at a different site may produce marrow films of normal cellularity. The need is manifest for more extensive studies of the distribution of the marrow in the sternums of large numbers of normal individuals of varying age groups. This question has been discussed by Custer (1932). Conversely, in cases of hypoplastic anæmia the presence of small residual areas of reactive marrow may result in sternal puncture occasionally yielding films of normal cellularity.

Accordingly it cannot be stated categorically that the appearance of hypoplasia in a single marrow film necessarily indicates hypocellularity of the marrow as a whole.

On the other hand, when several films made from separate flecks of sternal marrow show a consistent hypocellularity the chances of the diagnosis of hypoplastic anæmia being correct are increased. The possibility of these findings being fortuitous are rendered still more improbable if they are confirmed by a second sternal puncture at a different site.

It may therefore be stated that the demonstration of a hypocellular, normoblastic sternal marrow picture in a severe anæmia, macrocytic or normocytic in character, with a colour index within or above the normal range, in the absence of any evidence of a causative factor, is strongly suggestive of the condition being an anæmia of the type under discussion. If liver therapy has recently been administered, however, a reasonable period should be allowed to elapse for the occurrence of a possible reticulocyte response or a rise in the red-cell count before coming to a final decision. The reason for this, of course, is that in pernicious and certain other megaloblastic anæmias, the earliest demonstrable response to liver therapy is the conversion of the megaloblastic marrow picture to a normoblastic one. However,
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this consideration is probably chiefly of theoretical interest, since in our experience the sternal marrow pictures in pernicious and allied anaemias are uniformly hypercellular.

From the foregoing remarks it will be clear that for the diagnosis of idiopathic hypoplastic anaemia we consider the demonstration of normoblastic erythropoiesis in the sternal marrow to rank in importance equally with the appearance of hypocellularity.

A point of considerable academic interest is the mechanism underlying the production of a macrocytic anaemia by a hypoplastic normoblastic bone marrow. The production of macrocytes in pernicious anaemia has usually been explained by the abnormal maturation of megaloblasts, and in such conditions as macrocytic haemolytic anaemias it has been attributed to the hurried imperfect maturation of immature normoblasts in a hyperactive marrow. In hypoplastic refractory anaemia, however, the marrow is relatively inactive and normoblastic erythropoiesis is depressed, yet the peripheral blood may show macrocytosis of varying degree in the majority of cases. That the enlargement of the red cells seen in peripheral films was not merely apparent, such as may be found in conditions where the cells are unduly thin, resulting in their spreading over a larger area than normal, was shown by mean corpuscular volume determinations. In Case 16 periods of remission of the anemic state resulted in no diminution of the macrocytosis, while in each of the eight sternal punctures, normoblastic erythropoiesis was revealed. We are at a loss for a satisfactory explanation of the mode of production of macrocytes in this type of anaemia, but hold that their presence in conjunction with a hypocellular normoblastic marrow is of diagnostic significance.

Prognosis.—Of the twelve patients falling into the idiopathic hypoplastic group, nine are already dead, the average period elapsing since the onset of symptoms being about seven months. Of the remaining three cases the ultimate outlook for two of them (Nos. 15 and 16) is poor. The other, No. 14, appears to have been keeping in reasonably good health for over two years in spite of a moderately severe anaemia.

Summary

1. Sixteen cases of refractory anaemia have been studied in which sternal puncture has revealed a hypocellular, normoblastic marrow picture.
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2. Four of these cases which are described in detail were secondary to exposure to haemotoxics.

3. The remaining twelve cases were idiopathic in origin. In nine, the anaemia was progressive and proved fatal within a few months. Three have survived for periods exceeding two years. One of these cases which has pursued a relapsing course presenting unusual features is described in detail.

4. The value of sternal puncture in the diagnosis of hypoplastic anaemia is discussed.

Since this paper has been submitted for publication, the writers have had under their care four additional cases of severe macrocytic anaemia with hypocellular normoblastic marrows which have proved resistant to all forms of treatment.

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