and in the rejection of foreign protein will be required before these features can be explained.

Summary

An attempt was made to demonstrate a relationship between the biochemical, immunological, and clinical features of myeloma. Of the immunological responses tested, the isoagglutinin titre and the antibody response to T.A.B. vaccine were fairly uniformly impaired in the myeloma patients, as compared with controls. No gross depression of response was found on Mantoux-testing, and prolongation of homograft survival could not be proved. Survival of transfused incompatible red cells was markedly increased in two of the myeloma patients. Definite immunological defects were therefore shown to be present in myeloma, but this apparently may occur at any stage in the disease and cannot be correlated with the clinical or biochemical features. The presence of isolated immunological defects at all stages of the disease has been described only in various types of hypogammaglobulinaemia, and it seems likely that in myeloma there is a deficiency of functioning globulin, despite the excess of abnormal protein usually present. More knowledge of the factors responsible for the various immune responses tested will be required before the individual features can be explained.

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REFERENCES

Barr, M., and Fairley, G. H. (1961). *Lancet*, **1**, 1305.
Billingham, R. E., Krohn, P. L., and Medawar, P. B. (1951). *Brit. med. J.*, **1**, 1157.
Coons, A. H., Leduc, E. H., and Conolly, J. M. (1955). *J. exp. Med.*, **102**, 49.
Dacie, J. V. (1956). *Practical Haematology*, p. 91. Churchill, London.
Dammin, G. J., Couch, N. P., and Murray, J. E. (1957). *Ann. N.Y. Acad. Sci.*, **64**, 967.
Dancaster, C. P., Hussain, O. A., and Jackson, W. P. (1959). *Postgrad. med. J.*, **35**, 662.
Dempster, W. J., Lennox, B., and Boag, J. W. (1950). *Brit. J. exp. Path.*, **31**, 670.
Dubin, I. N. (1947). *Ann. intern. Med.*, **27**, 898.
Evans, R. W. (1948). *J. Path. Bact.*, **60**, 123.
Fairley, G. H., and Scott, R. B. (1961). *Brit. med. J.*, **2**, 920.
Good, R. A., and Mazzitello, W. F. (1956). *Dis. Chest*, **29**, 9.
Green, I., and Corso, P. F. (1959). *Blood*, **14**, 235.
Larson, D. L., and Tomlinson, L. J. (1953). *J. clin. Invest.*, **32**, 317.
Lawson, H. A., Stuart, C. A., Paull, A. M., Phillips, A. M., and Phillips, R. W. (1955). *New Engl. J. Med.*, **252**, 13.
Mackie, T. J., and Macartney, J. E. (1959). *Handbook of Practical Bacteriology*, 9th ed. Livingstone, Edinburgh.
Marks, J. (1953). *J. clin. Path.*, **6**, 62.
Mollison, P. L. (1956a). *Blood Transfusion in Clinical Medicine*, 2nd ed., p. 55. Blackwell, Oxford.
—— (1956b). Ibid., p. 343.
—— (1956c). Ibid., p. 336.
Moore, K. L., Graham, M. A., and Barr, M. L. (1953). *Surg. Gynec. Obstet.*, **96**, 641.
Nossal, G. J. V. (1959). *Brit. J. exp. Path.*, **40**, 301.
Painter, T. S., and Korst, D. R. (1959). *New Engl. J. Med.*, **260**, 15.
Porges, R. F. (1956). *J. Lab. clin. Med.*, **47**, 960.
Shaw, R. K., Szwed, C., Boggs, D. R., Fahey, J. L., Frei, E., Morrison, E., and Utz, J. P. (1960). *Arch. intern. Med.*, **106**, 467.
Silver, R. T., Utz, J. P., Fahey, J., and Frei, E. (1960). *J. Lab. clin. Med.*, **56**, 634.
Thièry, J. P. (1960). *Ciba Foundation Symposium—Cellular Aspects of Immunity*, p. 59. Churchill, London.
Tompkins, E. H. (1960). *Amer. J. Path.*, **37**, 175.
Woodruff, M. F. A. (1960). *The Transplantation of Tissues and Organs*, p. 64. Thomas, Springfield, Illinois.
Zinneman, H. H., and Hall, W. H. (1954). *Ann. intern. Med.*, **41**, 1152.

FAMILIAL HYPOCHROMIC ANAEMIA WITH HYPERFERRICAEMIA

A STUDY OF TWO FAMILIES

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Although hypochromic anaemia is generally due to iron deficiency it may also result from other disturbances in haemoglobin synthesis and be associated with normal or excessive body stores of iron. This can occur in association with chronic infection or lead-poisoning. It is also seen in the familial disease thalassaemia, which is characterized by a hypochromic anaemia, a high serum iron, and a lack of response to iron therapy. There is general agreement that thalassaemia is due to the expression of an abnormal autosomal gene. A number of cases which resemble thalassaemia and differ from it mainly in their manner of inheritance have also been described under different names. "Hereditary sex-linked anaemia" was first described by Cooley (1945) and Rundles and Falls (1946). This is a familial hypochromic anaemia which is often associated with haemochromatosis and is refractory to treatment. It is transmitted by females but achieves its full expression only in males. Other cases were described by Mills and Lucia (1949) as "familial hypochromic anaemia," by Garby *et al.* (1957) as "chronic refractory hypochromic anaemia," and by Heilmeyer *et al.* (1958) as "hereditary hypochromic sideroachrestic anaemia."

These cases have had many features in common and it is probable that they are examples of the same disorder (Dacie, 1960). In some otherwise similar cases no hereditary pattern could be established (Goldish and Aufderheide, 1953; Crosby and Sheehy, 1960). Other reports have described a similar hypochromic anaemia with iron overload distinguished, however, by a response to pyridoxine (Harris *et al.*, 1956; Verloop and Rademaker, 1960) or to crude liver extract (Horrigan *et al.*, 1957). The relationship of these anaemias is uncertain. The differences in their clinical and haematological presentation are perhaps due to differences in the biological expression of a common genetically determined biochemical defect.

The following report is a study of two families. In one a case of hypochromic anaemia responsive to pyridoxine therapy was associated with an apparently similar anaemia in a sibling which was refractory to pyridoxine. In the other the familial occurrence of the curious combination of refractory hypochromic anaemia with hyperferricaemia, duodenal ulceration, and skin pigmentation is described.

Case 1: Pyridoxine-responsive Anaemia

The patient was a retired police officer, aged 58, who first presented in 1952 complaining of attacks of "trembling" for which no cause could be found. A haemoglobin estimation was not performed at this time, but no clinical evidence of anaemia was found. He was seen again six years later because of exertional dyspnoea, which had become increasingly severe

during the previous eight months. On examination he was found to be grossly anaemic and in congestive cardiac failure. The liver was enlarged to 1 in. (2.5 cm.) below the costal margin but the spleen was not palpable.

Initial Investigations.—The haemoglobin (Hb) was 3.6 g./100 ml.; red cells 2,060,000/c.mm.; P.C.V. 16%; M.C.H.C. 22%; and M.C.V. 80 cubic microns. Reticulocytes, 1%. The white cells numbered 8,700/c.mm., with a normal differential count. In the film some of the red cells appeared normal but most showed marked hypochromia and anisocytosis with conspicuous poikilocytosis (Fig. 1). Haemoglobin electrophoresis revealed no abnormality. A sternal marrow aspirate showed a normoblastic hyperplasia with an orderly erythropoietic maturation and development. The total serum proteins

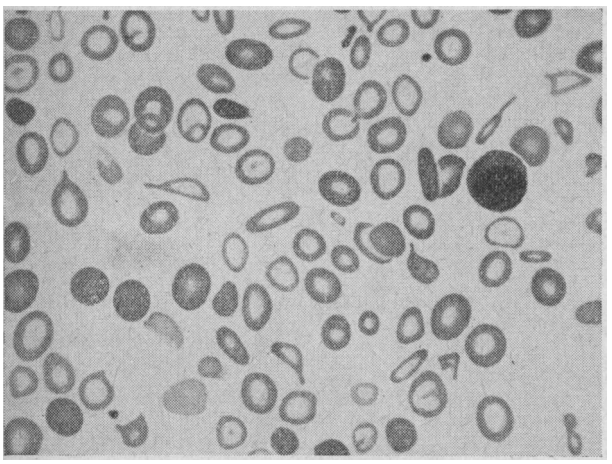

FIG. 1.—Case 1. Blood film. (×515.)

were reduced to 5.4 g./100 ml., with a marked reduction in the albumin fraction to 2.7 g./100 ml. Liver-function tests were normal. One of a series of stool examinations for occult blood was positive. A fractional test meal revealed marked hyperchlorhydria. An *x*-ray barium-meal examination suggested the presence of a small acute ulcer in the duodenum. As a consequence of this the anaemia was attributed to gastro-intestinal haemorrhage and treatment was directed towards correcting this by giving transfusions of concentrated red cells.

Treatment and Progress

During the next four months, despite continuous iron therapy, it proved impossible to maintain the haemoglobin level, and repeated transfusions were necessary. In this period he received the packed cells from 21 pints (11.9 litres) of blood (Fig. 2). This was followed by an incomplete remission of the anaemia, so that over the next 12 months the haemoglobin level gradually rose to 12.1 g./100 ml. although the red cells remained hypochromic.

The patient was not seen for a further year, when his haemoglobin was found to have fallen to 8.7 g./100 ml. Treatment

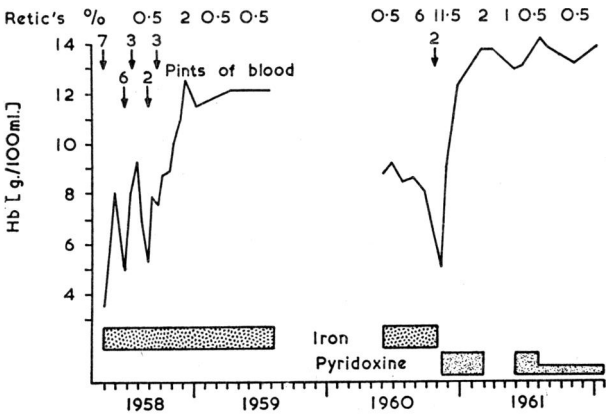

FIG. 2.—Case 1. Course and treatment.

with iron and ascorbic acid was recommenced, but during the next five months the haemoglobin gradually fell to 4.8 g./100 ml. At no time in this period was there evidence of external blood loss, and examination of the stools for occult bleeding was persistently negative. The possibility of intestinal malabsorption was considered, but the fat content of the faeces was normal.

There was no evidence of haemolysis, the reticulocyte count remained low, and the faecal urobilinogen excretion was 60 mg./day. The serum iron was found to be 470 μg./100 ml. and the total iron-binding capacity (T.I.B.C.) 482 μg./100 ml. This marked hyperferricaemia suggested that the patient suffered from one of the hypochromic iron-loading anaemias. At this time, too, his skin had acquired a slate-grey pigmentation, the liver had enlarged to 3 in. (7.5 cm.) below the costal margin, and the spleen had become palpable. His clinical condition had greatly deteriorated and was complicated by a return of congestive cardiac failure, bilateral thrombophlebitis of the deep veins of the calves, and gross peripheral limb oedema. The sternal marrow showed a normoblastic hyperplasia. There was a marked predominance of polychromatic normoblasts with few later forms. When the bone-marrow smears were stained for iron many of the normoblasts were seen to have numerous siderotic granules in their cytoplasm.

After an initial transfusion, pyridoxine 150 mg. daily was given by mouth. This was followed by a reticulocyte response reaching 11.5% on the tenth day of treatment. A further sternal marrow again showed an erythroid hyperplasia, but this time orthochromatic normoblasts were plentiful. During the next 13 weeks the haemoglobin gradually rose to 13.7 g./100 ml. and the serum iron fell to 150 μg./100 ml. Despite a marked improvement in the haemoglobin level and red-cell count, the morphological changes in the peripheral blood were not completely reversed. Hypochromia and poikilocytosis were still conspicuous in the film; the M.C.V. being 74 cubic microns and M.C.H.C. 29%. During these 13 weeks of pyridoxine therapy the clinical condition of the patient improved dramatically. After his recovery it was thought justifiable to carry out a skin and liver biopsy. The former showed increased melanin pigmentation of the epidermis but no evidence of iron deposition in the dermis. The liver, however, was the seat of a well-marked haemochromatosis (Fig. 3). At this time

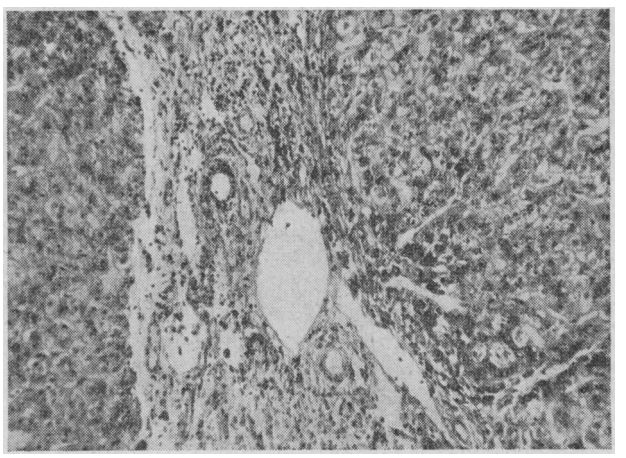

FIG. 3.—Case 1. Liver biopsy. (Haematoxylin and eosin. ×100.)

the survival of the patient's red cells labelled with ^{51}Cr was determined and found to be normal. Surface counting with a collimated probe detector showed no evidence of sequestration of the labelled cells in the liver or spleen.

The administration of pyridoxine was stopped after four months. During the next three months the haemoglobin fell slightly from 13.7 to 13 g./100 ml. and the serum iron rose from 150 to 183 μg./100 ml. Towards the end of this period measurements of xanthurenic acid excretion before and after a tryptophan load were performed. These gave normal results. Following the reintroduction of pyridoxine therapy the haemo-

globin rose to 14.1 g. and the serum iron fell to 126 μg. The patient has remained well for seven months on a maintenance dose of 50 mg. daily.

Family Study

There was no history of anaemia in any other member of the patient's family. However, the peripheral blood was examined and the serum iron estimated in the patient's two brothers and 24 of their children and grandchildren. All were normal except for one brother, aged 69, in whom evidence of a similar hypochromic anaemia was found. This brother had no dyspepsia or symptoms attributable to anaemia, and on examination there was neither hepatomegaly nor splenomegaly. The haemoglobin, however, was 11.2 g./100 ml., M.C.V. 74 cubic microns, and M.C.H.C. 31%. The white-cell, platelet, and differential white-cell counts were normal. The peripheral blood smear showed hypochromia, microcytosis, and poikilocytosis of the red cells. The serum iron was 148 μg./100 ml. and T.I.B.C. 235 μg./100 ml. Examination of the sternal marrow aspirate showed a normoblastic hyperplasia, and, when appropriately stained, the presence of prominent iron granules in the cytoplasm of many of the normoblasts.

Survival of the patient's ^{51}Cr-labelled red cells was normal, $T\frac{1}{2}^{Cr}$ being 28 days ($T\frac{1}{2}^{Cr}$ range of normal in this laboratory =25–32 days). The half-clearance time of an intravenous dose of ^{59}Fe, 107 minutes, and the plasma iron turnover of 0.89 mg. daily per 100 ml. of whole blood, were both within normal limits. The iron utilization, however, was somewhat below normal, being 65.8%.

In view of the normal serum iron, the quantity of iron in the marrow, and the depressed utilization of administered iron it was clear that this man's hypochromic anaemia was not due to iron deficiency but was similar to that of his brother. He was therefore given 150 mg. of pyridoxine daily by mouth for 10 days. This failed to produce a reticulocyte response and was not followed by a rise in the haemoglobin level.

Case 2: Sex-linked Anaemia with Pigmentation and Duodenal Ulceration

The patient was a seaman, aged 31, when he first presented complaining of attacks of abdominal pain and dyspepsia. An *x*-ray barium-meal examination showed the presence of a duodenal ulcer. His haemoglobin was found to be 8.5 g./100 ml. and the blood film showed marked hypochromia of the red cells. He was started on an ulcer regime and given a prolonged course of oral iron therapy without benefit.

Eighteen months later a recurrence of severe abdominal pain and vomiting necessitated his admission to hospital. Laparotomy confirmed the presence of duodenal ulceration, but no surgical procedure was thought necessary. The liver was enlarged and a biopsy showed the presence of large amounts of iron in both the parenchymal and Kupffer cells together with fibrous bands beginning to radiate out from the portal tracts.

Six months later he was again admitted to hospital because of increasing weakness. On examination he was clearly anaemic and the presence of a generalized grey-brown skin pigmentation was noted. He stated that he had always been pigmented and that several of his relatives were similarly coloured. The liver was enlarged 2 in. (5 cm.) below the costal margin, but the spleen was not palpable. Slight epigastric tenderness was present.

Investigations and Progress

The haemoglobin was 8.7 g./100 ml.; red cells 4,000,000/c.mm.; P.C.V. 30%; M.C.H.C. 29%; and M.C.V. 74 cubic microns. The reticulocyte count was 1.75%, the platelets 200,000/c.mm., and white cells 6,900/c.mm., the differential count being normal. The red cells in a stained peripheral blood smear were dimorphic. While some were normal in size and haemoglobinization, the majority were microcytic hypochromic and showed marked poikilocytosis. Haemoglobin electrophoresis showed only haemoglobin A to be present with no increase in the A_2 component. The serum iron was 240 μg./100 ml. An aspirated sample of sternal marrow revealed a normoblastic hyperplasia with poor haemoglobinization of the later forms. On staining the bone-marrow for iron the cytoplasm of many of the normoblasts was found to contain coarse granules of free iron. The serum bilirubin was 0.7 mg./100 ml. and urobilinogen excretion 476 mg. over a period of three days. There was no evidence of haemolysis, the $T\frac{1}{2}$ of the patient's ^{51}Cr-labelled cells being 26 days. The plasma half-clearance time of ^{59}Fe was 79 minutes, giving an increased plasma iron turnover of 2.1 mg. daily per 100 ml. of whole blood. The utilization of ^{59}Fe was decreased to only 5.6% of the dose.

A urinary amino-acid chromatogram was normal. Estimations of urinary xanthurenic acid revealed a basal excretion of 60 mg./24 hours, which rose to 85 mg./24 hours after a loading dose of 5 g. of DL-tryptophan. After a four-day course of 150 mg. of pyridoxine daily by mouth the basal xanthurenic acid excretion fell to 4.8 mg./24 hours and to 28 mg./24 hours after the tryptophan load. These results suggested a deficiency of pyridoxine (Greenberg *et al.*, 1949), and the patient was therefore given 150 mg. of this vitamin daily by mouth for 12 days. There was, however, no reticulocyte response nor rise in the haemoglobin. Courses of several preparations of liver extract ("campolan," "hepatex," and "hepolan"), yeast, nicotinic acid, pantothenic acid, and riboflavin also failed to produce an improvement.

Family History

There was a history of anaemia, pigmentation, and duodenal ulceration or dyspepsia in five of the patient's close relatives on the maternal side of the family (Fig. 4). The patient's mother

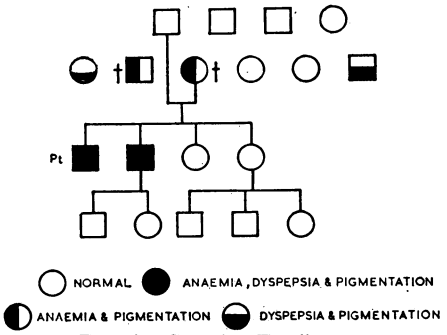

FIG. 4.—Case 2. Family tree.

had been pigmented and had died 14 years previously, suffering from anaemia and cholelithiasis. One of her brothers was stated to have died from anaemia and so-called "Addison's disease." Unfortunately no further details of these cases were available. One of his mother's sisters had undergone a gastroenterostomy because of a duodenal ulcer, and it had been noted that she was excessively pigmented and had a hypochromic anaemia. The anaemia, however, responded completely to iron therapy. Two other sisters were unavailable for examination but were apparently well. The mother also had one surviving brother, who was found to suffer from dyspeptic symptoms and was pigmented. He was not anaemic and his serum iron was normal. A skin biopsy showed increased amounts of epidermal melanin but no evidence of iron deposition in the dermis.

The patient's father, two paternal uncles, and an aunt were examined and were found to be free from dyspeptic symptoms or anaemia and their serum iron was normal. Two sisters and the children of one showed no abnormalities. The patient had one brother, aged 39, who was markedly pigmented and suffered severely from dyspepsia. He was found to have a hypochromic anaemia similar to that of the patient. The haemoglobin was 8.7 g./100 ml. and the serum iron 263 μg./100 ml. A barium-meal examination showed the presence of a duodenal ulcer. Treatment with pyridoxine 150 mg. daily was given, but the anaemia showed no response. Neither of this brother's children showed any abnormality.

Discussion

The hypochromic iron-loading anaemias form as yet an incompletely delineated group of diseases. Sex-linked anaemia (Cooley, 1945) is characterized by a hypochromic

microcytic peripheral blood picture in the presence of raised levels of serum iron and frequently of haemochromatosis. It is familial and reaches its fullest expression in males although a mild anaemia may also occur in females. It has so far proved refractory to all forms of haematinic therapy. Cases closely resembling sex-linked anaemia but without a family history have been described, and a similar condition, also generally sporadic, which is responsive to pyridoxine has been recognized (Harris *et al.*, 1956; Verloop and Rademaker, 1960; Jones and Hutt, 1961). In two cases of "iron-loading anaemia" described by Horrigan *et al.* (1957) and Horrigan (1961) a response was obtained with crude liver extract as well as pyridoxine. While the majority of cases of pyridoxine-responsive anaemia have shown normoblastic erythropoiesis, in the first case of Dawson *et al.* (1961) occasional "megaloblast-like cells" were present, and in Maier's (1957) case erythropoiesis was frankly megaloblastic in character.

The aetiology and relationship of these anaemias are uncertain. They can be distinguished from thalassaemia by their hereditary pattern and absence of an increase in either foetal or A_2 haemoglobin. They also differ from the refractory normoblastic anaemia described by Dacie *et al.* (1959), as in this condition macrocytosis often occurs and hypochromia is inconspicuous. There is some evidence that sex-linked anaemia and pyridoxine-responsive anaemia may be variants of the same disorder. They both mainly affect males. One case of sex-linked anaemia is reported to have responded to pyridoxine (Bishop and Bethel, 1959), and although the pyridoxine-responsive cases are generally sporadic the condition has also been described in more than one member of a family (Medal *et al.*, 1961). Furthermore, in the pyridoxine-responsive cases the response is often only partial, suggesting that the essential abnormality of haemoglobin synthesis is not fully corrected.

It has been suggested that the quantities of iron in the haemoglobin-forming cells inactivate pyridoxal phosphate, which is required for the formation of delta-aminolaevulinic acid necessary for haemoglobin synthesis. The effect of pyridoxine is to overcome this inactivation of pyridoxal phosphate and thus to correct an epiphenomenon rather than a basic defect (Bishop and Bethel, 1959). It may be, however, that pyridoxine has a more fundamental effect in correcting a deficiency in one part of a complex metabolic pathway and that a further deficiency exists. Horrigan (1961) believed that both pyridoxine and an unidentified liver factor have a close metabolic association in erythropoiesis. He suggested that a deficiency of the liver factor might be partially compensated for by pyridoxine in the same way as a deficiency of vitamin B_{12} can be compensated for by folic acid.

The affected members of the two families we have described had a similar anaemia. The bone-marrow findings were also indistinguishable and the more severely affected cases had a gross iron overload, pigmentation, and hepatic fibrosis. Studies were made using radioactive tracer techniques, and these showed similar patterns; using ^{51}Cr, the red-cell survival of labelled cells from the patient's peripheral blood was found to be normal. After an intravenous injection of ^{59}Fe the plasma-iron turnover was found to be normal or somewhat increased, while iron utilization was decreased. These latter findings would suggest either a continued turnover of iron through the non-erythropoietic pools in the body or ineffective erythropoiesis. The technique does not allow a differentiation between defective haemoglobin synthesis with impaired delivery of formed red cells and the production of abnormal cells which are rapidly destroyed either in the medulla or shortly after they enter the circulation. Previously described cases of both pyridoxine-responsive and sex-linked anaemia have been found to have had either a normal (Garby *et al.*, 1957; Dawson *et al.*, 1961) or a shortened (Gelpi and Ende, 1958; Jones and Hutt, 1961) red-cell survival. Jones and Hutt (1961) have reported ineffective erythropoiesis in a pyridoxine-responsive case.

The results of the tryptophan load test in the two cases are of interest. In the pyridoxine-responsive case the test gave no indication of a deficiency of pyridoxine, while the second case, which was refractory to pyridoxine, had a tryptophan test which strongly suggested a deficiency of the vitamin. In the cases described by Bishop and Bethel (1959), Verloop and Rademaker (1960), and Jones and Hutt (1961) the tryptophan test also proved unreliable in predicting the possibility of response to pyridoxine.

Of the two brothers in the first family the anaemia of only one responded to pyridoxine. The refractory case had a similar though milder anaemia and had less evidence of iron overload. This would support the belief that the vitamin does not correct the basic defect in the disease but only an epiphenomenon resulting from iron overload. It is difficult, however, to explain on this basis why the propositus of the second family, despite a severe anaemia of similar type and grossly excessive iron stores, showed no response to pyridoxine.

A feature of the pyridoxine-responsive case was an episode of thrombophlebitis which affected both the patient's legs. It occurred when the anaemia was in relapse and quickly improved after transfusion and pyridoxine therapy. Attacks of phlebitis appear to be a frequent complication of iron-loading anaemia (Mills and Lucia, 1949; Gelpi and Ende, 1958; Byrd and Cooper, 1961). Their cause is unknown, and in the present case it cannot be ascribed to a deficiency of pyridoxine because in previous reports phlebitis has been especially associated with sex-linked anaemia, refractory to pyridoxine, and has often been precipitated by splenectomy.

It is of some interest that in the second family six members of two generations suffered from various combinations of anaemia, pigmentation, and duodenal ulceration or dyspepsia. In at least two members all three features were present together. We have been unable to find a report of a similar family in the literature. The character of the anaemia, its familial nature, and its tendency to affect males suggest a relationship to sex-linked anaemia. In a number of the reports of cases of sex-linked and pyridoxine-responsive anaemia the presence of duodenal ulceration or dyspepsia has been mentioned (Rundles and Falls, 1946; Erslev *et al.*, 1960; Byrd and Cooper, 1961; Dawson *et al.*, 1961; and Case 1 above) and pigmentation has been present in cases developing haemochromatosis. McAlpine (1959) has also commented on a possible association between haemochromatosis and peptic ulceration. In our family, however, pigmentation and duodenal ulceration occurred in the absence of anaemia with elevation of the serum iron or other evidence of haemochromatosis. Indeed, in one instance the patient was found to be iron-deficient and to respond to iron therapy.

The three features of this syndrome are clearly genetically determined, but from the family history it is uncertain whether they are all carried by one gene with a variable expression or are due to the coincidental presence of several genetic traits.

Summary

Two families are described. In the first a case of hypochromic anaemia responsive to pyridoxine was associated

with a similar anaemia in a sibling which was refractory to pyridoxine. In the second, several members suffered from varying combinations of refractory hypochromic anaemia with hyperferricaemia, pigmentation, and duodenal ulceration.

The similarities between pyridoxine-responsive anaemia and other cases of hypochromic iron-loading anaemia refractory to treatment are emphasized. An apparent association of duodenal ulceration or dyspepsia and pigmentation with this group of anaemias is noted and contrasted with the dissociation of these features in our second family.

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REFERENCES

Bishop, R. C., and Bethel, F. H. (1959). *New Engl. J. Med.*, **261**, 486.
Byrd, R. B., and Cooper, T. (1961). *Ann. intern. Med.*, **55**, 103.
Cooley, T. B. (1945). *Amer. J. med. Sci.*, **209**, 561.
Crosby, W. H., and Sheehy, T. W. (1960). *Brit. J. Haemat.*, **6**, 56.
Dacie, J. V. (1960). *The Haemolytic Anaemias*, 2nd ed., Part 1, p. 277. Churchill, London.
—— Smith, M. D., White, J. C., and Mollin, D. L. (1959). *Brit. J. Haemat.*, **5**, 56.
Dawson, D. W., Leeming, J. T., Oelbaum, M. H., Pengelly, C. D. R., and Wilkinson, J. F. (1961). *Lancet*, **2**, 10.
Erslev, A. J., Lear, A. A., and Castle, W. B. (1960). *New Engl. J. Med.*, **262** 1209.
Garby, L., Sjölin, S., and Vahlquist, B. (1957). *Brit. J. Haemat.*, **3**, 55.
Gelpi, A. P., and Ende, N. (1958). *Amer. J. Med.*, **25**, 303.
Goldish, R. J., and Aufderheide, A. C. (1953). *Blood*, **8**, 837.
Greenberg, L. D., Bohr, D. F., McGrath, H., and Rinehart, J. F. (1949). *Arch. Biochem.*, **21**, 237.
Harris, J. W., Whittington, R. M., Weisman, R., jun., and Horrigan, D. L. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **91**, 427.
Heilmeyer, L., Emmrich, J., Hennemann, H. H., Keiderling, W., Lee, M., Bilger, R., and Schubothe, H. (1958). *Folia haemat. (Frankfurt)*, **2**, 61.
Horrigan, D. L. (1961). *Blood*, **18**, 535.
—— Whittington, R. M., Weisman, R., jun., and Harris, J. W. (1957). *Amer. J. Med.*, **22**, 99.
Jones, N. F., and Hutt, M. S. R. (1961). *Lancet*, **1**, 1199.
McAlpine, S. G. (1959). *Brit. med. J.*, **2**, 618.
Maier, C. (1957). *Schweiz. med. Wschr.*, **87**, 1234.
Medal, L. S., Elizondo, J., Gallardo, J. T., and Gittler, C. (1961). *Blood*, **17**, 547.
Mills, H., and Lucia, S. P. (1949). Ibid., **4**, 891.
Rundles, R. W., and Falls, H. F. (1946). *Amer. J. med. Sci.*, **211**, 641.
Verloop, M. C., and Rademaker, W. (1960). *Brit. J. Haemat.*, **6**, 66.

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A CLINICO-HAEMATOLOGICAL STUDY

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The occurrence of moderate to moderately severe anaemia in kwashiorkor has been observed by almost all workers. Normocytic orthochromic anaemia is the form most commonly reported in this disease. Its mechanism is not quite clear. It is refractory to treatment with iron, liver extract, vitamin B_{12}, and folic acid. It has been variously regarded as a protein-deficiency anaemia (Altmann and Murray, 1948) or a manifestation of protein malnutrition associated with liver damage, aggravated by infections, and when there are heavy demands on protein supplies. High-protein feeding results in an improved clinical condition and a coincident rise in haemoglobin and plasma-protein levels (Woodruff, 1955). On the other hand, Trowell and Simpkiss (1957) stated that a review of the published work showed no conclusive evidence of a rise in haemoglobin in anaemic cases of kwashiorkor treated with protein-rich diets only. In fact, their studies revealed that the mean haemoglobin level was lower when those cases had otherwise improved, and that iron-dextran complex given intramuscularly improved the haemoglobin and stopped the usual fall.

For the past few years one of us (M. K. S.) has been examining bone-marrows of children with kwashiorkor microscopically and was rather impressed by consistently finding a hypoplastic picture. Since the clinical and haematological manifestations in malnourished children show a certain variation in different parts of the world, the present study was undertaken to determine the type of anaemia, the role of liver dysfunction, the effect of high-protein diet on haemopoiesis, and certain clinical manifestations as they occur in this region.

Material and Methods

Twenty-two untreated cases of kwashiorkor were admitted to hospital for this study. The patients were aged 1 to 4½ years. The approximate total calories and protein taken by each child daily before admission were calculated. Three children were still entirely on the breast and receiving only 2–3 oz. (57–85 ml.) of milk per day. The disease was classified as mild, moderate, or severe according to the generally accepted criteria. Oedema was assessed as grade I when present on the feet only, grade II when it involved the feet and the face, and grade III when it was generalized. Although the early symptoms are invariably present for a long time before oedema appears, for the purpose of this study the duration of the disease was calculated from the time the oedema appeared (see Table I).

On the children's admission the haemoglobin estimation (Leitz electrophotometer), R.B.C., W.B.C., reticulocyte count, and absolute values and smear examinations for morphological variations in red blood cells were done. Evidence of haemolytic anaemia was sought by estimating serum bilirubin, red-cell fragility, and direct and indirect Coombs test. Bone-marrow was studied in 18 cases. Simultaneously, liver biopsies and serum protein estimations (biuret method) were done in 19.

These children were put on a high-protein diet along with skimmed milk and protein hydrolysates, supplying a protein intake of 4–5 g./lb. (8.8–11 g./kg.) of body weight per day. No haematinics or vitamin preparations were given except vitamin A to treat the ocular lesions. Blood transfusion had to be given in two cases as a life-saving measure