and that pressure in this way is responsible for the sudden distension of the endolymph system in cases of Ménière's syndrome.

Summary

Reports are given of a number of cases in which a lesion of the stomach or duodenum was associated with Ménière's syndrome. The latter usually followed the symptoms of the gastro-intestinal lesions, and onset or exacerbation of the labyrinthine disturbance was associated with increase in those of the gastro-intestinal lesion. Medical or surgical treatment of the latter relieved the symptoms of the former, suggesting the labyrinthine disturbance was secondary. The significance of the observations in relation to the aetiology of Ménière's syndrome is discussed.

I thank Mr. R. C. B. Ledlie for permission to publish the details of Case 3, Miss A. H. Baker and Mr. R. W. Raven, who operated on Case 5, and Mr. W. A. Mill and Mr. C. P. Malley, who carried out the aural investigations.

REFERENCES

- Aird, I. (1949). *A Companion in Surgical Studies*. Livingstone, Edinburgh.
- Atkinson, M. (1940). *Canad. med. Ass. J.*, **42**, 326.
- Brunner, H. (1939). *Laryngoscope*, **49**, 877.
- Dean, L. W. (1939). *Medicine of the Ear*, edited by E. P. Fowler, jun. Nelson, New York.
- Dix, M. R., and Hallpike, C. S. (1952). *Ann. Otol. (St. Louis)*, **61**, 987.
- Dohlman, G. (1939). *Acta oto-laryng. (Stockh.)*, **27**, 245.
- Elstner, H. L., and Waugh, J. M. (1957). *Surgery*, **41**, 674.
- Fischer, J., and Wolfson, L. E. (1943). *The Inner Ear*. Grune and Stratton, New York.
- Hahn, O. (1929). *Brun's Beitr. klin. Chir.*, **148**, 255.
- Hallpike, C. S., and Cairns, H. (1938). *J. Laryng.*, **53**, 625.
- and Wright, A. J. (1939). *Proc. roy. Soc. Med.*, **32**, 1646.
- Johnson, L. F. (1954). *A.M.A. Arch. Otolaryng.*, **59**, 492.
- Kobrak, F. (1928). *Handbuch der Neurologie des Ohres*, **2**, 535, edited by G. Alexander and O. Marburg. Urban and Schwarzenberg, Berlin.
- Lorente de Nó, R. (1938). Cited by S. S. Stevens and H. Davis's *Hearing, Its Psychology and Physiology*. Wiley, New York.
- Meyer, C. (1940). *Pract. oto-rhino-laryng. (Basel)*, **3**, 92.
- Ogilvie, R. F. (1941). *Brit. J. Surg.*, **28**, 362.
- Passe, E. R. G. (1951). *Proc. roy. Soc. Med.*, **44**, 760.
- Portmann, M., and Portmann, C. (1954). *A.M.A. Arch. Otolaryng.*, **59**, 543.
- Strong, M. S. (1957). *Ibid.*, **65**, 340.
- Vogel, K. (1929). *Z. Hals-, Nas- u. Ohrenheilk.*, **23**, 39.
- Volterra, M. (1925). *Zbl. inn. Med.*, **46**, 876.
- and Schupfer, F. (1934). *Arch. ital. Anat. Embriol.*, **33**, 844.
- Wolf, S. (1946). *J. clin. Invest.*, **25**, 938.
- Wyburn-Mason, R. (1958). *The Reticulo-endothelial System in Growth and Tumour Formation*. Kimpton, London.

A review of how colour prejudice has developed over the centuries, and some suggestions on how it may be counteracted, are given in a pamphlet entitled *Colour and Commonsense*, by Kenneth Little (Fabian Society and Commonwealth Bureau, 2s. 6d.). In a foreword Mr. Norman Manley, Chief Minister of Jamaica, draws attention to the fact that in his country "a wide variety of races and their admixtures" live together in mutual respect, "in spite of 300 years of colonialism and the legacy of slavery." Mr. Little, who is reader in anthropology at Edinburgh University, traces the growth of the colour bar through the institution of slavery and its rationalization by the racialist myths of the nineteenth century, into which Darwin's ideas on the origin of species were dragged and misinterpreted. In suggesting ways to prevent individuals from forming an antipathy to coloured people the author stresses the need to present children with natural and objective information. As he says: "Younger children are rarely colour-prejudiced." If they are, they have learnt it from their parents, and here he advises on how the press and B.B.C. could help more.

TWO CASES OF AUTO-IMMUNE HAEMOLYSIS AND APLASIA

BY

J. BURSTON, M.B., B.Sc.

O. A. N. HUSAIN, M.D.

M. S. R. HUTT, M.D., M.R.C.P.

AND

E. I. TANNER, M.B., B.Chir.

From the Louis Jenner Laboratory, St. Thomas's Hospital, and the Group Laboratory, Lambeth Hospital, London

It has been recognized for several years that marrow aplasia is the basis of some of the haemolytic crises in congenital spherocytosis (Owren, 1948; Dameshek and Bloom, 1948; Gasser, 1950) and also in sickle-cell anaemia (Singer, Motulsky, and Wile, 1950; Chernoff and Josephson, 1951). More recently, reports have appeared of aplastic episodes in idiopathic immune haemolytic anaemia (Davis *et al.*, 1952; Linke, 1952; Eisemann and Dameshek, 1954; Seip, 1955; Henneman and Falck, 1957). This report records two further cases in which hypoplasia of the marrow was associated with an auto-immune type of haemolytic anaemia. Radioactive ^{59}Fe and ^{51}Cr studies were carried out, using the techniques described by Wetherley-Mein *et al.* (1956, 1958).

Case 1

A man aged 76 was first seen on November 9, 1955, with symptoms of anaemia which had been increasing for two to three months. Examination at this time showed him to be anaemic but with no other abnormal physical signs. Blood examination revealed: Hb, 5.92 g./100 ml.; R.B.C., 1,300,000/c.mm.; P.C.V., 16%; M.C.V., 123 cubic microns; M.C.H.C., 37%; W.B.C., 2,700/c.mm. (polymorphs 45%, lymphocytes 54%, monocytes 1%). The red blood cells showed macrocytosis and anisocytosis, and there were two normoblasts per 200 white blood cells. Platelets appeared to be plentiful. A diagnosis of pernicious anaemia was made on these results, and on November 10 100 μg . of cyanocobalamin (vitamin B_{12}) was given intramuscularly as a therapeutic trial.

He was seen again on November 25, when his symptoms and pallor were more severe and he was a little jaundiced. Blood examination showed: Hb, 3.85 g./100 ml.; R.B.C., 740,000/c.mm.; P.C.V., 10.5%; M.C.V., 142 cubic microns; M.C.H.C., 36.5%; reticulocytes 2%; W.B.C., 2,000/c.mm. (polymorphs 48%, lymphocytes 50%, monocytes 1%). The film appearances had not changed.

Because of this marked deterioration he was admitted to hospital immediately. Further investigations were performed. Aspiration of sternal marrow on two consecutive days revealed a very poorly cellular specimen on each occasion. Only 6% of the cells were erythroblasts, and one-third of these showed transitional megaloblastic changes. Of the remaining cells, 65% were lymphocytes, 5% neutrophil polymorphs, 13% band neutrophils, 6% neutrophil metamyelocytes, 3% neutrophil myelocytes, 1% monocytes, and 1% plasma cells. A histamine test meal revealed no free acid. Serum bilirubin was 1.1 mg./100 ml. and platelets were 47,000/c.mm.

In view of the hypoplastic marrow picture he was treated with repeated small blood transfusions, and because of the transitional megaloblastic appearance of the remaining erythroblasts he was given folic acid, 15 mg. twice daily. ^{59}Fe studies showed the picture of complete functional aplasia of the marrow with a red-cell utilization of only 2%

(see Fig. 1). He was discharged on December 6 after further transfusion, with a haemoglobin of 11.5 g./100 ml., being then regarded as a case of aplastic anaemia.

Within three weeks of discharge he was readmitted with severe anaemia, and blood examination revealed: Hb, 3.68 g./100 ml.; R.B.C., 1,200,000/c.mm.; P.C.V., 11%; M.C.H.C., 33.5%; M.C.V., 89 cubic microns; reticulocytes, 0.3%; W.B.C., 1,700/c.mm. (polymorphs 44%, lymphocytes 54%, monocytes 2%); platelets, 74,000/c.mm. Direct Race-Coombs test, ++; indirect Race-Coombs test, weakly positive against a panel of O cells. Despite difficulty with cross-matching a transfusion of packed red cells was given, and following this a ^{51}Cr red-cell survival test was carried out, using donor cells. This showed an 18% loss per day (normal 1-4%); and, in view of this evidence of severe shortening of the red-cell life, 10 mg. of prednisone was given three times daily. Following this, transfusion had a more prolonged beneficial effect, and within 16 days the direct Race-Coombs test was negative. As a result of transfusion and steroid therapy his haemoglobin rose to 11.5 g./100 ml., and it was then maintained without transfusion at about 13 g./100 ml. for one year despite slow reduction of the steroid dose. This maintenance of a satisfactory level of haemoglobin was good evidence of the functional capacity of the marrow, which was also demonstrated by a rise in the reticulocyte count, which rose from 0.4% in January, 1956, to 4.6% in April. A second ^{51}Fe study at this time showed a normal pattern (see Fig. 1) with 100% utilization of the tracer dose injected. The sternal marrow, which was examined on June 11, 1956, was now found to be richly cellular, in contrast to the previous aspirates.

Erythropoiesis was prominent, the erythroblasts again showing some transitional megaloblastic features. Mature polymorphs were reduced in number and megakaryocytes were still scanty.

This satisfactory clinical and haematological state was maintained in spite of successive decreases in the dose of prednisone and its final withdrawal at the beginning of November, 1956.

In mid-February, 1957, the direct Race-Coombs test became weakly positive again for the first time for 13 months, and there was a fall in the haemoglobin level associated with a rise of reticulocytes (see Fig. 1). Prednisone therapy was again started, and this resulted in a rise of the haemoglobin level, which was maintained over the next month. In early April the patient contracted an upper respiratory infection, and on April 7 was admitted to hospital with bronchopneumonia.

On admission his haemoglobin was 12.1 g./100 ml.; reticulocytes, 1.1%; W.B.C., 1,250/c.mm. (polymorphs 58%, lymphocytes 42%); platelets, 90,000/c.mm. Direct Race-Coombs test positive. His lung infection was treated with penicillin and streptomycin, though the response was rather slow and he was in hospital for six weeks before he was fit to return home. During this period there was considerable depression of marrow function, as shown by the pancytopenia with a low reticulocyte count. Prednisone was given throughout, though the dose had been cut to 5 mg. twice daily for 10 days at the onset of the infection. Once the infection was overcome the haemoglobin level began to rise, reaching a figure of 19.25 g./100 ml. in August. Following this the prednisone was gradually withdrawn and the haemoglobin fell to about 15 g./100 ml. This level has been maintained without treatment for six months with no haematological evidence of occult haemolysis.

Case 2

A man aged 68 was admitted to hospital in October, 1956, complaining of shortness of breath for the past three days. About six months previously a right above-knee amputation

FIG. 1.—Chart of Case 1.

had been undertaken for vascular insufficiency, and in 1931 he had had a gastro-enterostomy for a chronic gastric ulcer.

On examination he was found to be grossly anaemic and had signs of cardiac failure, as shown by a raised jugular venous pressure, crepitations at both lung bases, and sacral oedema. There were no other abnormal physical signs and his spleen was not palpable.

Blood examination revealed: Hb, 3.7 g./100 ml.; R.B.C., 940,000/c.mm.; P.C.V., 11%; M.C.H.C., 33%; M.C.V., 102 cubic microns; W.B.C., 2,400/c.mm. (polymorphs 30%; lymphocytes 54%, eosinophils 16%); platelets, 350,000/c.mm.; reticulocytes, less than 1%. The direct Race-Coombs test was positive. Sternal marrow biopsy revealed a hypoplastic marrow with numerous fat globules in the film. The differential count showed: segmented polymorphs 36%, band polymorphs 13%, meta-myelocytes 10%, myelocytes 3%, lymphocytes 10%, eosinophils 9%, eosinophil myelocytes 4%, pro-erythroblasts 1%, normoblasts A 4%, B 3%, C 7%.

The patient was treated with small repeated blood transfusions, and after about 10 days his haemoglobin had risen to 10 g./100 ml. Throughout this time his direct Race-Coombs test had remained positive, but no atypical antibodies could be detected using the indirect Race-Coombs technique or with trypsinized red cells. A ^{51}Cr survival of his labelled red cells showed a 6% loss of ^{51}Cr per day (normal 1-4%). In view of the evidence of increased red-cell destruction he was started on prednisone, 10 mg. three times a day, and discharged to attend as an out-patient (see Fig. 2). Over the next six weeks his haemoglobin remained around 9 g./100 ml., with the help of two further blood transfusions. ^{59}Fe studies revealed an iron utilization of only 26% (normal 70-80%), confirming that his marrow was still hypoplastic.

He was readmitted on November 30 complaining of a cough and pain in the right side of his chest. A chest x-ray film showed an extensive consolidation of the right upper zone, probably with cavity formation, and tubercle bacilli were found in his sputum. Antituberculous treatment with isoniazid, streptomycin, and P.A.S. was begun, but the P.A.S. had to be withdrawn within a few days because of a high fever. A few days later the prednisone was reduced to 5 mg. three times a day.

A second chest x-ray examination about two weeks after the first showed that there had been extensive spread of disease into the left upper and mid-zones and further consolidation of the right lung. His general condition improved slightly over the next two weeks, at the end of which time, when his haemoglobin was found to be only 8.1 g./100 ml., his prednisone was increased again to its previous level. Over the next six weeks his haemoglobin gradually rose to 11.5 g., although he had had no blood transfusion (see Fig. 2). His reticulocytes rose to 4% and his direct Race-Coombs test remained positive, suggesting continuing haemolysis with some recovery of marrow function.

He was then transferred to another hospital to continue his antituberculous treatment. He remained there until his death six months later. On admission (February 15, 1957) blood examination revealed: Hb, 8.5 g./100 ml.; R.B.C.,

2,660,000/c.mm.; M.C.V., 103 cubic microns; M.C.H.C., 30%. W.B.C. count 22,600/c.mm. (polymorphs 78%, lymphocytes 19%, eosinophils 2%, monocytes 1%; reticulocytes, 1.8%); direct Race-Coombs test negative. During his stay in this hospital the tuberculous process in his lungs remained active in spite of treatment. His haemoglobin at first remained steady at about 9 g./100 ml., but then dropped gradually to 6 g. despite an increase in prednisone dosage; the direct Race-Coombs test again became positive in March, remaining positive until May 13. His condition was then further complicated by the discovery of positive occult blood in his stools, and on x-ray examination he was found to have a small gastric ulcer. Though treatment, with blood transfusions, was given, his condition continued to deteriorate, with sepsis of bedsores and a terminal episode

FIG. 2.—Chart of Case 2.

of bronchopneumonia, from which he died on August 20, 1957. His haemoglobin just prior to death was only 3.6 g./100 ml., and this was again associated with a positive direct Race-Coombs test.

Post-mortem examination revealed evidence of basal bronchopneumonia and active fibrocasseous tuberculosis at the right apex. The marrow in the spine and sternum had a homogeneous pinkish-brown colour, but the midshaft marrow in the femur was a little more fatty. There was a functioning gastro-enterostomy but no evidence of an active ulcer at necropsy. The spleen was about twice the normal size and contained a few small infarcts. Histological examination of the tissues confirmed the macroscopical diagnosis of bronchopneumonia and fibrocasseous tuberculosis. The marrow showed hyperplasia of the myeloid elements with a gross reduction in the number of erythroblasts and a normal proportion of megakaryocytes. The spleen showed anaemic infarcts with some hyperplasia of the sinus reticulum, and haemosiderosis. There was no evidence of extramedullary haemopoiesis.

Discussion

The association of a short red-cell life with a failure of red-cell production in refractory and hypoplastic

anaemias was emphasized by Bomford and Rhoads (1941), and in recent years the advent of radioactive techniques has stressed this dual mechanism in many types of anaemia. Loeb *et al.* (1953) reported several cases of "chronic bone-marrow failure" with short red-cell life, but in none was there evidence of an auto-immune mechanism.

Eisemann and Dameshek (1954) report a case with a simultaneous onset of hypoplasia and haemolysis associated with a positive Race-Coombs test; splenectomy was performed on this patient because of failure of response to other therapeutic manœuvres, and the operation resulted in a complete haematological recovery except for the persistence of a weak positive Race-Coombs test. These authors concluded that a splenic factor may have been operating on the erythropoietic tissue in the marrow, causing hypoplasia, or, alternatively, that the specific aregenerative state of the nucleated red cells in the marrow was the result of a direct action of erythrocyte antibodies on the red-cell precursors.

Hennemann and Falck (1957) describe a case of idiopathic acquired immune haemolytic anaemia in a patient who died in a pseudo-aplastic crisis, and a further case of primary aplastic anaemia of three years' duration in a man of 61 who showed latent haemolytic characteristics with a negative Race-Coombs test but who finally developed a fatal haemolytic crisis due to incomplete warm auto-antibodies. They discussed the relationship between haemolytic anaemia and aplastic anaemia and emphasized that their association may lead to difficulties in diagnosis. Crosby and Rappaport (1956) stressed that reticulocytopenia in auto-immune haemolytic anaemia does not necessarily indicate marrow aplasia or an acute aregenerative crisis, but may also be due to alterations in the maturation of erythroblasts or in the life-span of the reticulocyte.

The clinical, haematological, and radioactive studies in our two patients indicate that they had a similar mechanism. They show, in the initial stages of the disease, marked marrow hypoplasia associated with a short red-cell life due to an auto-immune mechanism. In both cases there was gradual recovery of marrow function and also of the haemolytic component associated with steroid therapy. In the first case, reduction of the steroid therapy after stabilization of the haemoglobin led to a recrudescence of the haemolysis, and this was exacerbated by an episode of infection shortly afterwards, which also led to a further phase of marrow depression. The patient made a remarkable recovery from this episode as a result of antibiotic and steroid therapy; the evidence of haemolysis and antibody formation slowly disappeared, and after a frankly polycythaemic phase the patient was haematologically normal six months after stopping steroid therapy. In this case the low white cell count and the platelet count roughly parallel the haemoglobin level, suggesting that a similar process may have been operating for these formed elements.

In the second case assessment of the mechanism is more difficult because of the associated tuberculous infection, and in the later stages because of the evidence of gastro-intestinal bleeding. It is evident that there was some improvement of marrow function associated with steroid therapy as shown by the spontaneous rise in haemoglobin and increase of reticulocytes shown in January, 1957. In the terminal phases of the disease

the rapidly falling haemoglobin suggests that both haemolysis and aplasia were contributory mechanisms, though blood loss must also have played some part. Although there is evidence in both cases to indicate the place of infection in their exacerbations there is no evidence that they initiated the process.

The close association between the degree of haemolysis and of marrow function in these cases suggests that the concept of antibody effect in erythrocyte precursors in the marrow may well be correct (Eisemann and Dameshek, 1954), and this is further borne out by the effectiveness of the steroid therapy, which is known to reduce antibody production in auto-immune haemolytic anaemia (Fudenberg *et al.*, 1958). This theory, however, fails to explain why these aplastic phases are not more common in idiopathic immune haemolytic anaemia, unless it is due to some undetected specific feature of the antibody or, alternatively, to an inherent defect in the marrow. Although a case can be made out for distinguishing cases of aplastic anaemia with haemolysis from cases of acquired haemolytic anaemia with aplasia, this separation may obscure the fact that they have common aetiological factors.

Summary

Two cases of acquired haemolytic anaemia with associated aplasia of the bone marrow are described. In each case there was morphological evidence of aplasia, and failure of red-cell production was confirmed using radioactive iron tracer technique. Evidence of haemolysis was demonstrated by standard serological methods and also by radioactive chromium-tagged red-cell survival studies.

Remission of the marrow failure occurred in each case, though episodes of pulmonary infection led to an exacerbation of the haemolysis and aplasia.

It is postulated that in these two cases an antibody was present which produced destruction of red-cell precursors in the marrow as well as leading to a shortened red-cell life in the general circulation. The beneficial effect of steroid therapy on these two mechanisms of anaemia would support this belief.

We thank Dr. H. J. Anderson for permission to publish Case 2, and Dr. A. C. Dornhorst for access to Case 1 and for his advice in the preparation of this paper.

REFERENCES

- Bomford, R. R., and Rhoads, C. P. (1941). *Quart. J. Med.*, **10**, 235.
 Chernoff, A. I., and Josephson, A. M. (1951). *A.M.A. Amer. J. Dis. Child.*, **82**, 310.
 Crosby, W. H., and Rappaport, H. (1956). *Blood*, **11**, 929.
 Dameshek, W., and Bloom, M. L. (1948). *Ibid.*, **3**, 1381.
 Davis, L. J., Kennedy, A. C., Baikie, A. G., and Brown, A. (1952). *Glasg. med. J.*, **33**, 263.
 Eisemann, G., and Dameshek, W. (1954). *New Engl. J. Med.*, **251**, 1044.
 Fudenberg, H., Barry, I., and Dameshek, W. (1958). *Blood*, **13**, 201.
 Gasser, C. (1950). *Sang.*, **21**, 237.
 Hennemann, H. H., and Falck, I. (1957). *Acta haemat. (Basel)*, **18**, 219.
 Linke, A. (1952). *Verh. dtsch. Ges. inn. Med.*, **58**, 724.
 Loeb, V., Moore, C. V., and Dubach, R. (1953). *Amer. J. Med.*, **15**, 499.
 Owren, P. A. (1948). *Blood*, **3**, 231.
 Seip, M. (1955). *Acta med. scand.*, **153**, 137.
 Singer, K., Motulsky, A. G., and Wile, S. A. (1950). *J. Lab. clin. Med.*, **35**, 721.
 Wetherley-Mein, G., Epstein, I. G., Foster, W. D., and Grimes, A. J. (1958). *Brit. J. Haemat.* In press.
 — Hutt, M. S. R., Langmead, W. A., and Hill, M. J. (1956). *Brit. med. J.*, **1**, 1445.