been lost. The clue was provided by the patient saying that after the stroke he had lost his phantom leg. This is the patient I mentioned in the first lecture as resembling the patient of Head and Holmes (1912) who lost his phantom after a parietal vascular lesion. From this patient it would appear that to walk adequately one must know the position of the limb in space, and, if one is walking on an artificial limb, then it is only effective if it is possessed by a phantom leg which supplies it with the knowledge that is necessary to make it function as a limb rather than just as a support, and an inefficient one at that.

The ataxic walk of the individual with severe cerebellar disturbance must be due in part to the inefficiency of the automatic grading of muscle effort produced by the disorganization of the γ fibre mechanism as already suggested in an earlier part of the lecture, and the use of the more forceful, but uncontrolled α fibre system, so that improper force is used. If one watches the feet of a patient with inadequate cerebellar control it is possible to see constant contraction and relaxation of the foot muscles going on, so that the toes are clawing into the ground—again this is due to the use of a nervous control not designed for the purpose.

There is, however, another side to cerebellar control, and that is equilibration. For it is possible to have the cerebellum so disorganized in its older part—the flocculo-nodular lobe which forms the greater part of the roof of the fourth ventricle—that there may be gross disorder of equilibration. The patient staggers violently from side to side and is quite unsafe on his feet. Yet on formal testing for cerebellar ataxia as in the heel-knee-shin test there is no disorder. This is because the control of the γ system is intact.

It is remarkable how difficult it is for the patient with a severely damaged cerebellum to compensate alone—how simple it is for the compensation to be effected by another. The patient who can walk only with a stagger from side to side may, if he links an arm with a normal person, walk reasonably well. I have seen such a patient do ordinary relatively sedate ballroom dancing apparently so well and so disproportionately to his ordinary walk that he came labelled as a hysteric.

It appears, therefore, that for the equilibration difficulty sufficient stabilization can be provided by another person, but only so long as the γ system is intact. I remember Riddoch demonstrating this with great verve and ending the demonstration by saying that "clearly one cerebellum was enough for two."

Fatigue

I am brought finally to a few words on fatigue in muscle performance, as in walking or in running. At one time the theory of fatigue in profound effort was attributed to fatigue in the central nervous system, but it has been shown that this is inaccurate, and that fatigue is a peripheral phenomenon due to the failure of the circulation to remove metabolic products of muscular contraction. This is easily demonstrated by fatiguing a limb and arresting the circulation at the moment of cessation of muscular contraction, when there will be no recovery of power until the circulation is established. This is evident as applying to severe effort, as when doing heavy muscular work, but it is also the case for skilled fine movements. It was found experimentally that in skilled tasks, even in the lightest such as writing, the muscles are often working nearer the limit of muscular endurance than is imagined, but that owing to the muscles' proprioceptive servo control fatigue is compensated for automatically until considerable fatigue occurs, when the muscle will suffer a relatively sudden breakdown in its performance.

Conclusion

I have dealt with certain aspects only of the means by which we sit, stand, and walk. These lectures have been really a consideration of not sitting, not standing, and walking very badly, but it is only by study of the dissolution of such processes that we can ever hope to elucidate the means by which we manœuvre ourselves into a desired posture as when sitting; the means by which we maintain it, as when standing; and the means by which we co-ordinate all our muscular activity and keep the muscles contracting without overdue fatigue, as in walking.

REFERENCES

Critchley, M. (1953). *The Parietal Lobes.* Arnold, London.
Dimsdale, H., and Logue, V. (1957). Communication to Association of British Neurologists.
Gastaut, H., and Fischer-Williams, M. (1957). *Lancet*, **2**, 1018.
Gilliatt, R. W. (1954). *J. Physiol. (Lond.)*, **123**, 43P.
Gowers, W. R. (1901). *Epilepsy and Other Chronic Convulsive Diseases.* Churchill, London.
—— (1907). *Borderland of Epilepsy.* Churchill, London.
Granit, R. (1955). *Receptors and Sensory Perception.* Yale Univ. Press, New Haven.
Guttmann, L., and Whitteridge, D. (1947). *Brain*, **70**, 361.
Hammond, P. H., Merton, P. A., and Sutton, G. G. (1956). *Brit. med. Bull.*, **12**, 214.
Head, H. (1920). *Studies in Neurology.* Oxford Univ. Press.
—— and Holmes, G. (1912). *Brain*, **34**, 102.
Jackson, J. Hughlings (1931-2). *Selected Writings*, edited by J. Taylor. Hodder and Stoughton, London.
Lange, J. (1936). *Handbuch der Neurologie*, edited by O. Bunike and O. Foerster, vol. 6. Springer, Berlin.
Lhermitte, J. (1939). *L'Image de Notre Corps.* Nouvelle Revue Critique, Paris.
—— and Trelles, J. O. (1933). *Encephale*, **28**, 413.
Liddell, E. G. T., and Sherrington, C. S. (1924). *Proc. roy. Soc. B*, **96**, 212.
Liljestrand, G., and Magnus, R. (1919). *Pflügers Arch. ges. Physiol.*, **176**, 168.
Matthews, P. B. C., and Rushworth, G. (1957a). *J. Physiol. (Lond.)*, **135**, 245.
—— —— (1957b). Ibid., **135**, 263.
Munk, H. (1890). *Ueber die Functionen des Grosshirnrinde*, 2 Aufl. Hirschwald, Berlin.
Nielsen, J. M. (1946). *Agnosia, Apraxia, Aphasia*, 2nd ed. Hoeber, New York.
Pearson, K. (1911). *Grammar of Science*, 3rd ed. Black, London.
Renshaw, B. (1941). *J. Neurophysiol.*, **4**, 167.
Russell, W. R. (1957). *Proc. roy. Soc. Med.*, **51**, 9.
Schilder, P. (1935). *The Image and Appearance of the Human Body.* Kegan Paul, London.
Sharpey-Shafer, E. P. (1953a). *Brit. med. J.*, **2**, 860.
—— (1953b). *J. Physiol. (Lond.)*, **122**, 351.
—— (1956a). *Brit. med. J.*, **1**, 506.
—— (1956b). Ibid., **1**, 1072.
Sittig, O. (1929). *Zbl. Neurol.*, **53**, 429.
—— (1931). *Über Apraxie. Abh. Neurol. Psychiat.*, Heft 63.
Symonds, C. (1950). *Proc. roy. Soc. Med.*, **43**, 507.
Taylor, N. B. G., and Noble, R. L. (1950). *Proc. Roy. Soc. exp. Biol. (N.Y.)*, **73**, 207.
Walshe, F. M. R. (1924). *Brain*, **47**, 159.
Ward, A. A., jun. (1947). *J. Neurophysiol.*, **10**, 89.
Williams, D. J., and Wilson, T. G. (1957). Communication to Association of British Neurologists.

HAEMORRHAGIC THROMBOCYTHAEMIA

REPORT OF TWO CASES TREATED WITH RADIOACTIVE PHOSPHORUS

BY

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Epstein and Goedel (1934) first suggested the term "haemorrhagic thrombocythaemia" for the bleeding disorder which is characterized by a persistently raised platelet count. Although bleeding accompanying thrombocytopenia is commonly seen in hospital practice, the association of haemorrhage and thrombocythaemia is extremely rare, and probably no more than 30 cases have been reported in the world literature. Fanger *et al.* (1954) reviewed 28 cases of thrombocythaemia, but in six of them haemorrhagic manifestations were not present. Hardisty and Wolff (1955) analysed the clinical and haematological features of 18 reported cases of haemorrhagic thrombocythaemia plus a further five of their own. Of these 23 patients, 19 were over the age of 40 and there were almost equal numbers of males and females. Bleeding most commonly occurred from the nose and alimentary tract, and,

although bruising was not uncommon, purpura was rarely observed. Blood loss invariably resulted in a hypochromic anaemia, and all cases showed a raised platelet count and leucocytosis.

In addition to bleeding, patients with haemorrhagic thrombocythaemia may have thrombotic episodes. Presumably, these are closely related to the excessive number of platelets, but the mechanism of the bleeding is unknown. Approximately half of the reported cases showed abnormal bleeding-times; otherwise the standard tests of haemostatic function were normal. Hardisty and Wolff (1955) found a qualitative deficiency of the platelets in their five cases, as evidenced by their behaviour in the thromboplastin generation test, but were of the opinion that this was not the only factor involved.

The object of this paper is to present clinical and haematological details, including investigation of the blood-clotting mechanism, of a further two cases of this rare bleeding disorder and to report the beneficial effects of treatment with radioactive phosphorus (^{32}P).

Case 1

A road-worker aged 58 was referred to the department of surgery of Leeds General Infirmary on October 9, 1956, because of chronic bleeding from the alimentary tract for at least six years.

A history was obtained of good health until 1944, when he began to have attacks of abdominal pain. They were at first infrequent. and he was not seen at hospital until April, 1950, when he was found to be anaemic and tender in the epigastrium and right iliac fossa. Occult bleeding from the bowel was detected, and blood examination showed: haemoglobin, 8 g./100 ml.; red cells, 3,410,000/c.mm.; colour index, 0.79; white cells, 16,400/c.mm. (polymorphonuclears 74%, lymphocytes 23%, monocytes 3%). Radiological examination of the alimentary tract failed to reveal any source of bleeding. A diagnosis of peptic ulcer was considered most likely, and treatment of the anaemia with oral and later parenteral iron was advised.

In November, 1950, tonsillectomy was carried out. A good deal of haemorrhage occurred and a bleeding point had to be ligated.

During the following six years he was admitted to various hospitals on numerous occasions because of recurrent alimentary bleeding. Investigations carried out during this period revealed a chronic hypochromic anaemia with leucocytosis, but repeated radiological examinations of the alimentary tract, gastroscopy, and sigmoidoscopy failed to reveal a source of haemorrhage. In April, 1953, a laparotomy was performed, but no abnormality of the stomach, duodenum, small gut, liver, gall-bladder, or spleen was observed. The possibility of a bleeding disorder was apparently not considered, and there is no record of a platelet count having been done, although in 1955 a blood film was reported as showing abundant platelets.

During 1956 the bleeding became more severe and he was admitted to hospital for blood transfusions on eight occasions between January and September. In October a second laparotomy was performed (Professor J. C. Goligher). The stomach and duodenum were explored, but they contained no obvious blood. The jejunum and ileum also looked normal, and blood was first encountered in the terminal 2–3 ft. (30–60 cm.) of the ileum. Blood was also present in the colon, but no source of haemorrhage was discovered. The liver and spleen looked normal. Repeated blood transfusions were necessary post-operatively, and, in addition to melaena, epistaxis and haemoptysis occurred. On October 24, haematological investigation was requested.

Physical examination showed only anaemia. Blood examination gave the following results. Blood group B, Rh positive; haemoglobin, 6.8 g./100 ml.; red cells, 2,620,000/c.mm.; reticulocytes, 1%; mean cell volume, 89 cubic microns, mean corpuscular haemoglobin concentration, 29%; E.S.R. (Westergren), 21 mm. in the first hour. Platelets numbered 2,110,000/c.mm. and the platelet layer in the haematocrit tube measured 11 mm. The bleeding-time was five minutes (Duke), and Hess's capillary resistance test was negative. White cells 73,600/c.mm. (metamyelocytes 1%, neutrophils 89%, eosinophils 2%, basophils 1%, lymphocytes 4%, monocytes 3%). The blood film showed hypochromia and target cells were present. Bizarre forms of platelets, abnormal in shape and size, were present. Fifteen nucleated red cells per 100 white cells were observed, but no megakaryocytes were seen in the peripheral blood. Sternal bone-marrow aspirate was hypercellular, and erythropoiesis and granulocytopoiesis were normal. Mature megakaryocytes were abnormally numerous and surrounded by sheets of platelets. Many immature forms were also present (Fig. 1).

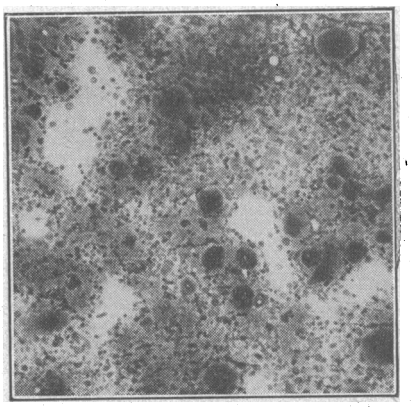

FIG. 1.—Case 1. Bone-marrow film from sternal puncture (Wright's stain), showing increased number of megakaryocytes surrounded by masses of platelets. (×70.)

Investigation of Blood-clotting Mechanism.—Clotting-time (Lee and White), 4 minutes; one-stage prothrombin time (Quick), 15 seconds (control, 15 seconds); prothrombin consumption (Biggs and McFarlane), normal; clot retraction (McFarlane), normal. Calcium clotting time of normal plasma was not increased by addition of patient's plasma. The thromboplastin generation test (Biggs and Douglas, 1953) was normal when the patient's serum was added to the control platelet suspension and the control alumina-adsorbed plasma. It was also normal when the patient's alumina-adsorbed plasma was added to the control serum and control platelet suspension and when the patient's platelet suspension, before dilution and after dilution 1 in 8, was added to the control alumina-adsorbed plasma and control serum. No defect of blood clotting could therefore be detected and the platelet factor seemed normal.

Progress and Treatment (Fig. 2)

During the six weeks from the end of October to mid-December repeated blood examinations showed a hypochromic anaemia, leucocytosis, and thrombocythaemia, the platelet count ranging from 1 to 2.5 million/c.mm. The bleeding-time was usually normal, but occasionally prolonged up to 10 minutes. Melaena continued and blood transfusions were necessary on nine occasions. Cortisone was administered for three and a half weeks in November, without any beneficial effect. On December 14, 3 millicuries of radioactive phosphorus (^{32}P) was given intravenously, the platelet count at that time being 2 million/c.mm. and leucocytes 58,000/c.mm. Two further blood transfusions were necessary during the next 10 days, and the patient was discharged from hospital at his own request on December 24. When seen a week later the haemoglobin had fallen to 6.9 g./100 ml. and a further transfusion was given.

On January 21, 1957, he was seen as an out-patient and was feeling well. No obvious bleeding from the bowel had been observed since his discharge from hospital two weeks earlier and blood examination showed: haemoglobin, 11 g./100 ml.; white cells, 7,600/c.mm.; platelets, 860,000/c.mm. By February 8 the platelet count was 340,000/c.mm. and the haemoglobin 11.5 g./100 ml. Two weeks later the platelets had risen to 910,000/c.mm. and

occult blood was again found in the stool. A further injection of 3 mC of ^{32}P was given and a course of intramuscular iron ("imferon") prescribed. Thereafter the blood picture returned to normal. Repeated testing of the stool for occult bleeding was carried out, but no further bleeding was observed and the patient regained full activity.

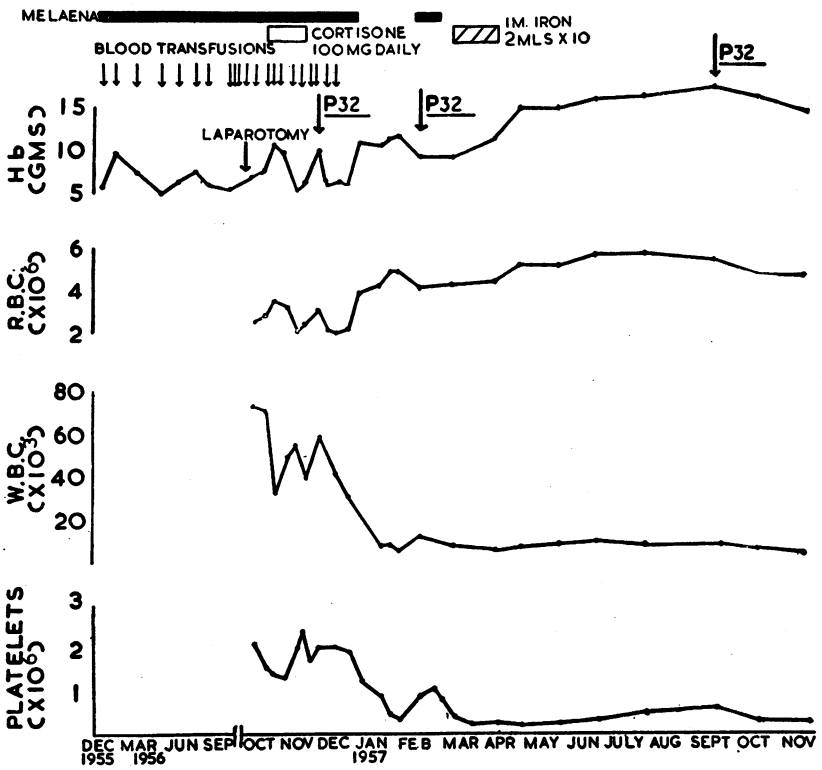

FIG. 2.—Effect of radioactive phosphorus (^{32}P) on the blood picture and bleeding tendency in Case 1.

A third injection of ^{32}P was given on September 20, when the platelet count rose to 600,000/c.mm. When last seen on November 25, 1957, the patient was symptom-free and blood examination showed: haemoglobin 14.8 g./100 ml.; red cells, 4,800,000/c.mm.; white cells, 3,800/c.mm.; platelets 320,000/c.mm.

There had been no evidence of bleeding for over nine months, whereas during the year prior to treatment with ^{32}P he had continuous melaena requiring blood transfusions at intervals of between 7 and 28 days.

Case 2

A maintenance engineer aged 53 gave a history of recurrent episodes of bleeding from the alimentary tract since 1944. Details of his case up to 1952 are deficient, but in February of that year he was admitted to Otley General Hospital under the care of Dr. R. N. Tattersall, complaining of weakness and increasing pallor. The liver was enlarged, hard, and irregular, and the spleen was palpable. Blood examination revealed an iron-deficiency anaemia (haemoglobin, 8 g./100 ml.; red cells, 4,150,000/c.mm.; white cells, 12,800/c.mm.), and the sternal marrow aspirate showed a reactive hyperplasia of the red-cell series. Portal hypertension was diagnosed. Liver-function tests were, however, normal and a barium swallow showed no evidence of oesophageal varices. Improvement in the blood picture followed a course of intravenous iron ("ferrivenin") and a satisfactory haemoglobin level was maintained thereafter until June, 1953, when a hypochromic anaemia again developed. In September, 1953, the blood findings were: haemoglobin, 5.8 g./100 ml.; red cells, 3,700,000/c.mm.; white cells, 17,400/c.mm.; platelets, 145,000/c.mm. A blood film showed marked hypochromia, anisocytosis, and microcytosis, and a polymorphonuclear leucocytosis. Blood transfusions were given, and in October a splenectomy was performed at the Otley General Hospital (Mr. D. Chamberlain).

Pathological Examination of Spleen.—It weighed 568 g. and on section had a rather "beefy" appearance. Microscopically, considerable fibrosis was evident with dilatation of sinuses, the appearances being consistent with a diagnosis of portal hypertension.

Post-operative Course

Six days after operation melaena was observed. Blood transfusions were given and blood examination a week later showed: haemoglobin, 10.1 g./100 ml.; white cells, 37,000/c.mm. (polymorphs 83%, lymphocytes 17%, nucleated red cells, 2 per 100 white cells); platelets, 1,140,000/c.mm.; bleeding-time, 7½ minutes. Melaena persisted during the following two months and repeated blood transfusions were necessary. Spontaneous improvement then occurred and the patient was discharged home on December 21. Thereafter he was seen as an out-patient at regular intervals during the succeeding three years, but melaena necessitating admission to hospital for blood transfusions still occurred. Blood examination always revealed a similar picture—namely, hypochromic anaemia, thrombocythaemia (range 880,000 to 2,100,000/c.mm.), and leucocytosis (range 20,000 to 64,000/c.mm.).

In November, 1954, he was admitted to the Leeds General Infirmary and a laparotomy was performed (Mr. G. H. Wooler) on account of recurrent melaena. Thrombosis of the splenic vein, spreading to the portal vein, was observed, and the liver was enlarged and cirrhotic. Gastric varices were ligated and the pyloric region was devascularized. A month later he developed pyloric obstruction and a gastro-enterostomy was carried out. Intermittent bleeding from the bowel, however, continued.

When first seen by me in December, 1956, the patient was anaemic and the liver was enlarged, hard, and irregular. Blood examination showed: blood group A, Rh positive; haemoglobin, 9.6 g./100 ml.; red cells, 3,500,000/c.mm.; colour index, 0.9; reticulocytes, 2%; M.C.V. 87 cubic microns; M.C.H.C., 29%; white cells, 57,600/c.mm. (neutrophils 90%, eosinophils 1%, lymphocytes 9%); platelets, 2,100,000/c.mm. The bleeding-time was five minutes and Hess's capillary resistance test was negative. A blood film revealed three nucleated red cells per 100 white cells and numerous platelets, many of which were abnormal, but no megakaryocytes. Sternal marrow aspirate showed a cellular bone marrow with normal erythropoiesis and granulocytopoiesis. Megakaryocytes were increased in number and many were observed disintegrating into masses of platelets.

Investigation of Blood-clotting Mechanism.—Clotting-time, 10 minutes; one-stage prothrombin time, 17 seconds (control, 15 seconds); clot retraction, normal. Thromboplastin generation was investigated as in Case 1 and was found to be normal when the patient's platelet suspension was mixed with control alumina-adsorbed plasma and control serum. Thromboplastin generation was not impaired when the patient's platelet suspension was diluted 1 in 8. As in Case 1, no defect in blood coagulation could be detected and the platelet factor seemed normal.

Although the possibility that the alimentary bleeding was a direct consequence of portal hypertension had to be considered, the blood picture was characteristic of haemorrhagic thrombocythaemia, and it was decided to treat him accordingly.

Progress and Treatment

He was admitted to the Leeds General Infirmary on February 15, 1957, for treatment with radioactive phosphorus. Blood examination then revealed a hypochromic anaemia: white cells, 56,000/c.mm.; platelets, 2,400,000/c.mm.; and the bleeding-time was raised to 8½ minutes. The faeces were examined daily for the presence of occult blood, and on each occasion a positive result was obtained. On February 22, 3 mC. of ^{32}P was given intravenously. A month later the platelet count had fallen to 410,000/c.mm. and bleeding had ceased. A course of intramuscular iron (imferon) was given, and on April 12 a further blood examination showed: haemoglobin, 13.8 g./100 ml.; red cells, 4,700,000/c.mm.; white cells, 18,000/c.mm.; platelets, 230,000/c.mm.

Thereafter he has been seen as an out-patient at monthly intervals. Examination of the faeces for occult bleeding has been consistently negative and the haemoglobin level normal. In June, the platelet and leucocyte counts rose and a further 3 mC. of ^{32}P was given. The red cells at this time had risen to 8,250,000/c.mm., and although the platelets and leucocytes returned to normal following treatment polycythaemia has persisted. When last seen, nine months after the start of treatment, he was symptom-free and the blood findings were: haemoglobin, 15 g./100 ml.; red cells, 8,400,000/c.mm.; white cells, 9,600/c.mm.; platelets, 265,000/c.mm.

There has been no evidence of bleeding for over eight months, whereas before treatment with ^{32}P melaena and chronic hypochromic anaemia were invariably present.

Discussion

The aetiology of thrombocythaemia and the mechanism of the associated bleeding tendency remain largely unexplained. Two factors concerning the aetiology of thrombocythaemia are, however, worthy of mention. Firstly, it is now generally recognized that the myeloproliferative disorders are closely related (Dameshek, 1951), and, whereas myeloid leukaemia and polycythaemia vera are characterized by a proliferation of myeloid and erythroid tissue respectively, excessive platelet production is the predominant feature in thrombocythaemia. The occurrence of episodes of polycythaemia in cases of thrombocythaemia, the high leucocytosis, and the presence occasionally of a small proportion of immature white cells and nucleated red cells in the peripheral blood support this concept. Similarly the occasional coexistence of haemorrhagic thrombocythaemia with myeloid leukaemia (Brugsch, 1933; Hardisty, and Wolff, 1955), myelofibrosis (Hardisty and Wolff, 1955), and polycythaemia vera (Epstein and Goedel, 1934; Uotila, 1938; Mortensen, 1948) also suggest that it is intimately connected with other proliferative disorders of the bone marrow.

The role of the spleen is a second important consideration. Hardisty and Wolff (1955) found that of 23 patients with haemorrhagic thrombocythaemia, approximately half had the spleen removed previously or the spleen was found to be atrophic. Splenectomy invariably gives rise to a temporary increase in the platelet and leucocyte counts, and on rare occasions haemorrhagic thrombocythaemia appears to follow directly on the removal of the spleen as in Case 2, in which the platelet count rose from a normal pre-operative level to 1,140,000/c.mm. within two weeks of splenectomy, accompanied by an increased bleeding-time and severe haemorrhage from the alimentary tract. The association of atrophy of the spleen with haemorrhagic thrombocythaemia was first observed by Epstein and Goedel (1934). The spleen in their case weighed only 7 g.; they considered it to be the most significant aetiological feature and concluded that the disorder was due to "splenic subfunction." Although in some instances the spleen would appear to be quite normal and in others enlarged, there seems little doubt that in a high proportion of cases of haemorrhagic thrombocythaemia the spleen, or rather its absence, is of direct aetiological significance.

Attempts have been made by several authors to divide thrombocythaemia on an aetiological basis into primary or idiopathic, and secondary types. Rarely it is primary or idiopathic, when it is not associated with any other pathological process and does not follow removal of the spleen. Case 1 appears to belong to this category. More often thrombocythaemia is secondary and follows splenectomy or is associated with splenic atrophy, polycythaemia vera, chronic myeloid leukaemia, or myelofibrosis.

The mechanism of the bleeding tendency in haemorrhagic thrombocythaemia remains unexplained. The bleeding-time in some instances is prolonged, otherwise routine investigations such as the clotting-time, clot retraction, prothrombin time, and capillary resistance are invariably normal. Hardisty and Wolff (1955) were of the opinion that the platelets were functionally abnormal, and in five patients demonstrated an abnormal thromboplastin generation test due to a qualitative deficiency of the platelets. In two of their patients the highly concentrated platelet suspensions yielded normal thromboplastin generation tests, but dilution of the suspension until it contained approximately the same number of platelets per c.mm. as the control suspensions resulted in deficient production of thromboplastin and delay in thromboplastin generation. In the remaining three patients abnormal results were obtained with both concentrated and diluted platelet suspensions. With the use of a similar technique, the thromboplastin generation tests in the two cases reported above were, however, unimpaired both before and after dilution of the patient's platelet suspension, in contrast to the findings of Hardisty and Wolff. In view of these contradictory results further studies on platelet function in thrombocythaemia are obviously indicated.

That the platelets are in some way intimately concerned with the bleeding tendency would seem to be borne out by the effect of treatment with radioactive phosphorus. In previously published papers little reference has been made to the treatment of this disorder, although Mortensen (1948), who regarded thrombocythaemia as allied to polycythaemia and leukaemia and therefore possibly amenable to radiotherapy, observed some beneficial effects of total-body irradiation. It was on similar grounds that treatment with ^{32}P was given a trial in the two cases described. The response in both instances was highly satisfactory and bleeding ceased as the platelet count returned to normal. Further injections of 3 mC. of ^{32}P were given when the platelet count again rose above normal, and on this regime both patients have continued in good health and free from bleeding episodes for nine and eight months respectively. In addition to lowering the platelet count ^{32}P also resulted in a fall of the leucocyte count to normal, and in Case 2 control of the haemorrhagic tendency was followed by a rise in the red-cell count to a polycythaemic level, which was further evidence of the close association of thrombocythaemia and other myeloproliferative disorders.

Summary

The clinical and haematological features of haemorrhagic thrombocythaemia are described and two further examples reported.

Haemorrhagic thrombocythaemia is usually associated with other myeloproliferative disorders or splenic atrophy. It may follow splenectomy but is rarely primary in that it is unassociated with other pathological processes. Case 1 belongs to the latter category, while Case 2 followed splenectomy.

The mechanism of the bleeding tendency is unknown. The bleeding-time is occasionally prolonged, but other

routine tests of haemostatic function are invariably normal. No deficiency of platelet factor as evidenced by the normal thromboplastin generation tests was detected in either of the above patients.

In both patients the platelet count returned to normal and bleeding ceased after treatment with radioactive phosphorus.

I thank Professor J. C. Goligher, Dr. R. N. Tattersall, and Mr. G. H. Wooler for permission to study patients under their care, and Dr. W. Goldie for investigation of the coagulation factors.

REFERENCES

Biggs, R., and Douglas, A. S. (1953). *J. clin. Path.*, **6**, 23.
Brugsch, H. (1933). *Folia haemat. (Lpz.)*, **49**, 454.
Dameshek, W. (1951). *Blood*, **6**, 372.
Epstein, E., and Goedel, A. (1934). *Virchows Arch. path. Anat.*, **292**, 233.
Fanger, H., Cella, L. J., and Litchman, H. (1954). *New Engl. J. Med.*, **250**, 456.
Hardisty, R. M., and Wolff, H. H. (1955). *Brit. J. Haemat.*, **1**, 390.
Mortensen, O. (1948). *Acta med. scand.*, **129**, 547.
Uotila, U. (1938). Ibid., **95**, 136.

CUSHING'S SYNDROME IN CHILDHOOD

REPORT OF CASE OF ADRENOCORTICAL CARCINOMA WITH EXCESSIVE ALDOSTERONE PRODUCTION

BY

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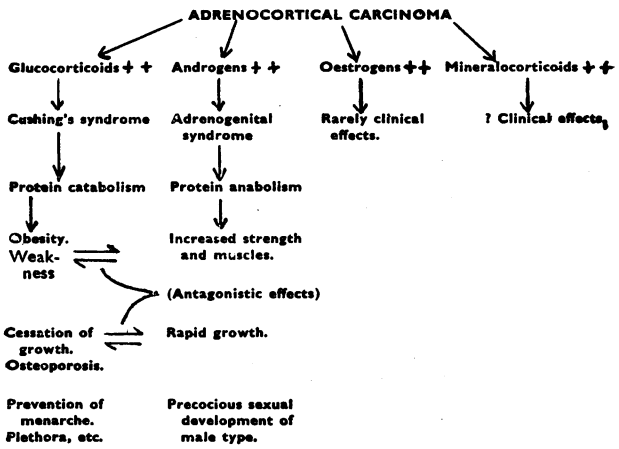
Adrenocortical overactivity in childhood may produce two distinct syndromes. The adrenogenital syndrome is caused by excessive production of androgens, and may manifest itself in three ways. If it starts in intrauterine life in a female, pseudohermaphroditism results; postnatally in a girl it produces virilism; in a boy the "pocket Hercules" variety of isosexual precocity results. An excess of glucocorticoids, on the other hand, gives rise to Cushing's syndrome, without masculinization.

Almost all cases of Cushing's syndrome in childhood are caused by adrenocortical carcinoma. Wilkins (1948) collected 70 cases of cortical carcinoma from the literature, and in his book (Wilkins, 1950) he reviewed 26 cases of Cushing's syndrome, all under the age of 10 years. Twenty-two of these were in girls; as in the adult, Cushing's syndrome in childhood is more common in females. A few other cases have been reported since then, and Guin and Gilbert (1956) produced a further review. The two cases of Cushing's syndrome not associated with carcinoma were reported by Chute *et al.* (1949) (bilateral nodular hyperplasia) and Powell *et al.* (1955) (bilateral cortical adenomas).

Functioning adenomas of the adrenal cortex at any age produce either pure Cushing's syndrome or a pure adrenogenital syndrome. Overproduction of the other two groups of adrenocortical hormones, the oestrogens and mineralocorticoids, appears to be of little importance in childhood. Oestrogen excess, leading to precocious pubertal development of female type, is extremely rare, while primary aldosteronism has not, to our knowledge, been described in childhood.

Unlike adrenal adenomas, carcinomas are biochemically pluripotent and produce excessive quantities of androgens, glucocorticoids, and also oestrogens (where these have been measured). In the case described below aldosterone was also found in great quantities in the urine. Consequently it is logical that the clinical picture may also be a mixed one in cases of carcinoma, being composed of features of Cushing's and the adrenogenital syndrome:



Since virtually all cases of Cushing's syndrome in childhood are caused by carcinoma one may expect to find evidence of the adrenogenital syndrome in all of them. On the other hand, only some adrenogenital cases (those with carcinoma) will show features of Cushing's syndrome. Now, in some ways the androgens and the glucocorticoids are mutually antagonistic, so that the resultant syndrome of excess of both may be variable. Thus androgens promote rapid skeletal growth and maturation, whereas cortisol (the chief glucocorticoid) abruptly terminates these. Androgens increase muscle bulk and power; cortisol diminishes these, producing fat from muscle and so increasing weakness. Cortisol actually opposes anabolism, leading to porosis of bone and gluconeogenesis with raising of blood sugar. Androgens tend to counteract these by promoting protein anabolism. In the case presented below the two opposing forces seemed so well titrated against each other that bone and tooth age and density, muscular configuration and power, and blood-sugar level did not appear to depart from the normal.

Case Report

A coloured girl was admitted to Groote Schuur Hospital at the age of 2½ years. Since the age of 1 year there had been an abnormally rapid gain in weight. At this age pubic and axillary hair first appeared. Three weeks before admission a facial eruption was noticed. There was no history of menstruation.

Physical examination revealed an obese child, with a Cushing-like facies and signs of virilism (Fig. 1). The obesity included limbs as well as trunk. Her height was 31½ in. (80 cm.) and weight 39 lb. (17.7 kg.). She had a plethoric appearance and a well-marked "buffalo-neck." There was an eruption on the face, which resembled adenoma sebaceum. Axillary and pubic hair were present and the clitoris was enlarged. Strong body odour was obvious. There was no true breast development. Her B.P. was 130/90; Hb, 15 g./100 ml.; P.C.V., 45%. The specific gravity of the urine was 1015. E.C.G. was normal. Blood chemistry: serum Na,