or to persisting activity by retained particles in the lung), and how far is progressive fibrosis no more than progressive healing? How far does the perpetuating fibrosis depend on secondary factors and no longer on the initiating agents—for example, intravascular coagulation or various types of autoallergy—and what is the nature of the variation of host responsiveness that allows one patient to be affected so much more severely than another?

When we know the answers to these we will be in a stronger position to develop new and safer forms of early and effective control.

References

- ¹ Hamman, L., and Rich, A. R., *Bulletin of the Johns Hopkins Hospital*, 1944, 74, 177.
- ² Ellman, P., and Ball, R. E., *British Medical Journal*, 1958, 11, 816.
- ³ Scadding, J. G., *British Medical Journal*, 1964, 2, 686.
- ⁴ Scadding, J. G., *British Medical Journal*, 1960, 1, 443.
- ⁵ Spector, W. G., and Willoughby, D. A., *Journal of Pathology and Bacteriology*, 1968, 96, 389.
- ⁶ Spector, W. G., *Proceedings of the Royal Society of Medicine*, 1971, 64, 941.
- ⁷ Boros, D. L., and Warren, K. F., *Immunology*, 1973, 24, 511.
- ⁸ Turk, J. L., *Proceedings of the Royal Society of Medicine*, 1971, 64, 942.
- ⁹ Jones, Williams, *Hospital Medicine*, 1967, 2, 21.
- ¹⁰ Greenwood, R., Smellie, H., Barr, M., and Cunliffe, A. C., *British Medical Journal*, 1958, 1, 1388.
- ¹¹ Papamichail, M., Holborow, E. J., Keith, H. J., Currey, H. L. F., *Lancet*, 1972, 2, 65.
- ¹² Bronsky, D., and Dunn, Y. O. L., *American Journal of Medical Science*, 1966, 250, 11.
- ¹³ Pepys, J., *Hypersensitivity Diseases of the Lungs due to Fungi and Organic Dusts*, Monographs in Allergy, ed. S. Karger. Basle, 1969.

- ¹⁴ Forjacs, P., *British Journal of Diseases of the Chest*, 1969, 63, 1.
- ¹⁵ Allison, A. C., Harrington, J. S., and Birbeck, M., *Journal of Experimental Medicine*, 1966, 124, 14.
- ¹⁶ Bruch, J., Report of Vth International Conference on Pneumoconiosis Research, ed. H. Reploh, and H. J. Einbrodt. Munster, 1967.
- ¹⁷ Heppleston, A. G., and Styles, J. A., *Nature*, 1967, 214, 521.
- ¹⁸ Heppleston, A. G., *British Medical Bulletin*, 1969, 25, 282.
- ¹⁹ Muir, D. C. F., *Clinical Aspects of Inhaled Particles*. London, Heinemann, 1972.
- ²⁰ Einbrodt, H. J., *Annals of Occupational Hygiene*, 1967, 10, 47.
- ²¹ Bell, D., and Elmes, P. C., *Proceedings of the Second International Congress on the Biological Effects of Asbestos*, Dresden, 1968.
- ²² Beattie, J., and Knox, J. F., in *Inhaled Particles and Vapours*, ed. C. N. Davies, p. 419. London, Pergamon, 1961.
- ²³ Pernis, B., in *Textbook of Immunopathology*, ed. P. A. Miescher, and H. Muller-Eberhard, p. 293. New York, Grune and Stratton, 1968.
- ²⁴ Burrell, R. G., Wallace, J. P., and Andrews, C. E., *American Review of Respiratory Diseases*, 1964, 89, 697.
- ²⁵ Burrell, R., and Cate, C. C., *Clinical and Experimental Immunology*, 1971, 9, 809.
- ²⁶ Beck, E. G., Holt, P. F., and Nasrallah, E. T., *British Journal of Industrial Medicine*, 1971, 28, 179.
- ²⁷ Soutar, C., Simon, G., and Turner-Warwick, Margaret, *British Journal of Diseases of the Chest*, in press.
- ²⁸ Lyons, J. P., Clark, W. G., Hall, A. M., and Cotes, J. E., *British Medical Journal*, 1967, 4, 772.
- ²⁹ Becklake, M. R., Fournier Masey, G., Rossiter, G. E., and McDonald, J. C., *Archives of Environmental Health*, 1972, 24, 401.
- ³⁰ Caplan, A., *Thorax*, 1953, 8, 29.
- ³¹ Wagner, J. C., and McCormick, J. N., *Journal of the Royal College of Physicians*, 1967, 2, 49.
- ³² Vigliani, E. C., and Pernis, B., *British Journal of Industrial Medicine*, 1958, 15, 8.
- ³³ Turner-Warwick, Margaret, and Haslam, P., *Clinical Allergy*, 1971, 1, 83.
- ³⁴ Pernis, B., Vigliani, E. C., and Selikoff, I. J., *Annals of New York Academy of Science*, 1965, 132, 112.
- ³⁵ Turner-Warwick, Margaret, and Parkes, R., *British Medical Journal*, 1970, 3, 492.
- ³⁶ Soutar, C., Parkes, R. W., and Turner-Warwick, Margaret, in preparation.
- ³⁷ Turner-Warwick, Margaret, and Weill, H., in preparation.
- ³⁸ Hughes, P., and Rowell, N. R., *Journal of Pathology*, 1971, 107, 141.

Today's Treatment

Blood and Neoplastic Diseases

Other Purpuras

P. BARKHAN

British Medical Journal, 1974, 2, 376-378

The second main group of causes of thrombocytopenia is that due to increased platelet destruction.^{1,2}

Autoimmune Thrombocytopenia

The idiopathic variety of autoimmune thrombocytopenia (I.T.P.) may present acutely with widespread purpura and frank bleeding—epistaxis, haematuria, menorrhagia, and gastrointestinal bleeding—or it may be chronic with minimal purpura but with troublesome epistaxes or menorrhagia.

ACUTE I.T.P.

Acute I.T.P. is often self-limiting but corticosteroids may hasten recovery and a short course of prednisolone, 0.75 mg/kg for a week, is worth using. The daily dosage should then be reduced gradually by 2.5 mg weekly. A more rapid reduction may be followed by relapse. If much blood has been lost, appropriate amounts of whole blood, preferably fresh, will need to be given but platelet transfusions are not usually used unless bleeding is life-threatening.

In children, I.T.P. may occur several weeks after one of the acute infectious fevers, such as chickenpox, measles, or rubella, or occasionally after glandular fever or cytomegalovirus infections, and then usually resolves spontaneously in three to six weeks. Clinical improvement often precedes a rise in the platelet count.

CHRONIC I.T.P.

Chronic I.T.P. usually arises insidiously, but occasionally it is a sequel of acute I.T.P. Patients with platelet counts above

Guy's Hospital, London S.E.1

P. BARKHAN, M.D., F.R.C.PATH., Consultant Haematologist

30,000/ μ l usually do not have troublesome bleeding or extensive purpura. Those with lower counts, usually below 20,000/ μ l, may have widespread purpura, epistaxes, haematuria, or menorrhagia—though some patients, despite severe thrombocytopenia, have little or no purpura and no bleeding.

Patients with extensive purpura and bleeding who have lost a lot of blood will need to be transfused with whole blood. Platelet transfusions are not usually used. They should also be given prednisolone, 0.75 mg/kg daily, for up to three weeks. This will often be clinically effective, even if the platelet count shows little or no rise, or it may be followed by an appreciable rise in the platelet count, sometimes to normal. Whether the platelet count rises or not, the dose of prednisolone should be reduced after three weeks, cutting the daily dose by 2.5 mg every week. If the bleeding and purpura are controlled, the prednisolone should be finally stopped. Some patients may need a maintenance dose to prevent recurrence of severe purpura but this should be as low as possible, preferably not above 10 mg daily in adults and proportionally less in children. Menorrhagia can be controlled with progesterone therapy.

The guide to prednisolone treatment should be the clinical state of the patient and not just the platelet count. Patients with low platelet counts and without troublesome bleeding do not require treatment. The most serious bleeding is intracranial, but this is rare, particularly if there is little or no purpura. The dangers of long-term corticosteroid therapy outweigh this risk. If a maintenance dose of prednisolone exceeding 10 mg/day in adults is needed then splenectomy should be considered (see below), provided the patient's general clinical state permits it.

For repeated epistaxes, especially if unilateral, the nose should be examined for bleeding points which can be cauterized. The management of menorrhagia and of tooth extraction is similar to that described for aplastic anaemia in last week's *B.M.J.* (p. 324).

Splenectomy

Splenectomy is reserved for those patients who do not respond clinically to a three-week course of high dosage prednisolone as described above, or for those whose bleeding becomes worse during this period or who require a relatively high maintenance dose of prednisolone to control their bleeding. Splenectomy should be avoided, if possible, in children below 4 years of age because of the later risk of fulminating septicaemia. About two-thirds of patients with I.T.P. respond completely to splenectomy. In most of the remainder haemostasis will be improved, even if the platelet count does not become normal or falls after reaching a normal level. Haemostasis usually improves quickly after ligation of the splenic pedicle and platelet transfusions are not usually necessary. For those patients who are on or will have been on corticosteroids an appropriate increase in dosage will be needed to cover the surgical period. Spleen scanning after infusing ^{51}Cr -labelled platelets is not useful for selecting patients for splenectomy. A failure to respond to corticosteroids does not preclude a successful response to splenectomy.

Immunosuppressive drugs such as azathioprine, cyclophosphamide, actinomycin D, or vinblastine have been used with variable success in patients with chronic I.T.P. or systemic lupus who do not respond at all to splenectomy or who are unfit for surgery.

NEONATAL THROMBOCYTOPENIA

Neonatal thrombocytopenia may occur in infants born to mothers with chronic I.T.P. or systemic lupus erythematosus, owing to transplacental passage of platelet antibodies from the

mother. The infant may develop much bruising, particularly around the head, as a result of the inevitable trauma associated with birth, and there is also an increased risk of bleeding from the umbilical stump and, more seriously, of intracranial haemorrhage. Nevertheless, there is often remarkably little purpura, the baby remaining well despite a low platelet count, and no specific treatment is required. For those with extensive purpura, a platelet concentrate from 2 units of blood should be given. The thrombocytopenia in these cases is self-limiting, the platelet count becoming normal in about three to six weeks. Very occasionally, neonatal thrombocytopenia results from platelet incompatibility between mother and baby, the mother forming platelet antibodies directed specifically against the baby's platelets, analogous to haemolytic disease of the newborn. This condition is self-limiting and usually does not require active treatment.

Drug-induced Thrombocytopenia

Selective thrombocytopenia can be produced by almost any drug in therapeutic amounts in immunologically susceptible people,³ though it tends to be more common with some drugs—for example, quinidine and the thiazides. A careful drug history is of crucial importance in patients who present with unexplained thrombocytopenia in the absence of other haematological abnormalities or other evidence of underlying disease. Recovery is usually relatively rapid after the removal of the offending drug, the platelet count returning to normal in one to two weeks. Failure of the platelet count to rise within two weeks after stopping a particular drug makes it unlikely that that drug caused the thrombocytopenia. Patients with severe bleeding will need whole blood transfusions, supplemented if bleeding is not controlled by the platelet concentrate from 6-12 units of blood. Prolonged thrombocytopenia after gold injections may persist for weeks after stopping therapy and in them the use of dimercaprol (BAL) has appeared to promote recovery.⁴

Thrombocytopenia and Splenomegaly (Hypersplenism)

Thrombocytopenia due to splenic pooling of platelets¹ may occur in patients with a greatly enlarged spleen, whatever the cause—for example, portal hypertension, chronic leukaemias, lymphomas and chronic infections such as malaria, bilharzia, and leishmaniasis. If the spleen does not shrink after appropriate treatment of the underlying disease and the platelet count remains low with troublesome purpura and bleeding then splenectomy will often be beneficial provided the bone marrow has been shown to contain normal numbers of megakaryocytes.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation^{2,5} may lead to haemostatic failure from severe thrombocytopenia and deficiency of coagulation factors. Apart from recognition and treatment of the precipitating factors, such as abruptio placentae, major surgery, liver failure, septicaemias, malignant disease, thrombotic thrombocytopenia purpura, haemolytic-uraemic syndrome, and the bites of venomous snakes and insects, it may be necessary initially to suppress coagulation with heparin and to correct the haemostatic deficiencies with transfusions of whole blood, plasma, and platelets and with concentrates of fibrinogen, prothrombin, or factor VIII.

Cardiopulmonary Bypass Surgery

Thrombocytopenia is a constant accompaniment of cardiopulmonary bypass surgery, the platelet count often falling to

30,000-40,000/ μ l. In most patients the thrombocytopenia persists for two to three days after operation and then rises spontaneously, platelet transfusions rarely being necessary. Transfusions of whole fresh blood and platelets are indicated when severe and persistent postoperative haemorrhage is associated with a platelet count below 30,000/ μ l.

Post-transfusion Purpura

Rarely, thrombocytopenic purpura occurs about a week after an ABO-compatible blood transfusion,¹ owing presumably to the stimulation by the transfused platelets of platelet auto-antibody production. The donor and the recipient's platelets are presumed to be antigenically different but the way in which platelet antibodies are produced remains to be explained. The condition is self-limiting and further transfusions containing platelets should not be given. If blood transfusion is required then washed red cells should be used.

Hereditary Thrombocytopenias

Hereditary thrombocytopenias⁶ are rare. For severe bleeding episodes fresh whole blood and platelet transfusions are helpful. Corticosteroids do not seem to be useful. Apart from some forms of the Wiskott-Aldrich syndrome, splenectomy is not of much value.

Non-thrombocytopenic Purpuras

Non-thrombocytopenic purpuras are common and include a heterogeneous group in which there is a defect of platelet function,⁷ either inherited or, much more commonly, acquired. There is a large group of vascular purpuras, including anaphylactoid purpuras, which are dealt with elsewhere.⁸

THROMBASTHENIA

Thrombasthenia is the best known of the inherited functional platelet disorders. Severe bleeding responds to transfusions of

fresh whole blood and platelets. For surgery, a large platelet transfusion (the concentrate from 8-12 units of blood in adults, and appropriately less in children) given immediately pre-operatively with 5 g of epsilon-amino caproic acid (EACA) and followed by further daily doses of 5 g thrice daily, orally or intravenously for 10 days, helps to promote satisfactory haemostasis. For dental extractions, careful packing of the socket with adsorbable material and 5 g EACA daily for five days is recommended.

ACQUIRED FUNCTIONAL PLATELET DISORDERS

Acquired functional platelet disorders occur in myeloproliferative disorders, particularly thrombocythaemia and polycythaemia—which are dealt with elsewhere in this series.

Drugs such as aspirin, phenylbutazone, or antihistaminics may affect platelet function and thus cause purpura. Withdrawal of drugs of this kind may be helpful in a patient with otherwise unexplained purpura.

Platelets are exceptionally rich in ascorbic acid,⁹ severe deficiency of which, as in scurvy, may cause purpura which responds to oral doses of 500 mg ascorbic acid daily for two weeks, and, in the long term, to a generally nutritious diet and attention to socio-economic circumstances.

The treatment of von Willebrand's disease, in which there is defective platelet function, is dealt with in the article on haemophilia and related disorders.

References

- ¹ Aster, R. H., in *Haematology*. 1st. ed., p. 1131, ed. by W. J. Williams *et al.* London, McGraw-Hill, 1972.
- ² Hardisty, R. M., and Ingram, G. I. C., *Bleeding Disorders. Investigation and Management*. Oxford, Blackwell, 1965.
- ³ Miescher, P. A., *Seminars in Haematology*, 1973, 10, 311.
- ⁴ England, J. M., and Smith, D. S., *British Medical Journal*, 1972, 2, 748.
- ⁵ Rapoport, S. I., in *Haematology*. 1st ed., p. 1234, ed. by W. J. Williams *et al.* London, McGraw-Hill, 1972.
- ⁶ Murphy, S., *Clinics in Haematology*, 1972, 1, 359.
- ⁷ Weiss, H. J., in *Haematology*. 1st. ed., p. 1166, ed. by W. J. Williams *et al.* London, McGraw-Hill, 1972.
- ⁸ Gottlieb, A. J., in *Haematology*, 1st. ed., p. 1176, ed. by W. J. Williams *et al.* London, McGraw-Hill, 1972.
- ⁹ Barkhan, P., and Howard, A. N., *Biochemical Journal*, 1958, 70, 163.

Any Questions?

We publish below a selection of questions and answers of general interest

Ventral Hernia after Laparotomy

What is the incidence of ventral hernia after laparotomy done through a paramedian incision? Why does it occur and what is the chance of a successful result with further surgery to repair such a hernia?

In Akman's large series¹ 22% of incisional herniae occurred after right lower paramedian incisions and 9.6% after right upper paramedian. Numbers on the left were so small as to be included in the "miscellaneous" group. Obney's earlier paper² from the same centre confirms the difference between right and left sides, and between lower and upper abdomen—in part at least a reflection of the fact that the three procedures most commonly resulting in incisional hernia are, in order of frequency, appendicectomy, pelvic operations such as hysterectomy, and cholecystectomy, while the incidence after gastric surgery is very low. The principal cause of in-

cisional herniation is a postoperative increase in intra-abdominal pressure (from coughing, retching, gastric or intestinal distension, or excessive weight gain) acting upon a wound weakened by infection or drainage, poor suturing technique, or, rarely, poor healing as in malignant disease. Infection is the most significant predisposing factor in all series for all incisions. Obesity, though common,^{1,2} may not be a cause.³ Paramedian incisions, even when damage to the laterally-entering motor nerves to the rectus muscle is carefully avoided, divide all musculo-aponeurotic layers of the abdominal wall, except the rectus muscle itself, almost perpendicular to the direction of their fibres and their lines of action. Hence the forces exerted on such a wound tend to disrupt it, and several authors, especially Kozoll,⁴ advocate the more frequent use of transverse incisions in abdominal surgery. The magnitude of the disrupting force is sufficient to break 34-gauge steel sutures,¹ and the force required to appose the aponeurotic edges in a ventral hernia are at least