prognosis is considered to be good. Many, notwithstanding their burden of mental tension, can be kept usefully employed by supportive out-patient treatment with short periods in hospital during exacerbations. For some, however, their distress becomes so overwhelming and their functional efficiency so seriously impaired that they are obliged to remain at home or in hospital in a state of invalidism.

The patient described here became incapacitated in this way, and leucotomy afforded a striking and continued relief of symptoms. The general change in personality similar to that which has been described by others (Hoch, 1949) has not materially interfered with her social rehabilitation.

Summary

A case is described in which persistent anxiety, tachycardia and raised basal metabolic rate unresponsive to other methods of treatment were successfully treated by bilateral prefrontal leucotomy.

A year has passed without relapse.

The general change in personality has been compatible with excellent social rehabilitation.

The case demonstrates some problems in diagnosis and treatment.

This work was done at the Bristol Mental Hospitals, and I am obliged to Dr. R. E. Hemphill for affording me facilities to study this case. I am particularly indebted to Dr. Max Reiss for assessing thyroid activity with radioactive iodine, to Dr. E. C. Turton for estimating the basal metabolic rates, and to Dr. K. R. L. Hall for carrying out special psychological tests.

REFERENCES

- Hoch, P. H. (1949). *Proc. roy. Soc. Med.*, Supplement 42, 23.
Murray, I. (1950). *British Medical Journal*, 2, 80.

CONGENITAL AFIBRINOGENAEMIA

BY

C. C. DE SILVA, M.D., M.R.C.P.

Professor of Paediatrics, University of Ceylon

AND

R. S. THANABALASUNDARAM, M.B., B.S.

Research Assistant, Department of Medicine, University of Ceylon

Bleeding, either spontaneous or due to trauma, may occur in a variety of conditions. One of these is due to a defect in the mechanism of blood-clotting. Hypotheses regarding the mechanisms involved in blood-clotting have changed during the last few years, but one concept that has not altered is the conversion of fibrinogen to fibrin by the enzyme thrombin. The following is a report of a case of congenital afibrinogenaemia.

Case Report

The patient was a male infant aged 11 months. His father was British and his mother of Eurasian extraction. The child was admitted on June 18, 1950, as an emergency for bleeding from the mouth. A lump had appeared on the right side of his face two weeks earlier and, as this would not resolve, the mother consulted her family doctor, who aspirated it from the inner aspect of the cheek. The bleeding continued for 12 hours, ceased after "an injection," but recurred. All attempts to arrest it failed, and the child was admitted to the Lady Ridgeway Hospital. In spite of treatment the bleeding continued for 24 hours after admission

and then ceased. The mother noticed small "blue" areas on various parts of the body—the right popliteal fossa and the left side of the chest—and she also stated that there was a tendency for three or four of these blue areas (each about the size of a halfpenny) to appear, especially on the chest and arms, whenever the child cut a tooth. With the eruption of the tooth the purpuric patches disappeared.

The child was full-term, the delivery was normal, and his birth weight was 5½ lb. (2.5 kg.). Umbilical haemorrhage began on the third day after birth and continued for seven days. This was quite copious and ceased after the local application of tincture of ferric chloride. When the child was 2 months old he had an attack of macroscopic haematuria for one night.

As the father had left Ceylon his family history is not available. There is no consanguinity of parents. One elder sibling, aged 4 years, gave no history of bleeding or any other illness.

The child was breast-fed for four months; a proprietary milk food was given for the next seven months. Orange juice in adequate quantities had been given from the age of 4 months. From the age of 7 months proprietary milk and cereal foods, calcium, and "abidec" drops had been administered. The infant could roll over at six months, but did not sit up at all.

On examination the child was extremely pale, with an icteric tinge of the skin; the tongue and lips were light pink in colour. A lymphangioma about the size of a lemon was present below the right lower jaw. There were a few localized areas of blue colour each about the size of a halfpenny over the left side of the chest, the right popliteal fossa, and the right tibial region. The small patch on the chest disappeared after a few days.

The child had an intermittent fever ranging from 100 to 102° F. (37.8 to 38.9° C.). He was given penicillin, 100,000 units three times a day for four days.

A blood count on June 24 showed: haemoglobin (5.4 g. Sahli), 31.7%; red cells, 1,820,000 per c.mm.; white cells, 7,800 per c.mm. (P. 42%, L. 58%); size of red cells, 7.8 µ (Pijper's halometer); bleeding time, 2½ minutes; clotting time, over 72 hours. On July 3 the marrow count showed: promyelocytes, 5%; myelocytes, 34%; metamyelocytes, 6%; polymorphs, 13%; eosinophil myelocytes, 3%; lymphocytes, 1%; megakaryocytes, 1%; normoblasts, 33%; proerythroblasts, 4%.

On July 6 a blood count showed: red cells, 1,820,000 per c.mm.; platelets, 60,000 per c.mm.; white cells, 25,400 per c.mm. (P. 27%, L. 73%, E. 0%); reticulocytes, 3%; haemoglobin, 35% (Dare's 5.6 g. %); colour index 0.96; bleeding time, 6½ minutes; clotting time, over 48 hours. Blood picture: anisocytosis, poikilocytosis, pessary forms, and polychromasia. Prothrombin time, over 24 hours (Quick's test, modified by Fullerton, 1940). (Control, 26 seconds.) Plasma proteins: albumin 3.48 g. %, globulin 2.22 g. %, fibrinogen nil—total 5.7 g. Tests for fibrinogen: (1) heating plasma at 60° C., no clot formation; (2) half saturation of plasma with NaCl, no precipitate. On the addition of "stypven" (Russell viper venom) no clot occurred even after 48 hours. The addition of 1 ml. of the child's blood to 0.5 ml. of normal blood resulted in clotting, suggesting that there was no antithrombic substance in the child's blood.

On July 7 the maternal grandmother's fibrinogen was 0.28 g. per 100 ml. and the mother's 0.21 g. per 100 ml. On July 10 the E.S.R. (micro-method) of the patient was 4 mm. at the end of one hour.

On July 8 the child was given a blood transfusion of 180 ml. of whole blood. There was a severe reaction, the temperature rising to 107° F. (41.7° C.), and the transfusion was stopped. Owing to technical difficulties the transfusion was given into the internal saphenous vein after exposure. The superficial wound was sutured and the vein clamped at two points and ligated. Oozing continued from the margins of the incision, and the application of adrenaline

swabs did not arrest the haemorrhage. The wound was closed with three mattress sutures. Menaphthone ("kapilon") (vitamin K), 1 ml., was given intramuscularly. Slight oozing continued for two days after the transfusion and ceased spontaneously four days later. Oozing started again after two days; it continued for eight days, but ceased 48 hours before death, on July 24—that is, 16 days after the transfusion.

On July 20 stypven was applied locally. On the 21st sterile gauze was soaked with 5 ml. of adult blood and applied to the wound. This was repeated on the 22nd and apparently controlled the bleeding, but the child was very restless and started vomiting. On July 22, 23, and 24 10 ml. of the mother's blood was injected intramuscularly each day. The child showed signs of dehydration on July 24, and 1 pint (570 ml.) of Ringer's solution with 5% glucose was given intraperitoneally. He was very dyspnoeic and was placed in an oxygen tent but died the same day. Permission for a necropsy was refused.

Discussion

Lack of fibrinogen may be either congenital or acquired. The acquired form may be transient and may be hypofibrinogenemia or afibrinogenemia. The cases reported by Moloney *et al.* (1949) and by Glanzmann *et al.* (1940) belong to the second category.

The congenital form of the disease is subdivided into two types: hypofibrinogenemia and afibrinogenemia. The latter has been reported in 10 cases (Rabe and Salomon, 1920; Breckoff, 1924; Opitz and Frei, 1921; Macfarlane, 1938; Schönholzer, 1939, two cases; Glanzmann *et al.*, 1940; Castex *et al.*, 1943; Henderson *et al.*, 1945; Corbett, 1947). It is an exceedingly rare condition and the period of survival is definitely shortened, though one patient was aged 22 at the time of the last report. Ours is the eleventh case and the first with any Oriental blood. All the reported cases, including our own, showed a haemorrhagic tendency throughout their lives. Five of these patients, so far as we have been able to ascertain, died during infancy or childhood. Like our own, the others have died of bleeding, which could not be arrested, from minor cuts, cerebral haemorrhage, and an infected haematoma. Two siblings of two separate cases died of umbilical haemorrhage in early infancy. Their fibrinogen had not been estimated, because a deficiency had not been suspected. Rabe and Salomon's original case lived to the age of 22 years.

In three instances the parents were first cousins. In our own case there was not only no consanguinity but the parents belonged to different countries, though the mother was partly of European extraction. Nine of the eleven cases were males; but the number is too small to be of any significance. Most of the writers do not mention the racial origin of their patients. Five of the eleven cases were in Germans, one was probably in a German Swiss, two were of British stock, one was South American, and one was Australian. They were all of pure white stock.

The bleeding time was definitely prolonged in all cases except two (Glanzmann *et al.*, 1940; Henderson *et al.*, 1945). In our case it was $6\frac{1}{2}$ minutes on one occasion. The platelets were normal except in two cases in which they ranged from 50,000 to 425,000 per c.mm. In our case it was 60,000 per c.mm. Unfortunately the count could not be repeated. The E.S.R. was low in every case in which it was investigated. This is to be expected, as the sedimentation rate is found to depend on the fibrinogen content. In our

case it was 4 mm. in one hour by the micro-method. This method is not accurate, but owing to the difficulties of obtaining samples of venous blood a more reliable method could not be used.

The blood is completely incoagulable. In our case no clot was formed on two separate occasions even after 48 and 72 hours.

In the capillary resistance test the positive pressure method (Hess) was used. No petechiae were seen. This agrees with the other reports. No negative pressure method (Scarborough, 1941) was employed.

The prothrombin time (Quick) was over 24 hours. The same result was obtained in the case of Henderson *et al.* (1945). This is to be expected, as the ultimate substance necessary for clot formation—that is, fibrinogen—is absent here.

Special Tests for Fibrinogen

Fibrinogen is coagulated by heating plasma to 58° C. No clot occurred in our case even at 60° C. This absence has been confirmed by (1) total absence of fibrinogen in the estimation of plasma proteins; and (2) no precipitate formed on half saturation of plasma with NaCl. That this non-coagulability was not due to the absence of thrombokinase was proved by adding Russell viper venom to the patient's blood. There was no clot formation. Lastly, we had to prove that this absence of clotting was not due to the presence of some antithrombic substance. We did this by adding 0.5 ml. of normal adult blood to 1 ml. of the patient's blood. A clot formed in a few minutes. All these facts prove that this was a case of afibrinogenemia and that the absence of clotting was due to the lack of fibrinogen.

Fibrinogen is found in normal blood plasma to the extent of 0.2 to 0.4 g. per 100 ml. Chemically it is a globulin. The main site of formation of this has been proved to be the liver (Drury and McMaster, 1928; Jones and Smith, 1930). They found that in hepatectomized rabbits, after replacement of circulating blood with defibrinated blood, no fibrinogen was formed, in contrast to controls, which showed 90% regeneration in six hours, the liver being the only site of formation. This readily explains the hypofibrinogenemia in liver diseases. Fibrinogen is also absent in certain toxic states like scarlet fever: this is probably due to a fibrinolysin. Doan (1949) states that there is in plasma a substance called plasminogen which gives rise to plasmin. Plasmin is a synonym for proteolytic enzyme activity or fibrinolysin. Fibrinolysin is concerned with the dissolution of fibrin and the destruction of fibrinogen. In certain states, such as scarlet fever, the conversion of plasminogen to plasmin may be increased, thereby preventing the clotting of blood. In the albumin fraction of the plasma there is an inhibiting enzyme, antiplasmin (Macfarlane and Biggs, 1948). Thus the presence of antiplasmin explains the less frequent occurrence of hypofibrinogenopenic states. If there is more plasmin than antiplasmin fibrinolysis would be increased.

Whether the bone marrow and the reticulo-endothelial system have any part in the formation of fibrinogen is doubtful, as shown in the experiments of Drury and McMaster. It is probable that in those states with bone marrow defect or infiltration some substance-like plasmin may have been produced, as in the production of heparin in similar states by cytotoxic drugs—for example, nitrogen mustard and irradiation

(Allen *et al.*, 1949). This is speculative. The thrombocytopenia present in these afibrinogenopenic states may be secondary and due to the excessive demand on platelets at the bleeding sites.

Macfarlane has shown the critical level of fibrinogen to be 0.06 g. per 100 ml., below which blood clotting is inhibited. In our case none of the above-mentioned factors could account for the lowering of the fibrinogen level. The plasma proteins show a normal albumin-globulin level and the A./G. ratio is 1.5:1. Clinically there was no evidence of any liver dysfunction, nor could the afibrinogenopenia be attributed to a toxic state. The condition here seems to have been due to some inborn defect of metabolism.

Fresh blood or plasma transfusions may be effective. Fraction I of Cohn (antihaemophilic globulin) contains the fibrinogen portion of plasma, and Diamond (quoted by Down, 1949) has reported its successful use in one of his patients, as a prophylactic to be given every third day. In our case no beneficial effect was shown by the blood transfusion.

Summary

A case of congenital afibrinogenemia is reported in an infant of 11 months of mixed European and Asian parentage.

Ten other cases collected from the literature are also reviewed.

The principal features in this case are the total absence of fibrinogen in the blood, the history of recurrent haemorrhages beginning three days after birth, the complete non-coagulability of the blood, the increased bleeding time, the thrombocytopenia, and the low erythrocyte sedimentation rate.

Death occurred from a severe haemorrhage due to a minor surgical wound inflicted for the purpose of giving a blood transfusion.

An intramuscular injection of maternal blood was of little avail in arresting the bleeding.

The aetiology of the hypofibrinogenopenic states is discussed.

Our thanks and acknowledgments are due to Professors Milroy Paul and P. B. Fernando, Drs. Terence Perera, Soma Weeratunge, and W. J. Gomes, and Mrs. N. P. Fernando; we are also indebted to our technical staff, Messrs. Justin de Silva, T. Ratnam, and S. Dissanayake.

REFERENCES

- Allen, J. G., *et al.* (1949). *J. Amer. med. Ass.*, **139**, 1251.
 Breckoff, E. (1924). *Maschr. Kinderheilk.*, **28**, 232.
 Castex, M. R., Pavlovsky, A., and Bonduel, A. (1943). *Medicina, B. Aires*, **4**, 46.
 Corbett, W. H. (1947). *Med. J. Aust.*, **1**, 114.
 Doan, C. A. (1949). *Ann. intern. Med.*, **31**, 967.
 Drury, D. R., and McMaster, P. D. (1928). *Proc. Soc. exp. Biol., N.Y.*, **26**, 490.
 Glanzmann, E., Steiner, H., and Keller, H. (1940). *Schweiz. med. Wschr.*, **70**, 1243, 1261.
 Henderson, J. L., Donaldson, G. M. M., and Scarborough, H. (1945). *Quart. J. Med.*, **14**, 101.
 Jones, H. W., and Smith, R. M. (1930). *Amer. J. Phys.*, **94**, 144.
 Macfarlane, R. G. (1938). *Lancet*, **1**, 309.
 — and Biggs, R. (1948). *Blood*, **3**, 1167.
 Moloney, W. C., Egan, W. J., and Gorman, A. J. (1949). *New Engl. J. Med.*, **240**, 596.
 Opitz, H., and Frei, M. (1921). *Jb. Kinderheilk.*, **94**, 374.
 Rabe, F., and Salomon, E. (1920). *Dtsch. Arch. klin. Med.*, **132**, 240.
 Scarborough, H. (1941). *Edinb. med. J.*, **48**, 555.
 Schönholzer, G. (1939). *Dtsch. Arch. klin. Med.*, **184**, 496.

A CORNEO-SCLERAL SUTURE IN CATARACT EXTRACTION

BY

H. B. STALLARD, M.B.E., M.D., Hon.LL.D., F.R.C.S.

Surgeon, the Moorfields Eye Hospital; Ophthalmic Surgeon, St. Bartholomew's Hospital

There is, I think, a growing trend of opinion, at least among some of the less conservative ophthalmic surgeons in this country and particularly in America, that a corneo-scleral suture is an important and purposeful essential in cataract extraction, both for the intra-capsular and for the extracapsular operation. Since 1933 I have used a corneo-scleral suture in all cataract operations and have tried several methods of suturing. I have been impressed by the security that a properly placed corneo-scleral suture affords during operation and for the subsequent days of post-operative care.

During operation the section may be quickly, accurately, and effectively closed immediately the lens is out of the eye, and so the rare but serious hazard of vitreous loss is either obviated or checked at once and catastrophe is averted.

After operation the wound is kept securely closed over the critical period, during which a small degree of re-opening may lead to iris prolapse and hyphaema, due to the tearing of newly formed blood vessels bridging the lips of the section. It is evident that a corneo-scleral suture reduces quite appreciably the incidence of iris prolapse and hyphaema; indeed, in the series of 80 cases in which the technique described below was used no case of post-operative prolapse and only five cases of hyphaema—2 mm. in two cases and 1 mm. in three cases—occurred, four of which were in patients known to be suffering from arterial hypertension.

One corneo-scleral suture placed in the 12 o'clock meridian is sufficient, but in cases in which the intra-ocular contents bulge forwards on completion of the section and in which the iris, despite accurate replacement, tends to move upwards and forwards towards the section wound, two or three corneo-scleral sutures are inserted at equidistant intervals in the section. In America some enthusiastic surgeons use as many as five sutures to close the wound securely.

It is, I think, preferable to insert the corneo-scleral suture before the section is made, when it is technically easier to do this with precision and accuracy than is the case after the section has been made. It is argued that a disadvantage of this "pre-fixed" suture, as it is called, is the greater skill needed to bring the cataract knife out of the eye exactly between the two arms of the suture. With a good assistant holding the two arms of the suture apart at the right moment, and with the correct degree of tension, this technical point is not difficult for an accomplished surgeon. For those who make the section with a keratome and enlarge it with scissors this does not apply.

Inaccuracy in the choice of exactly opposite points for the insertion of the needle in the lips of the incision is likely if the section is made first and the eye is soft. The slightest lack of precision in coaptation of the wound edges may lead to overriding of the section, with the immediate risk of aqueous leakage and a drawn-up pupil, and the ultimate complication of epithelium growing down into the wound. Also there is in some eyes, such as those of high myopes and those in whom the iris bulges

Presenting the university accounts for 1949–50 and the estimates for 1951–2 to Convocation in Oxford on June 6, Dr. Keith Murray said that during the eleven years from 1938 to 1949 Government assistance to the university had increased sevenfold. During 1949–50 the income of the university was £1,608,000. Of this sum £933,000 came from Government sources.