precipitating causes on a soil already prepared. Put in another way, the affective manifestation of anxiety and depression might seem to be some sort of preformed cerebral function occurring in the personality type and potentially manifesting itself when the right precipitating factor came along.

Malamud *et al.* (1941) take a similar view, and feel that in the "development of the psychoses the pre-morbid personality and catastrophic occurrences before the onset of the illness are of outstanding importance."

From a purely practical point of view, exhaustive evaluation of any physical anomalies seen in association with this type of illness, even if, as in these cases, the whole background seems to be characteristic of involutional depression, is clearly of the utmost importance.

Summary

Four cases of agitated depression are noted, all of which were associated with organic disease.

The depression, its symptoms, signs, and time of occurrence, together with the pre-morbid personality of the patient, were characteristic of the involutional type of illness.

The significance of this association is discussed.

I am grateful to Dr. R. E. Hemphill for permission to publish these cases and to Dr. K. R. L. Hall for his detailed psychological reports.

REFERENCES

- Ewen, J. H. (1947). *Mental Health*, 1st ed. Arnold, London.
 Gillespie, R. D. (1929). *Guy's Hosp. Rep.*, 79, 306.
 Hemphill, R. E., and Reiss, M. (1940). *J. ment. Sci.*, 86, 1065.
 — and Stengel, E. (1941). *J. Neurol. Psychiat.*, 4, 97.
 Henderson, D., and Gillespie, R. D. (1950). *Textbook of Psychiatry*, 7th ed. Oxford Medical Publications.
 Herman, M., Most, H., and Jolliffe, N. (1937). *Arch. Neurol. Psychiat.*, Chicago, 38, 348.
 Kraepelin, E. (1913). *Psychiatrie*, 8th ed.
 McAlpine, D. (1929). *Lancet* 2, 643.
 MacCurdy, J. T. (1925). *The Psychology of Emotion*. Harcourt, New York.
 McIntyre, H. D., and McIntyre, A. P. (1942). *Amer. J. Psychiat.*, 98, 720.
 McMenemy, W. H. (1941). *J. Neurol. Psychiat.*, 4, 48.
 Malamud, W., Sands, S. L., and Malamud, I. (1941). *Psychosom. Med.*, 3, 410.
 Muncie, W. (1948). *Psychobiology and Psychiatry*, 2nd ed. C. V. Mosby Company, St. Louis.
 Nielson, J. M., and Thompson, G. N. (1947). *Engrammes of Psychiatry*, 1st ed. Thomas, Springfield, Ill.
 Noyes, A. F. (1947). *Modern Clinical Psychiatry*, 2nd ed. Saunders, Philadelphia and London.
 Osgood, C. W. (1935). *J. Amer. med. Ass.*, 104, 2155.
 Palmer, H. D., and Sherman, S. H. (1938). *Arch. Neurol. Psychiat.*, Chicago, 40, 762.
 Rogers, A. W. (1915). *J. nerv. ment. Dis.*, 42, 693.
 Sachs, E. (1950). *J. ment. Sci.*, 96, 998.
 Spillane, J. D. (1947). *Nutritional Disorders of the Nervous System*. Livingstone, Edinburgh.
 Stengel, E. (1943). *J. ment. Sci.*, 89, 1.

A letter in *Science* (June 25, p. 914) records the results of a six-year investigation showing an unexpected correlation between susceptibility to poliomyelitis and genetic traits indicated by pigmentation of the skin, hair, and eyes. The writer, WALLACE L. MINTO, of New Jersey, U.S.A., says that of 1,183 poliomyelitis cases investigated, 1 only had blond hair, blue eyes, and fair skin, 17 had blond hair and brown eyes, while the remaining 1,165 had brown or black hair and eyes. All the fair patients had light attacks of the disease, only two of them having any permanent disability. The observations were limited to members of the Caucasian race. "Obviously, these observed ratios differ significantly from the occurrence of light pigmentation in the general population." The writer then goes on to make a plea that "this variation of susceptibility to poliomyelitis should be taken into account in any statistical study of the value of prophylactic measures"—that is, light- and dark-haired people should be equally distributed in the control and experimental groups.

INCOAGULABILITY OF BLOOD AFTER ACCIDENTAL HAEMORRHAGE

BY

H. C. MOORE, M.D.

(Director of Pathology, Rotunda Hospital, Dublin)

Of recent years there have been several reports concerning the phenomenon of incoagulability of the blood which sometimes follows accidental haemorrhage (Dieckmann, 1936; Moloney *et al.*, 1949; Weiner *et al.*, 1950; Goodfriend *et al.*, 1953; Stevenson *et al.*, 1953; and Weiner *et al.*, 1953). This blood incoagulability may give rise to severe post-partum haemorrhage, or to uncontrollable bleeding from the wound or even from suture points after caesarean section, and may be so severe as to cause death. It is sometimes associated with spontaneous haemorrhages in various parts of the body.

In spite of the obvious importance of this complication of accidental haemorrhage, and the need for the early recognition and correction of the condition, little or no attention has been paid to it in the British literature.

Case Report

A 10-para aged 40 had had nine previous normal confinements. She was not attending the antenatal department and was first admitted on March 6, 1953, 26 weeks pregnant and giving a history of slight vaginal bleeding for the past four days.

Examination revealed a uterus corresponding in size to the period of gestation. The cervix was normal and closed. The blood pressure was 125/70 and there was no albumin in the urine. Bleeding ceased and the patient was discharged home on March 11.

She was readmitted to hospital on April 3, giving a history of further slight vaginal bleeding. Liquor was draining at the time of readmission, but she was not in labour and a foetal heart could be heard. The pregnancy had now reached 30 weeks, but the uterus was much larger than the dates would suggest. A haemoglobin estimation gave a reading of 5.1 g. per 100 ml. The blood pressure was normal and there was no albumin in the urine. Blood-stained liquor continued to drain and definite labour pains began at 6 p.m. on April 7. Very slight pains continued and no anxiety was felt regarding her condition. At 3.50 a.m. on April 8 the patient had a typical eclamptic fit immediately following a two-hours sleep. The fit displayed tonic and clonic phases and was followed by a coma. The tongue was bitten. Urine showed a faint trace of albumin and the blood pressure was 110/90. Half an hour after the occurrence of the fit bulging membranes were visible at the vulva. These were ruptured and, using forceps, a small dead-born foetus, just over 3 lb. (1.4 kg.) was lifted out of the vagina. A completely separated placenta immediately came away after the delivery, with 10 oz. (285 ml.) of retroplacental clot. Ergometrine, 0.5 mg., and morphine, $\frac{1}{4}$ gr. (16 mg.), were given intramuscularly. The delivery was completed at 4.25 a.m.

A quarter of an hour after delivery about a pint (570 ml.) of watery non-clotting blood was expressed on rubbing up the uterus. The patient became shocked and immediate blood transfusion was begun. The first pint of blood was given rapidly and a second bottle started. In spite of further administration of ergometrine a continued trickle of non-clotting blood continued from the vagina, and expression a few minutes later produced a further half-pint (285 ml.) of non-clotting blood. At 5 a.m. she was becoming more deeply shocked and a third pint of blood was

started. The uterus was then packed firmly with 6-in. (15-cm.) gauze. There was no improvement in her condition and by 6 a.m. watery blood was draining copiously through the pack, and, despite the fact that the uterus was well contracted, it was evident that the pack was not serving any useful purpose. At this stage transfusion with fresh blood was begun, pending the arrival of fibrinogen. The transfusion of fresh blood did not result in any control of the bleeding. At 6.10 a.m. the clotting-time was measured by the Lee and White method; at eight minutes a minute fragment of clot had formed, but the remainder of the blood did not coagulate.

At 6.45 a.m. 2 g. of fibrinogen was given intravenously (human fibrinogen from the Blood Products Unit of the Lister Institute). A quarter of an hour later all bleeding had stopped and the pack was removed from the uterus. (On careful consideration it is estimated that the total blood loss in this case was about 45 oz.—1,420 ml.) At 7.10 a.m. the blood showed complete clotting in four minutes and the clot was stable. An hour later the clotting-time was eight minutes.

At 10 a.m., after no further vaginal bleeding, the urine was free from albumin and the blood pressure was normal. The puerperium was complicated by a severe right-sided femoral thrombosis, which responded well to a paravertebral block. The patient was discharged home well on May 10, the thirty-third day after confinement.

Obstetric Comment (Dr. E. W. L. Thompson).—From a clinical point of view the following features of this case should be particularly stressed: (1) the characteristic nature of the blood coming from the vagina; this was thin and watery with no formed clot, and quite unlike the blood lost in cases of atonic post-partum haemorrhage or from a traumatic source in the lower segment or cervix; (2) the complete failure of ergometrine to control the bleeding, although the uterus seemed to be well contracted after its administration; (3) the failure of a firmly applied intra-uterine pack to prevent further bleeding; and (4) hysterectomy, as a last resort, was under consideration as a possible means of controlling the haemorrhage, all the usual methods having failed. In view of the blood findings and the dramatic result following the administration of fibrinogen it is now realized that the operation could have resulted in uncontrollable oozing from the operation site.

Discussion

Severe post-partum haemorrhage is a well recognized complication of accidental haemorrhage. Of a total of 67 fatal cases of severe accidental haemorrhage analysed by Sheehan and Moore (1952), four had moderate and four had severe post-partum haemorrhage. Seven of these eight patients died within 14 hours of the onset of the accidental haemorrhage. All these patients were gravely shocked, but in at least three instances death was due partly to the post-partum haemorrhage. At the time these cases occurred it was thought that the haemorrhage was due to uterine atony, but in the light of modern observations it seems very probable that the real cause was an unrecognized incoagulability of the blood. In the past year at the Rotunda Hospital 64 cases of accidental haemorrhage have been encountered, and on clinical grounds 18 of them were classified as severe. Among these 18 cases two had post-partum haemorrhage of incoagulable blood; this includes the present case, in which blood loss was severe. The conclusion may be reached that severe haemorrhage as a result of incoagulability of the blood is not very common after accidental haemorrhage and probably occurs in only about 5% of severe cases. However, it should be pointed out that degrees of coagulation defects may be present without clinical manifestations.

The important fact that the tendency to post-partum haemorrhage is associated particularly with severe accidental haemorrhage has also been emphasized by Weiner *et al.* (1950, 1953), although Stevenson *et al.* (1953) describe cases of haemorrhage following accidental haemorrhage which were of only "moderate" severity.

The incoagulability of the blood follows the accidental haemorrhage and does not precede it (Weiner *et al.*, 1950); certainly in all cases the retroplacental haematoma is clotted. The coagulation defect is essentially transient and usually does not last more than 24 to 36 hours. Before delivery there is thus a danger of continuation of the retroplacental haemorrhage; Weiner *et al.* (1953) suggest that artificial rupture of the membranes has a beneficial effect on the coagulation mechanism at this stage, but Stevenson *et al.* (1953) say that the blood may remain incoagulable until delivery. The more serious complication is that the condition may continue long enough after the delivery to cause severe post-partum haemorrhage or bleeding from a section wound. In the present case, at the time of the post-partum haemorrhage the blood taken from the general circulation was incoagulable *in vitro*.

The actual defect of the coagulation mechanism seems to involve various factors, or probably a combination of them. (a) There is a fibrinogenopenia. Weiner *et al.* (1950, 1953) carried out serial fibrinogen estimations and established that there is a quantitative fibrinogen deficit. This may reach dangerous levels as early as one hour after the onset of accidental haemorrhage, or it may progress more slowly over a period of several hours. The critical level of plasma fibrinogen below which blood is incoagulable is stated to be in the region of 100 to 150 mg. per 100 ml. (Stevenson *et al.*, 1953; Weiner *et al.*, 1953). (b) The blood prothrombin falls slowly, and may be down to a third of its normal level at about eight or nine hours. (c) A fibrinolysin is present for an indefinite period, usually at about four to six hours after the onset of the accidental haemorrhage. This is identified *in vitro* by the dissolution of clot shortly after it has formed.

The reason for this disturbance of the coagulation mechanism is not yet settled. Some workers believe that the reduction of fibrinogen is due to the activity of a fibrinogenolysin or fibrinolysin. Others believe that it is due to a sudden and excessive usage of fibrinogen as a result of clotting in the body. Dieckmann (1936) postulated that the site of this was in the formation of the large mass of retroplacental clot. Schneider (1952) has suggested that multiple tiny thrombi are formed throughout the vessels of many organs as a result of the leakage of thromboplastin from the placenta into the general circulation, and that the body fibrinogen is used up in the formation of these thrombi. Some experimental evidence to support this hypothesis has been given by Seegers and Schneider (1951).

It has been mentioned that fibrinogenopenia may occur without any clinical evidence of bleeding. Nevertheless there is always the possibility that the fibrinogen will continue to diminish and that clinical manifestations will then appear. Tests have therefore been devised to detect "sub-clinical" fibrinogen depletion. Schneider (1952) employs a simple test to detect fibrinogenopenia; serial dilutions of the whole blood are made and the highest dilution in which there is a visible clot is the fibrin titre. Weiner *et al.* (1953) describe another simple test. Venous blood is collected in a test-tube and kept under observation. If no clot forms or if the blood fails to produce a normal-sized stable clot, this is regarded as enough evidence of a reduction in circulating fibrinogen. In certain cases there is formation of clot, but this dissolves again in a short time. The authors state that this instability of the clot is closely related to the tendency of the patient to haemorrhage. It occurs whenever the plasma value for fibrinogen is reduced to levels of 100 to 150 mg. per 100 ml. or in the presence of a fibrinolysin, or as a combined effect of both these changes. They find that if the clot remains stable for an hour at 37° C. the patient is unlikely to suffer further haemorrhage.

From the literature it appears that for satisfactory treatment of severe fibrinogenopenia it is necessary to administer 2 to 10 g. of fibrinogen intravenously. In the present case no determinations of the fibrinogen content of the blood were made, but within 20 minutes after the administration

of only 2 g. of fibrinogen the previously incoagulable blood formed a stable clot *in vitro* and the clotting-time was normal. Similar cases have been recorded by Weiner *et al.* (1950, 1953). There seems to be no doubt that the intravenous administration of fibrinogen is a very efficient treatment for this condition, and that 2 g. is probably the smallest useful amount. In cases with continuing bleeding, or in cases in which the tests show a subclinical fibrinogenopenia, the administration of fibrinogen can be repeated until the clotting mechanism is normal. It is clearly advisable that a supply of fibrinogen should be available in all obstetric hospitals.

It might reasonably be anticipated that adequate blood transfusion would be a satisfactory method of curing this fibrinogenopenia, since blood transfusion can restore normal coagulation in those non-pregnant cases suffering from congenital absence of fibrinogen (Biggs and Macfarlane, 1953). However, in the particular type of acquired fibrinogenopenia described here, blood transfusion is not a successful line of therapy. It is the practice in this hospital to give at least 3 pints (1,700 ml.) of blood to all patients with moderate or severe accidental haemorrhage as soon as they are admitted, but this treatment failed to control post-partum haemorrhage in the two patients mentioned in this paper. The same failure has been noted by other workers.

Summary

A case of severe post-partum haemorrhage following accidental haemorrhage showed incoagulability of the blood. This defect of the clotting mechanism is a not uncommon complication of accidental haemorrhage. It can and should be identified before delivery, so that specific treatment by the intravenous administration of fibrinogen can be given.

My thanks are due to Dr. E. W. L. Thompson, Master of the Rotunda Hospital, for his help with the case report; to Dr. W. E. R. Hackett, Director of the National Blood Transfusion Service, Dublin, for supplying the fibrinogen; and to Professor H. L. Sheehan, who read the script and made many valuable suggestions.

REFERENCES

- Biggs, R., and Macfarlane, R. G. (1953). *Human Blood Coagulation and its Disorders*. Blackwell, Oxford.
- Dieckmann, W. J. (1936). *Amer. J. Obstet. Gynec.*, 31, 734.
- Goodfriend, M. J., Shey, I. A., and Siegelbaum, H. L. (1953). *Ibid.*, 65, 1034.
- Moloney, W. C., Egan, W. J., and Gorman, A. J. (1949). *New Engl. J. Med.*, 240, 596.
- Schneider, C. L. (1952). *Amer. J. Obstet. Gynec.*, 64, 141.
- Seegers, W. H., and Schneider, C. L. (1951). *Ibid.*, 61A, 469.
- Sheehan, H. L., and Moore, H. C. (1952). *Renal Cortical Necrosis and the Kidney of Concealed Accidental Haemorrhage*. Blackwell, Oxford.
- Stevenson, C. S., Braden, R. G., Schneider, C. L., Johnson, J. F., and Seegers, W. H. (1953). *Amer. J. Obstet. Gynec.*, 65, 88.
- Weiner, A. E., Reid, D. E., and Roby, C. C. (1950). *Ibid.*, 60, 379.
- (1953). *Ibid.*, 66, 475.

A startling report on alcoholism among children was made last month by Dr. SUZANNE SERIN to the Academy of Medicine in Paris. Her suspicions were first aroused by the case of a boy, aged 7 years, who was referred on account of character difficulties and temper tantrums. Close questioning drew from him the admission, "J'ai peur, je vois le soir des ailes, non des mains, des choses blanches qui dansent sur la commode de ma chambre; c'est épouvantable," an answer that led to inquiries about his drinking habits. His parents told Dr. Serin that he drank about a litre of undiluted wine a day, and sometimes, "parce qu'on le trouve nerveux," a glass of port with two yolks of egg beaten into it. Since that case Dr. Serin has always inquired about the alcohol consumption of the children she sees, and in her paper she quotes three similar cases as examples of what she has found. One of the most interesting features of this infantile alcoholism is that it occurs among well-off, cultured families, not, as might be expected, in bad homes where the parents are drunkards.

CRYOGLOBULINAEMIA WITH CEREBRAL PURPURA

BY

R. J. MARSHALL, M.D., M.R.C.P., M.R.C.P.I.

Senior Tutor in Medicine, Queen's University, Belfast

AND

R. G. S. MALONE, M.B., B.Ch., B.A.O.

Assistant Lecturer in Pathology, Queen's University, Belfast

In 1947 Lerner and Watson proposed the term "cryoglobulin" for an abnormal blood protein which undergoes reversible precipitation on exposure of the serum to low temperatures. Barr *et al.* (1950) described the clinical and pathological features of a patient who suffered from recurrent attacks of Raynaud's phenomenon, and whose blood contained on various occasions 4.9 to 9.8 g. of cryoglobulin per 100 ml. In a review of the literature these authors found eight other instances of high-grade cryoglobulinaemia; since then further cases have been reported by Lucey *et al.* (1950), Rörvik (1950), Blades (1951), Luckey *et al.* (1951), Cugudda (1952), Muirhead *et al.* (1952), McFarlane and Dovey (1952), Griffiths and Gilchrist (1953), and Hutchinson and Howell (1953).

This paper records the occurrence of cerebral purpura in a patient with cryoglobulinaemia, an association, to our knowledge, not hitherto described.

Case Report

A man aged 56 was seen in the out-patient department complaining of pain in the lower part of the chest of two months' duration. Clinical examination was negative and blood counts were normal. Four months later he attended again and was admitted to a medical ward for investigation.

The patient was found to have moderate pallor of the skin and mucous membranes. The spine, thorax, and shoulder-girdles were extremely tender on pressure. X-ray examination showed collapse of the eleventh and twelfth dorsal vertebrae; in the remainder of the skeleton there were numerous round translucent areas typical of multiple myeloma. The urine contained 1+ albumin but no Bence Jones protein. Sternal puncture showed a cellular marrow, 79% being myeloma cells of varying degrees of maturity. It was difficult to obtain samples of venous blood owing to its greatly increased viscosity. When samples of venous blood were allowed to stand at room temperature (25° C.) clot retraction was slow and imperfect, and the serum settled into two layers of approximately equal volume; the upper was a straw-coloured fluid and the lower a firm pearly-white gel. On heating to 37° C. the gel liquefied, and on subsequent cooling it again became solid. Long needle-shaped crystals formed when a drop of warmed serum was allowed to cool on a slide. The formol-gel test, carried out on the fluid fraction of the serum, was strongly positive. Laboratory investigations showed: haemoglobin, 11.3 g. per 100 ml.; erythrocytes, 3,000,000 per c.mm.; E.S.R. (Westergren), 141 mm. in one hour; E.S.R. (Wintrobe), 14 mm. in one hour; cold agglutinin titre, 1:4; serum calcium, 17.2 mg. per 100 ml.; blood urea, 113 mg. per 100 ml.

The patient's condition rapidly deteriorated, and he sustained several pathological fractures of the ribs during a fit of coughing. Eight days after admission he was given 7 mg. of nitrogen mustard by intravenous injection. On the following day he lapsed into coma. Retinoscopy revealed papilloedema with engorged veins and extensive retinal haemorrhages. Death occurred 16 days after admission.