clinical treatment. The following is an account of the practical details of this biuret method for fibrinogen estimation :

Reagent:

Sodium potassium tartrate	..	9 g.
CuSO ₄ .5H ₂ O	..	3 g.
Potassium iodide	..	5 g.
0.1 N NaOH	..	to 1 litre
Distilled water	..	to 1.9 litres

Thrombin Solution:

P.D. & Co. thrombin topical in 50% glycerol-saline.

Procedure.—Take blood in the Heller-Paul (Wintrobe) oxalate mixture. If possible secure 3 ml. of plasma. Add 20 units of thrombin per ml. of plasma. Clotting should occur within about 5 seconds, and rapidly even at 5° C. Provided that the plasma clots within 60 seconds, upwards of 97% of the fibrinogen will be precipitated in one hour, even if clotting occurs and is allowed to continue at a temperature as low as 5° C. After one hour at 5° C. or 37° C. the clot is spilled out on to a filter paper or a paper towel (preferable) and the plasma expressed in three or more stages. The clot is washed in distilled water, and the fluid again expressed. The clot is then transferred to a boiling-tube containing 0.5 ml. N NaOH, and dissolved by heating in a boiling-water bath for two to three minutes. Then 9.5 ml. of the biuret reagent is added and the colour developed by heating in a water-bath at 30–32° C. for 30 minutes. A reagent blank is prepared by the addition of 9.5 ml. of the reagent to 0.5 ml. N NaOH with similar incubation at 30° C. for 30 minutes. The optical density of the test is read against the reagent blank in a photo-electric colorimeter at 555 μ , each tube being at about 30° C. The instrument is calibrated by duplicate estimations by the Kjeldahl method. The reagent described gives a colour which follows Beer's law.

Summary

Two methods of confirming the clinical diagnosis of acquired fibrinopenia in pregnancy are described. Patients who show a Schneider titre of 1 in 100 or less (plasma fibrinogen probably below 120 mg.) should be regarded as potential victims of a haemorrhagic diathesis. If haemorrhage occurs it cannot be checked without restoring the blood fibrinogen. Even if there is no manifest haemorrhage, disastrous bleeding may be provoked by active intervention. Since stored blood for transfusion will have a fibrinogen content of 200 mg. per 100 ml. or less, it may not be possible to raise the blood fibrinogen to a safe level by transfusion of whole blood. If pure fibrinogen is not available a rapid restoration of clotting power may be achieved by the intravenous injection of triple- or quadruple-strength plasma (1 pint (570 ml.) of quadruple-strength plasma yields about 4.4 g. of fibrinogen).

REFERENCES

- Barry, A. P., and Geoghegan, F. (1954). *Irish J. med. Sci.*, 189.
 Feeney, J. K. (1954). *J. Irish med. Ass.*, 35, 310.
 Moloney, W. C., Egan, W. J., and Gorman, A. J. (1949). *New Engl. J. Med.*, 240, 596.
 Quick, C. J. (1951). *Physiology and Pathology of Haemostasis*, pp. 156–158. Kimpton, London.
 Schneider, C. L. (1952). *Amer. J. Obstet. Gynec.*, 64, 141.
 Shea, S. M. (1954). *Irish J. med. Sci.*, 36–37.
 Weiner, A. E., Reid, D. E., and Roby, C. C. (1950). *Amer. J. Obstet. Gynec.*, 60, 1015.

The British Red Cross Society's report for the year 1954 has just been published. It contains information about the various activities undertaken by the British Red Cross Society, such as first-aid and ambulance work, nursing, blood transfusion, welfare, and the administration of auxiliary hospitals, homes, and settlements. Some of the homes for old people established by the Society are for permanent residents, while others receive short-stay guests. The report states that the demand for the latter type of accommodation is increasing.

BLOOD COAGULATION FAILURE IN OBSTETRICS

EFFECTS OF DEXTRAN AND PLASMA

BY

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In the course of a study of coagulation failure associated with hypofibrinogenaemia in obstetrics (to be reported in detail elsewhere), a review was carried out of maternal deaths, and of cases of accidental ante-partum haemorrhage, among 85,000 deliveries in the practice of certain hospitals in Birmingham, Liverpool, and London between 1937 and 1955. Eight cases of coagulation failure were discovered, seven of them serious and four being fatal. In five the condition complicated accidental ante-partum haemorrhage. One of the most interesting findings of the inquiry was that only one of the cases occurred prior to 1951, the remainder being encountered during the period 1951–5. This is in keeping with the fact that, although coagulation failure in association with accidental haemorrhage was described as early as 1901 (De Lee), very few instances were recorded until the present decade, while the last few years have seen a spate of case reports and articles on the subject in medical journals throughout the world.

There seems little doubt that the recent increase in the incidence and clinical importance of this problem is real and not apparent, and consideration of the available evidence suggests that the most likely explanation for it is the introduction and widespread use of artificial macro-molecular substitutes for blood and plasma. In this country the most popular preparation of this kind is dextran,* and it is remarkable that it is only since it was widely adopted about five years ago that cases of afibrinogenaemia have been relatively common. Moreover, in six of the seven cases mentioned above which occurred during the 1951–5 period, dextran was transfused in comparatively large amounts—the average amount per case was a little more than 3½ pints (2 litres)—and most of it was given before there was evidence of the blood failing to clot. In the seventh case, failure of the blood to coagulate was a transient phenomenon which disappeared quickly, without causing serious anxiety, when 2 pints (1.1 litres) of whole blood was transfused. Moreover, in one of the above cases serial haematological studies revealed a striking deterioration in the quality of the clot formation within a period of 15 minutes during which 1 pint (570 ml.) of dextran was administered. In another of our patients 5 pints (2.8 litres) of dextran was given as part of the treatment of atonic post-partum haemorrhage, and this appeared to precipitate coagulation failure, which had not been present previously. The clotting function in this case was not properly restored until 12 hours later, by which time 6 pints (3.4 litres) of blood had been transfused.

These observations receive support from the published accounts of other cases. McKay *et al.* (1955) described a case in which coagulation failure developed rapidly after

*Dextran is a complex polysaccharide of large and variable molecular size. Commercial preparations vary, but in the one used in most of these cases 63% of the molecules fell within the weight range of 130,000–250,000. It was administered as a 6% solution in normal saline.

the administration of dextran, the basic coagulation defect being hypofibrinogenaemia, while Soulier *et al.* (1952) and Lepage *et al.* (1952) describe cases which followed the administration of polyvinylpyrrolidone, a similar type of large molecular plasma substitute. Hodgkinson *et al.* (1955), in a recent extensive review of coagulation defects in obstetrics, has also commented on the possible association between the coagulation disorder and the use of "plasma expanders" of the dextran type.

Apart from clinical data such as the above, there is experimental evidence to support the conjecture that dextran can exercise an adverse effect on the coagulation mechanism, and this is discussed later.

Mechanism of the Coagulation Disorder

The coagulation disorder occurring in obstetric patients is now generally accepted as being the biphasic one suggested by Schneider (1951, 1952a), and it is illustrated diagrammatically in Fig. 1. An initial state of increased coagulability (*Phase I*) is induced by the release of thromboplastic material into the general circulation from the placental site or as a liquor amnii. This leads to precipitation of fibrinogen as fibrin, which forms multiple tiny emboli in the pulmonary and other capillary beds. In certain cases the plugging of the blood vessels may lead to focal areas of

FIG. 1.—Mechanism of coagulation disorder.

necrosis in various organs (McKay *et al.*, 1953) and, if very extensive, can cause sudden death. Deposition of fibrin, and possibly fibrinolysis (or fibrinogenolysis), leads to a depletion of circulating fibrinogen which, if sufficiently severe, results in failure of blood clotting (*Phase II*).

There seems little doubt that the end-result of the process, and the main factor in the coagulation failure, is severe hypofibrinogenaemia (or afibrinogenaemia), although the mechanism may not be precisely as postulated, and other agents such as Factor V (accelerator globulin) may be secondarily involved.

The level of fibrinogen in the blood of normal women in labour at term, according to our observations, averages 0.45 g.% (range 0.35–0.55 g.), but this can be reduced to as low as 0.1 g.% in cases of abruptio placentae without the patient showing clinical evidence of coagulation failure.

The critical level at which coagulation fails and at which uncontrollable haemorrhage is liable to occur is between 0.07 and 0.1 g. %.

Effect of Dextran

Ricketts (1952) and Fletcher *et al.* (1952) showed by *in vitro* experiments with fibrinogen solutions that, under certain conditions, dextran can react with and inactivate fibrinogen by forming a dextran–fibrinogen compound which may precipitate. However, since only 10% of the fibrinogen was involved in this reaction, these workers concluded that it was unlikely to be of clinical significance. Laurell (1951), as a result of experiments on rabbits, attributed a "fibrinoplastic" action to dextran whereby it encourages the formation of fibrin from fibrinogen, especially when the molecular weight averages 75,000. Adant (1954), working with dogs, showed a decrease in fibrinogen levels following dextran infusion, and concluded that the initial fall is the result of haemodilution but that a second fall has another mechanism. The levels were rapidly re-established in the intact but not in the hepatectomized animal. Carbone *et al.* (1954) recorded haemorrhagic manifestations in two patients treated with large quantities of dextran, and, in experiments on human subjects, demonstrated a decrease in the fibrinogen levels following dextran infusions.

There is therefore considerable clinical and experimental evidence to show that dextran can exert an unfavourable action on the coagulation mechanism. By itself this may not often be sufficient to result in clinical manifestations of coagulation failure, but in the patient already suffering from hypofibrinogenaemia (as are approximately 30% of patients with moderate or severe accidental ante-partum haemorrhage) it may be enough to tip the scales, converting a sub-clinical blood change into a state of uncontrollable bleeding.

Dextran exerts this effect (a) by simple dilution of the already decreased fibrinogen content, and (b) by encouraging precipitation of fibrinogen as fibrin or forming a fibrinogen–dextran compound and thus acting as a contributory factor to *Phase I* of the coagulation disorder (see Fig. 1). The second effect is possibly not operative in all cases, its occurrence probably depending on (a) the relative concentrations of dextran and fibrinogen, and (b) the molecular weight of the dextran employed.

Effects of Plasma

Prior to the introduction of dextran, most patients in urgent need of blood-volume restoration received plasma transfusions pending the availability of compatible blood. The fibrinogen content of plasma is high, even when stored for long periods. Samples prepared by reconstitution of dried plasma which had been stored at room temperature for three years were found to contain an average of 0.35 g.% of fibrinogen. Thus, unlike dextran, plasma transfusion helps to restore the fibrinogen level to normal. The increased incidence of afibrinogenaemia and of hypofibrinogenaemia severe enough to cause serious haemorrhage coincides with the decreased use of plasma which came about a few years ago.

Plasma transfusions fell from favour because of the considerable risk of hepatitis which was noted, particularly during the war years, when "large pool" plasma was used. In recent years "small pool" plasma has replaced the older type preparations, and Lehane *et al.* (1949) showed that with this the risk of hepatitis is no greater than when whole blood is used. Stored citrated blood also retains much of its original fibrinogen content, and estimations performed on blood stored for 8 to 16 days show an average level of 0.29 g. %.

Recognition of Hypofibrinogenaemia

The persistent escape of incoagulable blood from the placental site or from obstetrical and surgical wounds provides obvious clinical evidence of the final stage of the blood disturbance. It is clearly desirable, however, to have

means of recognizing fibrinogen depletion before it reaches a dangerous level, especially as we have evidence that such a level can be present for some time before frank haemorrhage develops.

In the course of our investigations the fibrinogen content of blood was estimated, using the micro-Kjeldahl distillation apparatus. This method takes several hours, so it is obviously of little practical value. Other less accurate methods, such as serial dilution clotting (Schneider, 1952b), clot observation (Weiner *et al.*, 1950), micro-electrophoresis

Fig. 2 gives a photographic illustration of a series of tests performed by this method during the course of an accidental ante-partum haemorrhage.

Treatment of Hypofibrinogenaemia

1. *Preventive.*—Hypofibrinogenaemia is demonstrable in 30-40% of cases of severe or moderately severe accidental ante-partum haemorrhage, but it is rarely of such a degree as to manifest itself clinically. Further lowering of the fibrinogen level to the extent of making the blood incoagulable is avoided by: (a) Reduction of intrauterine pressure by early rupture of the membranes, thus diminishing the risk of absorption of thromboplastin from the placenta into the maternal circulation. (b) The encouragement of rapid delivery for the same reason. Rupture of the forewaters helps to achieve this but it also raises the question of the places of oxytocin and caesarean section; these and other obstetrical considerations are outside the scope of this communication. (c) The avoidance of dextran or other similar artificial blood substitutes; emergency transfusion should be with "small pool" plasma if blood is not immediately available.

2. *Curative.*—If coagulation failure does develop, fibrinogen replacement is urgently indicated. This can be achieved by transfusion of the fibrinogen fraction isolated from human plasma (Weiner *et al.*, 1950). Reid *et al.* (1953) recommend a dose of 8-12 g., but there would seem to be no necessity to give more than is required to restore blood-clotting. This can be sometimes achieved by very small amounts, Barnett and Cussen (1954) having been successful with less than 0.5 g. in two cases. Fibrinogen preparations, however, are in short supply in this country, although they may be obtainable from Regional Transfusion Centres. An

Fig. 2.—Rapid fibrinogen assays in case of abruptio placentae. (See key.)

KEY TO FIG. 2

Tube		C	1	2	3	4	5	6
Specimen		Normal control	Patient's 7 a.m.	8 a.m.	9 a.m.	10 a.m.	11.50 a.m.	2 p.m.
Rapid test results	Initial clot	7 secs.	15 secs.	15 secs.	10 secs.	10 secs.	10 secs.	8 secs.
	At 60 secs.	Stable clot	Poor clot serum ++	Poor clot serum +	Stable clot	Stable clot	Stable clot	Stable clot
	At 1 hour	Normal clot	Clot dissolved	Clot partially dissolved	Almost normal clot	Normal clot	Normal clot	Normal clot
Fibrinogen level (micro-Kjeldahl) g. %		0.350	0.175	0.237	0.237	Specimen clotted	0.306	0.237
Fibrinolytic activity		Nil	79%	13%	26%	" "	14%	8%
Treatment and progress				Plasma $\frac{1}{2}$ pint A.R.M.	Blood $\frac{1}{2}$ pint	Blood $\frac{1}{2}$ pint	Delivery. Blood 1 pint	—

(Barnett and Cussen, 1954), and the Shea colorimetric method (Barry *et al.*, 1955), are described, but none of these are rapid enough, nor can they be easily performed at the bedside.

A modified form of the test recently described in the advertisement of "fibrindex"™ was found to be an eminently practical if rough method for assaying fibrinogen in the delivery room. To 0.2 ml. of citrated blood in a small test-tube is added 0.2 ml. of thrombin solution, freshly prepared by dissolving 50 N.I.H. units of dried thrombin in 1 ml. of saline, both these being obtainable in ampoules. If the fibrinogen level is normal, clotting is evident within 5-10 seconds and the clot is firm and stable at 60 seconds. Thereafter it contracts with the extrusion of serum. Delay of the initial clotting beyond 15-20 seconds and liquefaction or disintegration of most of the clot at 60 seconds indicate that the fibrinogen level is considerably reduced, while absence of clot formation during 60 seconds is evidence of afibrinogenaemia. The interpretation of the test is greatly facilitated for the occasional user by setting up a control tube with blood from a normal patient; the amount of thrombin solution prepared allows for this. The great advantage of this method is that a result is obtained within one minute, and this can be vital in certain circumstances.

*This is not at present available in the United Kingdom. The thrombin used was prepared by S. Maw Son and Sons, Ltd.

excellent substitute is nevertheless readily available in most maternity units—namely, dried plasma ("total plasma solids": Barry *et al.*, 1955). If this is reconstituted to double strength by simply adding half the usual volume of water—that is, 200 ml.—it provides a solution containing approximately 0.7 g.% of fibrinogen, and 1 to 2 pints (0.5 to 1 litre) of this should be sufficient to correct afibrinogenaemia in the majority of cases. Indeed, it appears doubtful if there is any advantage in using the fibrinogen fraction, because it carries the same hepatitis risk as does plasma, and the latter may in addition contribute other coagulation factors.

Hypofibrinogenaemia in Conditions Other than Abruptio Placentae

It should here be mentioned that although afibrinogenaemia occurs most commonly as a complication of accidental ante-partum haemorrhage it is also reported in association with abortion, hydatidiform mole, intrauterine death of the foetus, amniotic embolism, and tumultuous action of the uterus in labour. The above arguments apply equally to the management of these conditions. Moreover, a similar mechanism may operate in non-obstetric procedures, such as thoracic surgery. The lung is almost as rich in thromboplastin as is the placenta, so its handling at operation may set in train the sequence of blood changes resulting in

afibrinogenaemia (Soulier *et al.*, 1952; Baumann, 1952). It may well be, therefore, that dextran carries a risk in this field, as it does in obstetrics.

Summary

Plasma should be preferred to dextran as an emergency blood-volume restorer in conditions in which hypofibrinogenaemia is apt to develop. The most important of these is accidental ante-partum haemorrhage, others being retention of a dead foetus *in utero*, and hydatidiform mole.

The transfusion of dextran or similar preparation in any circumstance should be limited to 1 to 2 pints (0.5 to 1 litre).

Hypofibrinogenaemia can be recognized quickly by a simple thrombin coagulation test before there is clinical evidence of its presence.

In cases of coagulation failure due to fibrinogen deficiency, transfusion of double-strength plasma offers a readily available method of treatment.

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REFERENCES

- Adant, M. (1954). *C.R. Soc. Biol. (Paris)*, **148**, 391.
 Barnett, V. H., and Cussen, C. A. (1954). *British Medical Journal*, **2**, 676.
 Barry, A. P., Feeney, J. K., and Geohagan, M. D. (1955). *Ibid.*, **2**, 12.
 Baumann, J. (1952). *Rev. Hémat.*, **7**, 20.
 Carbone, J. V., Furber, F. W., Scott, R., and Crosby, W. H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **85**, 101.
 De Lee, J. B. (1901). *Amer. J. Obstet.*, **44**, 785.
 Fletcher, F., Martin, L. E., and Ratcliffe, A. H. (1952). *Nature (Lond.)*, **170**, 319.
 Hodgkinson, C. P., Luzadre, J. H., Piper, P. W., Swinehart, L. A., and Remp, D. G. (1955). *Obstet. and Gynec.*, **5**, 465.
 Laurell, A. B. (1951). *Scand. J. clin. Lab. Invest.*, **3**, 262.
 Lehané, D., Kwantes, C. M. S., Upward, M. G., and Thomson, D. R. (1949). *British Medical Journal*, **2**, 572.
 Lepage, F., Eyquem, A., and Petit, P. F. (1952). *Rev. Hémat.*, **7**, 72.
 McKay, D. G., Merrill, S. J., Weiner, A. E., Hertig, A. T., and Reid, D. E. (1953). *Amer. J. Obstet. Gynec.*, **66**, 507.
 — Littlejohn, T. W., and Schoenbucker, A. K. (1955). *Obstet. and Gynec.*, **5**, 85.
 Reid, D. E., Weiner, A. E., and Roby, C. C. (1953). *Amer. J. Obstet. Gynec.*, **66**, 465.
 Ricketts, C. R. (1952). *Nature (Lond.)*, **169**, 970.
 Schneider, C. L. (1951). *Surg. Gynec. Obstet.*, **92**, 27.
 — (1952a). *Amer. J. Obstet. Gynec.*, **63**, 1078.
 — (1952b). *Ibid.*, **64**, 141.
 Soulier, J. P., Mathey, J., Le Bollock, A. G., Daumet, P., and Fayet, H. (1952). *Rev. Hémat.*, **7**, 30.
 Weiner, A. E., Reid, D. E., and Roby, C. C. (1950). *Amer. J. Obstet. Gynec.*, **60**, 379.

In 1951 the London County Council decided to improve the main drainage works at Northern Outfall, which were constructed in 1864 as part of the Metropolitan Board of Works scheme for the collection and disposal of sewage. The new construction is to ensure the adequate treatment of sewage, and is the council's contribution to the improvement of the quality of Thames water, which has deteriorated recently. Work at present in hand, or proposed, includes the finishing of the detritus pits started before the war; the construction of primary sedimentation channels to treat up to 200 million gallons (909 million litres) per day; sludge digestion plants to treat up to 4,000 tons (4 million kg.) of sludge per day; and a diffused air plant to treat an additional 60 million gallons (273 million litres) of sewage effluent per day. The total cost is estimated to be about £8,465,000. The whole of the sludge produced will be digested, and 2½ million cubic feet (70,000 cubic metres) of methane gas will be available as power for driving the eight 960-horse-power gas turbines to be installed in the power house. By the end of 1957 these works should be operating and the condition of the effluent discharged into the river made satisfactory at all times.

USE OF CORTICOTROPHIN GEL AND CORTISONE IN TREATMENT OF SEVERE AND INTRACTABLE ASTHMA

BY

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In the same year as Hench *et al.* (1949) reported the dramatic effect that cortisone produced in rheumatoid arthritis, Bordley *et al.* (1949) reported the "unequivocal benefit within 4-48 hours" that five chronic asthmatics derived from injections of corticotrophin. Since 1949 there have been many reports from abroad (including Carey *et al.*, 1950; Rose *et al.*, 1951; Schwartz, 1951; Shulman *et al.*, 1951; Baldwin and de Gara, 1952; Arbesman *et al.*, 1952; Baldwin *et al.*, 1955), and a few from this country (Ball, 1954; Savidge and Brockbank, 1954; Pearson, 1955), confirming the striking, though temporary, relief that can be obtained in the large majority of cases of otherwise intractable asthma with short courses of corticotrophin or cortisone.

Gay and Murgatroyd (1954) reported favourably on their results with corticotrophin gel in 76 patients. They gave only one injection a day, and emphasized the value of this therapy in "ambulatory" patients, thus avoiding the cost of hospital admission.

Long-term continuous therapy with these hormones is also being reported, and indications are that continued relief can be obtained (Baldwin *et al.*, 1955).

There are contraindications to the use of these hormones, and some cases of asthma do not respond. Furthermore, the relief produced is only temporary, symptoms recurring soon after the treatment is stopped. It is the main purpose of this article to measure the results of short-term therapy with cortisone, corticotrophin, and hydrocortisone in cases of severe and/or intractable asthma.

Material and Methods

Our observations are based on 63 courses of treatment on 50 adult patients—44 asthmatics (Table I) and 6 chronic bronchitics with persistent wheezing. The six chronic bronchitics were all male, their ages ranging from 37 to 66 years.

TABLE I.—Data on the 44 Asthmatics

	Sex		Present Age		Type of Asthma	
	Male	Female	Under 40 Years	40+ Years	Extrinsic	Intrinsic
No. of cases	12 (27.3%)	32 (72.7%)	9 (20.5%)	35 (79.5%)	2 (4.5%)	42 (95.5%)

The youngest was aged 17, two were over 70.

Twenty of the patients were treated by Dr. Leslie Gay, of the Johns Hopkins Hospital, when he visited Cardiff in June, 1954, bringing with him supplies of corticotrophin gel and hydrocortisone. As requested by Dr. Gay, they were patients whose asthma had been intractable to all previous therapy: 10 were treated as out-patients and 10 as in-patients. The remaining 30 were treated in hospital, and whether corticotrophin or cortisone was used depended mainly on its availability.