TABLE II.—*Clotting-time in Minutes with Continuous Intravenous Infusion of Heparin*

No.	Controls		Hours																	
			1	2	4	6	8	10	12	15	18	21	24	27	30	33	36	39	42	45	48
1	8	8	14	22	22	22½	20	26	18	25	19	27	25	—	26	23	21	20	22	22	28
2	11	12	18	30	21	23	23	22	26	24	23	22	24	—	—	—	21	24	—	—	—
3	11½	11	20	31	35	20	36	20	25	24	22	22	30	29	28	—	—	—	26	30	30
4	7	9	14	19	20	19	22	24	—	—	26	18	23	17	21	23	—	21	25	—	—
5	8	8	12	20	22	24	23	Died													
6	8	9	18	19	24	26	25	25	23	19	26	27	25	23	26	35	16	31	29	19	21

compared with six patients receiving intravenous injections every six hours. Four patients were treated by both methods.

The clotting-time during intravenous infusion was maintained at a therapeutic level during the whole of the administration whereas with the intermittent technique the clotting-time fluctuated from high levels to levels approaching normal. With a standard dose the response was fairly constant from patient to patient, and in ordinary practice frequent measurements of the clotting-time are unnecessary when heparin is given by the continuous technique. This agrees with the findings of Walker (1945).

Some workers have suggested that the initially high clotting-times which result when the intermittent technique is used may be dangerous (Murray, 1947 ; Duff *et al.*, 1951) and Duff *et al.* maintain that, especially in situations where there is a possibility of haemorrhage—for example, from a peptic ulcer—the clotting-time should never exceed three times that of the control. The continuous technique obviates this difficulty.

The avoidance of frequent intravenous injections also facilitates the management of the patient by the house-physician, especially during the night, and the patients themselves are not greatly disturbed by an infusion which requires little attention and which in no way restricts their movement in bed. Furthermore, the method ensures an open intravenous channel for the administration of drugs which may be required in the event of a sudden collapse, when venepuncture may become difficult because of vasospasm. The risk of thrombophlebitis is negligible, thrombophlebitis being a troublesome complication when heparin is administered via a steel needle (Duff *et al.*, 1951). There is no danger of overhydration provided the amount of fluid given is restricted to 1 litre of 5% glucose per 24 hours.

The replacement of a steel needle by a "polythene" cannula has greatly increased the ease and safety of continuous administration of intravenous fluids, including heparin. That this is so makes it possible for one to consider giving heparin continuously for longer periods of time, Engelberg (1959) having suggested that heparin is superior to the oral anticoagulants.

Summary

Continuous and intermittent methods of intravenous administration of heparin were compared in 16 patients with myocardial infarction. The clotting-time in six patients given heparin by six-hourly intravenous injections ranged from normal to over 120 minutes. In another six patients given heparin by continuous intravenous infusion of 40,000 units of heparin per 24 hours the clotting-time was maintained at two to three times the control value. Four patients had experience of both methods. Heparin introduced by continuous infusion gives a more even prolongation of the clotting-time than the intermittent method, and is simpler for the physician and less disturbing to the patient. It is concluded that during the first 48 hours after a myocardial infarction continuous intravenous infusion of heparin is the method of choice and routine measurement of the clotting-time is unnecessary.

I wish to thank Professor E. J. Wayne and Dr. R. Hume for advice and encouragement in the preparation of this paper.

ADDENDUM.—Since this work was completed over 150 cases have been treated by continuous infusion of 40,000 units of heparin per day for two days, no measurement being made of the blood clotting-time. In no case were signs of heparin overdosage or other serious complications found.

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Preliminary Communications

Intrauterine Transfusion of Foetus in Haemolytic Disease

In the management of the pregnancy complicated by rhesus sensitization the guidance given by amniotic-fluid pigmentation (Bevis, 1956 ; Walker, 1957 ; Mackay, 1961 ; Liley, 1961, 1963) has greatly reduced the perinatal mortality from haemolytic disease. In the National Women's Hospital, Auckland, with a policy of selective induction based on amniocentesis findings, this perinatal mortality has fallen steadily from 22% in 1957–8 to 9% in 1962. It was obvious that no further reduction could be expected from conventional treatment when of 7 perinatal deaths in 80 consecutive rhesus-sensitized pregnancies one baby had multiple congenital abnormalities and the other six were all hydropic before 34 weeks' gestation. Transfusion *in utero* appeared the logical procedure for these very severely affected babies early in the third trimester, and intraperitoneal transfusion seemed the simplest technique.

CASE REPORT

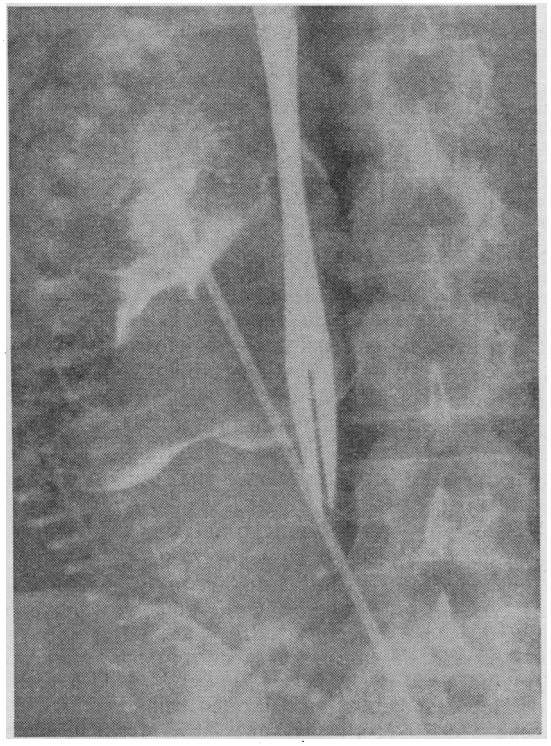
The mother, aged 32, was pregnant for the fourth time. Her first pregnancy was normal, with a surviving 4,090-g. male infant. In her second pregnancy intrauterine death occurred a few days before delivery at term. Antibodies were present at 10 weeks in her third pregnancy and reached a titre of 1:64 by indirect Coombs test at 29 weeks. Mild hypertension had developed and stillborn macerated twins were delivered at 30 weeks. In her fourth pregnancy at 30 weeks by menstrual dates a specimen of bright yellow amniotic fluid was sent by post to this hospital. The spectral absorption curve (Bevis,

1956; Walker, 1957) of this fluid showed a very large peak at 450 mμ, the optical density of the deviation from linearity at this wavelength being 0.536. In view of the hopeless prognosis indicated by this peak (Liley, 1961, 1963) the patient's practitioner transferred her to the care of the professorial unit.

On admission at 30 weeks 3 days by dates she was found to be obese at 91.6 kg. and mildly hypertensive; B.P. 145-155/85-90. The uterus was large for her dates, although there was no reason to challenge the maturity on menstrual history, quickening, or subsequent *x*-ray examination. The patient was group A, ccddee, D^u-negative with Hb 11.8 g./100 ml. An antibody screen confirmed anti-D to a titre of 1:128 with ficin-treated cells and by indirect Coombs test. This antibody level did not alter during the remainder of the pregnancy.

The patient and her husband were an intelligent couple, and the prognosis for the foetus, the possibility and uncertainty of intrauterine transfusion, and the potential hazards to the mother were fully explained to and discussed with them. However, any attempt on the foetus was deferred for 10 days while some weeping abdominal skin ulceration, a reaction to adhesive plaster, was vigorously treated. A glucose-tolerance test and isotopic renogram were normal and the blood-pressure settled to 110-140/70-80 without sedation or strict bed-rest.

At 32 weeks 1 day, under local anaesthesia, 20 ml. of 76% "urografin" was injected into the amniotic cavity and antero-posterior and supine lateral films were taken. These showed a left antero-lateral placenta and the foetus as a vertex R.O.L. with no evidence of hydrops or obvious ascites. Five hours later, with a premedication of 100 mg. of pethidine, 25 mg. of promethazine hydrochloride, and 0.6 mg. of atropine, the patient was returned to the *x*-ray department and a further antero-posterior film taken with paperclips attached with "sellotape" as skin markers. The swallowed contrast medium in the foetal gut defined the target in two dimensions and the previous lateral film indicated the depth. Under local anaesthesia an 8-cm. gauge 16 Tuohy needle was inserted to the amniotic cavity and the stylet withdrawn. A syringe of sterile saline was attached and the needle advanced until resistance to slow steady injection showed that the tip lay in the foetal abdominal wall. With a slight advance free injection was again possible into the foetal peritoneum. No ascitic fluid could be aspirated. A "portex" epidural catheter shortened to 30 cm. was now fed up to the hub of the Tuohy needle and the needle withdrawn on to the mother's skin. The position of the catheter was checked by *x*-ray examination and 100 ml. of packed warmed group O, Rh-negative cells fully compatible with mother's serum was injected over 20 minutes. Antibiotic cover was provided by 1 g. of streptomycin and 1,000,000 units of penicillin injected into the amniotic cavity at amniography, half this dose injected slowly as the catheter was withdrawn through the foetal and maternal tissues, and a four-day course of penicillin and streptomycin given to the mother.



Contrast medium and the coiled catheter in the foetal peritoneal cavity. The Tuohy needle has been withdrawn and lies on the mother's abdominal skin.

Eight days later an attempt to repeat the transfusion failed, since with uterine enlargement and a slight change in foetal position the 8-cm. needle could just reach but not penetrate the abdominal wall. However, two days later—that is, at 33 weeks 4 days by dates—a successful puncture was made easily with an 18-cm. gauge 16 Tuohy needle. An epidural catheter shortened to 45 cm. was fed through this needle. On withdrawal of the needle and injection of 3 ml. of urografin the characteristic biconcave shadows of dye between loops of bowel and crescents of dye under the domes of the diaphragm confirmed the correct placement of the catheter (see Fig.). Over 20 minutes 110 ml. of packed warmed cells was injected. Antibiotic cover was provided as on the previous occasion. The foetal heart gave no concern during either injection, and the mother had no discomfort during or after the procedure.

At 34 weeks 3 days surgical induction by Drew Smythe catheter was performed and a polythene catheter inserted. The cervix was firm and undilated and the foetus was lying obliquely as a breech. Twenty-eight hours later, with no progress and the foetal lie uncorrected after eight hours of oxytocin nasal spray and eight hours of oxytocin drip, caesarean section was performed. At laparotomy the sites of uterine puncture were well healed with no adhesions. A male infant weighing 2,560 g. was delivered. He was pale and slightly jaundiced. The abdomen was moderately distended, with a liver edge palpable 5 cm. below the right costal margin and an easily felt enlarged spleen. Two small pigmented scars in the left lower quadrant of the abdomen showed the puncture sites of the successful transfusions and four smaller scars the pricks of the unsuccessful attempts. The placenta weighed 700 g. and had the pale hyperplastic appearance of severe haemolytic disease. Cord blood showed Hb 8.4 g./100 ml., a strong positive direct Coombs reaction, bilirubin 6.8 mg./100 ml., and 350 nucleated R.B.C./100 W.B.C. Central venous blood at the start of exchange transfusion 48 minutes later had an Hb of 6.2 g./100 ml. Fractionation by the method of Singer, Chernoff, and Singer (1951) showed Hb F 43%, Hb A 57%.

The exchange transfusion of 155 ml./kg., using O, Rh-negative blood, occupied one and one-quarter hours. Shortly after delivery a respiratory distress syndrome of moderate severity appeared, but the baby's breathing improved steadily over the next 20 hours. *X*-ray examination showed no evidence of bowel damage. A tapered course of A.C.T.H. was begun. With a rising serum bilirubin a second exchange transfusion was carried out at 19 hours, using 14 ml. of concentrated serum albumin and 170 ml. of blood/kg. Serum bilirubin averaged 17, 14, 12, and 11 mg./100 ml over the next four days. Apart from being slow to feed and to regain his birth weight, the baby has given no further concern to the age of 4 weeks.

COMMENT

It could be asked whether this baby might have survived without foetal transfusion. Although the previous obstetric history is strongly suggestive of progressive haemolytic disease there were no haemotological or post-mortem examinations of these stillborn infants. Moreover, a mildly affected infant is always a possibility even after stillbirth early in the third trimester. However, the size of the pigment peak in the amniotic fluid leaves little room for doubt that this foetus was very severely affected. In our experience a peak of this size has been accompanied invariably by a foetus dead or hydropic before 34 weeks' gestation and usually before 33 weeks. Further, the high

fraction of Hb A in the baby at delivery at 34½ weeks suggests that roughly half the circulating blood was donor blood, for the normal proportions of Hb F and Hb A are not altered by haemolytic disease (Ponder and Levine, 1949).

This case is the fourth pregnancy on which this procedure has been performed. In the first two the foetus was already hydropic and death occurred within 24 hours of the transfusion. In the third case two transfusions were performed by the described technique at 31 and 33 weeks. Death occurred within a few hours of the second transfusion, and a mildly hydropic foetus was delivered.

It is apparent that timely discovery and selection of these cases is critical, and only amniotic-fluid analysis can provide the necessary precision. Amniography can exclude gross ascites, and the persistence of swallowed dye in the foetal gut provides a convenient permanent marker which enables solid viscera to be avoided. There was no sign of trauma to abdominal viscera at post-mortem examination on the first three babies. In the absence of ascites the detection by needle of planes free from resistance to injection of saline has proved a simple method of locating the peritoneal cavity. The prompt introduction of a catheter with generous slack and withdrawal of the needle removes any risk of trauma from foetal or maternal movement or Braxton Hicks contractions.

Reports on intraperitoneal transfusions in neonates and infants (Macdougall, 1958 ; Mollison, 1961 ; Scopes, 1963) suggest that both the rate of absorption and total proportion absorbed into the circulation are not entirely predictable. In foetal transfusion further uncertainty is added by a lack of knowledge of the combined blood volume of the foetus and placenta, and the possibility of some leakage from the puncture site on withdrawal of the catheter. For these reasons it cannot be expected that the procedure will restore the foetus to normal. The aim of the exercise is simply to arrest deterioration if possible and gain a few extra weeks of gestation so that the skilled paediatric care of severe haemolytic disease is not nullified by gross prematurity.

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Medical Memoranda

Oral Neomycin : A Possible Anaesthetic Hazard

Neomycin, given orally, quickly inhibits the coliform inhabitants of the intestine ; 97% of the drug escapes unabsorbed via the faeces and the remaining 3% is rapidly excreted in an active form by normal kidneys (Poth *et al.*, 1950). Parenteral therapy produces a high blood level, two main toxic effects of which are renal and eighth-nerve damage ; therefore neomycin is generally used topically or orally (Waisbren and Spink, 1950).

CURARE-LIKE ACTION OF NEOMYCIN

Another dangerous side-effect of neomycin became known when Pridgen (1956) reported four cases of respiratory arrest after instillation of neomycin into the peritoneal cavity. This effect was confirmed by numerous reports, which have been included in two recent reviews (Bodley and Brett, 1962 ; Emery, 1963).

The effect of neomycin upon respiratory function has been the subject of several studies. Short *et al.* (1959) carried out animal experiments and concluded that respiratory depression originated from neuromuscular blockade and not a central mechanism. Corrado and Ramos (1958) demonstrated, in animal experiments, evidence of neuromuscular block with intravenous neomycin and antagonism to this block by calcium and neostigmine. Pittinger and Long (1958) added that the block is potentiated by ether, and Corrado *et al.* (1959) reported, from animal experiments, that intraperitoneal neomycin causes neuromuscular block. They noted marked synergism with sodium citrate, ether, and curare, and found calcium to be a better antagonist than neostigmine.

Suggested precautions when using neomycin include the following. (1) Observe a maximum dose: 0.5 g. (Hoffman, 1960) to 1 g. (Mann and Levin, 1960). (2) Irrigate the peritoneal cavity with 0.5% solution of neomycin, or 0.25% in the presence of active peritonitis, leaving little or none in the peritoneal cavity (Poth, 1960). (3) Avoid using neomycin until the effects of anaesthetic agents have worn off (Kownacki and Serlin, 1960).

RENAL FUNCTION

Serum neomycin levels are determined not only by the amount available and the rate of absorption but also by the rate of excretion. Last and Sherlock (1960) administered oral neomycin to 27 patients with acute and chronic hepatic insufficiency in doses rarely exceeding 4 g. daily. Circulating neomycin was found in seven patients. Development of blood neomycin levels was related to the development of oliguria. In one case, without oliguria, absorption was sufficient to cause permanent deafness. Kunin *et al.* (1960) noted that oral neomycin in patients with azotaemia produced progressively elevated serum levels. In patients with cirrhosis of the liver and azotaemia the serum levels were generally higher than in those without renal failure, and in some cases were comparable to those seen in normal persons after parenteral therapy.

A search of the literature has failed to reveal any published case of neomycin-induced respiratory arrest resulting from oral administration. However, it seems possible that a patient with impaired renal function taking neomycin by mouth might have enough neomycin circulating to produce neuromuscular block and consequent respiratory insufficiency if subjected to anaesthesia in which drugs known to potentiate neomycin were used.

CASE REPORT

A man aged 70 was admitted to hospital in 1962 with a history of passing bright-red blood per rectum four days