Discussion

Radioimmunoassay has provided a safe, quick, sensitive clinical estimate of plasma digoxin levels in adults (Smith, Butler, and Haber, 1969; Chamberlain *et al.*, 1970) and in children (Coltart, Cree, and Howard, 1972). Therapeutic plasma levels are between 1 and 2 ng/ml. However, these levels are estimated at least 6 hours after administration of the drug when full equilibration has taken place between tissue stores and plasma. The pharmacodynamics of digoxin in children have been previously described by Hernandez and his colleagues (1969) using tritiated digoxin. The high plasma levels obtained in this study are due, at least in part, to the fact that the samples were taken before full equilibration had taken place.

Though between 220 and 440 ml of blood were exchanged, when digoxin concentrations were between 1·3 ng/ml and 12 ng/ml, the digoxin levels were maintained, presumably by re-equilibration of the plasma with the large tissue stores of the drug. A similar situation has been found in adult patients undergoing cardiopulmonary bypass (Coltart *et al.*, 1971), in which procedure the plasma is heavily diluted by the volume of blood priming the bypass machine. However, though no digoxin is administered on the day after surgery, these patients have a digoxin concentration identical with the preoperative figure. Thus in both exchange transfusion and cardiopulmonary bypass, the large tissue stores of digoxin not only limit any tendency for an acute fall in plasma concentration, but also allow a restoration of plasma level as re-equilibration occurs.

Electrocardiographic changes during digoxin therapy in neonates in heart failure have been described (Levine and Blumenthal, 1962). Significant cardiographic changes including arrhythmias have been noted during exchange transfusions (Van Praagh, 1961). Monitoring was used during all exchanges in this study and no significant changes were seen.

Summary

A sensitive method for assaying plasma digoxin has made it possible to assess the effect of exchange transfusion on plasma digoxin levels and to quantitate the amount removed during an exchange. Plasma digoxin levels before and after exchange were similar. It therefore seems unnecessary to revise dosage schedules when digoxin therapy is to be used during an exchange transfusion.

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Automated Method for Exchange Transfusion

Despite prophylactic measures against isoimmunization, haemolytic disease of the newborn remains a common problem, and many exchange transfusions still have to be undertaken in special baby units. A number have to be done also for hyperbilirubinaemia. Orthodox procedures continue to be laborious, time consuming, and occasionally hazardous.

The method of Ata and Holman (1966) has the great asset of providing continuous flow in by the umbilical vein at a rate to match that dripping out from one umbilical artery. This completely obviates the relatively large blood volume changes necessarily produced by other methods, which is probably one of the most dangerous factors in exchange transfusions, and is one reason for them having to be so time consuming. Everyone experienced in this work knows the discomfort and

apparent pain caused by the pumping of the blood into the baby even extremely slowly, and extrasystoles are common during this phase of the procedure. The continuous flow method is less laborious and has the great advantage of completely eliminating changes in volume, and also about 2 ml of dead space at each pumping action.

We have used the Ata and Holman method with considerable success, but found it open to improvement in needing some method of controlling and matching output and input flow rates automatically. A technique by which this can be achieved is now presented.

Method

The technique is dependent upon using a two-channel blood impeller, and the machine found most suitable for the purpose is the Holter Infusion pump, Model 912. Using the widest bore pump chambers available, the throughput rate per channel can be varied between about 100 ml and 650 ml per hour. The pump chambers are matched and the manufacturers' claim of a maximum variation of $\pm 3\%$ between the channels has been confirmed; this is perfectly acceptable for the purpose.

The umbilical vein and one artery are catheterized as in the Ata and Holman method. The technique of artery catheterization requires practice, but, with patience, can soon be mastered. Dilating the artery with a silver probe before trying to insert the catheter has been found to facilitate matters, and its importance cannot be overstressed. Even so, arterial spasm, particularly in very young babies (first 24 hours), can cause difficulty. Once blood starts spurting from the artery after withdrawal of the probe, the insertion of the catheter usually presents no difficulties. (The spurting can be easily controlled by kinking the artery and this is important at the time of insertion of the catheter.)

Before undertaking the catheterizations, the impeller is made ready and primed. A 100 ml burette type infusion set is attached to the bottle or bag of donor blood, which is then suspended. This is then connected by a special female Luer connector to one pump chamber tube and to a male fitting at the other end, any extension tubing bearing male and female Luer ends (such as manometer tubing) is attached. The latter is for connecting to the venous catheter. This channel is then primed with blood and inserted into the impeller and constitutes the input line. The output line consists of two similar extension tubes, one at each end of the second pump chamber tube, one for connecting to the arterial catheter, and the other going to waste into a 100 ml measuring cylinder.

Originally we primed the output line with heparinized saline and had a two-way tap at the junction between the arterial catheter and the connecting tube so that heparinized saline could be injected into the line from time to time to prevent clotting. This was found to be unsatisfactory and heparinization of the baby (see below) was found to be completely effective and perfectly safe. The output line, therefore, may be inserted into the impeller without priming of any kind.

The impeller is then allowed to run for a few seconds to ensure that all is in working order, and that all air has been expelled from the input line. The artery and vein are then catheterized, and heparin in saline is injected through the venous catheter. We have found an effective and safe dose of heparin to be 100 units per kg body weight in 2 ml saline. This is repeated after each 200 ml of the transfusion, at which time routine calcium gluconate is injected (10%, 2 ml), the same also being given at the end of the transfusion. The connecting tubes are now attached to the catheters and all is ready. We have found it useful to place a two-way cock between the vein catheter and the connecting tube going to it. This can be used for the heparin and calcium gluconate injections. The impeller is switched on and allowed to run at a suitable speed.

Although theoretically the whole exchange could be made continuously, it is found convenient to stop temporarily after each 100 ml so that the volumes of input and output can be matched and recorded, the burette filled, and the waste cyclinder emptied, and checks made all round for leaks. Obviously the whole apparatus must be watched throughout for any indications of discontinuity of the process. The baby too should be monitored throughout the procedure. Larger babies can well tolerate a rate of 400 ml per hour, or even more (the maximum of which the impeller is capable being about 650 ml per hour). Smaller babies may show the usual signs of distress at such a flow rate, and 200 ml per hour is more suitable. For very small and ill babies a rate of less than 200 ml per hour may have to be used.

The traditional total volume of twice the baby's calculated blood volume is usually exchanged, but this can be increased or decreased according to the indications in the individual case.

At the end of the procedure the catheters are extracted and the umbilical stump is sutured in the usual way. Any spurting of blood from the artery is readily controlled by pressure and kinking the stump.

Equipment. The essentials for this method (see Fig.) are: (1) Holter Infusion Pump No. 912; (2) 1 pair largest size pump chambers ('natural') for above; (3) 2 pairs connectors (2 male and 2 female) for pump chambers; (4) 1 silver probe (medium size); (5) 1 two-way cock; (6) 1 standard umbilical vein catheter (Portex FG6 or FG9, or equivalents); (7) 1 infant feed catheter (Meredith 5. Ch or 3. Ch or equivalents) for umbilical artery; (8) 3 connecting tubes (e.g. Portex manometer tubes, or Baxter anaesthetic extension sets); (9) 1 infusion set, with 100 ml burette; (10) 1 infant 'cut-down' set; and (11) 1 100 ml measuring cyclinder.

Items (2), (3), (4), and (5) are autoclaved together as a special pack by the Central Sterile Supply Department, as is item (10). Items (6), (7), (8), and (9) are disposable and are supplied presterilized in individual packs by the manufacturers.

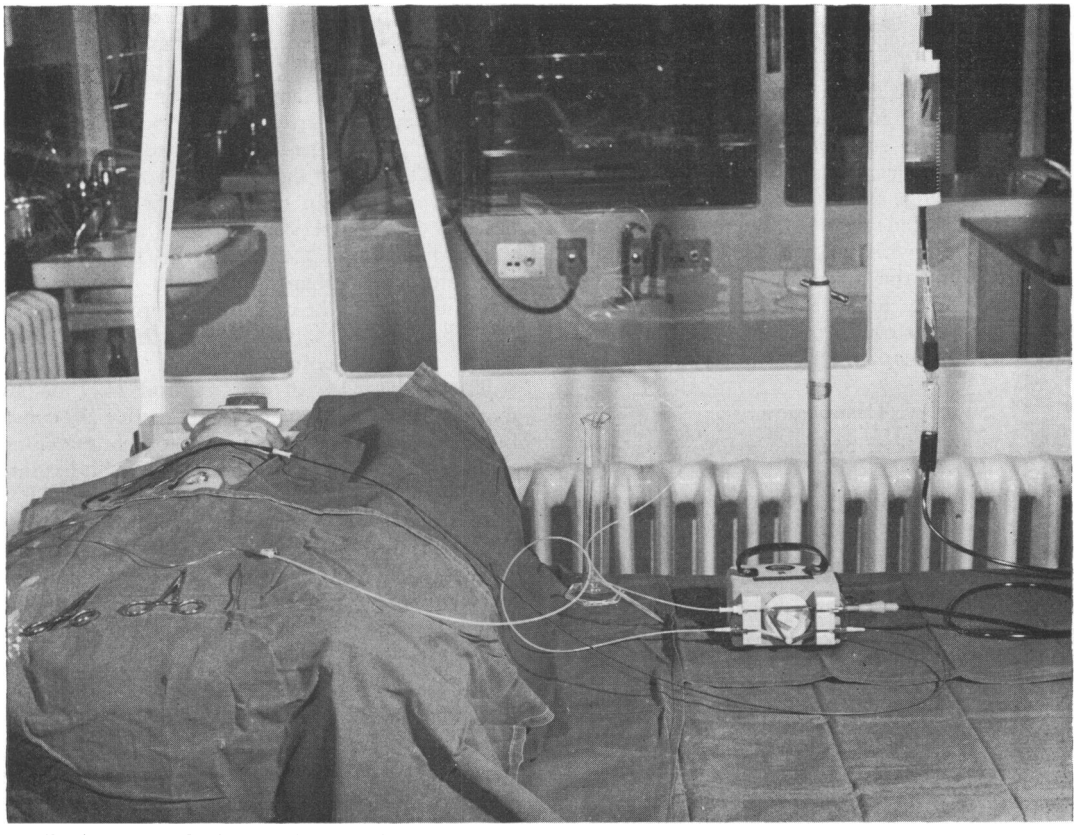

FIG.—*Equipment ready for starting transfusion. For demonstration, the catheters have not been inserted. The lines have been loaded into the Holter pump.*

Summary of procedure. (1) Make input line ready, and prime with blood; (2) make output line ready; (3) insert lines into impeller and allow to run for a few seconds; (4) cut off cord stump, insert vein catheter, and inject first dose of heparin; (5) dilate artery and insert catheter; (6) connect catheters to respective connecting tubes; and (7) switch on impeller.

Results

To date we have done 34 transfusions in 23 babies (19 babies with haemolytic disease of the newborn, and 4 with hyperbilirubinaemia). There have been 2 deaths, both in the early stages of development of the procedure when we were using the impeller at a fast rate. At necropsy the babies were shown to have contributory disease which had been unsuspected (a large atrial septal defect in the first and neonatal pneumonia in the second). Some difficulty was encountered in 2 other babies, both prematures with hyperbilirubinaemia and some degree of respiratory distress. In one the transfusion was abandoned after an exchange of 290 ml in 125 minutes on account of extreme tachycardia. The other baby had respiratory arrest after 300 ml had been exchanged in 80 minutes, but was easily resuscitated; the transfusion was abandoned. Both of these babies were transfused in incubators with oxygen, but probably at too fast a rate. Apart from these 2 cases, and the 2 early catastrophes, the babies have tolerated the procedure well and have shown far less disturbance than with orthodox methods. Most of the babies have been completely undisturbed and have usually slept peacefully throughout. The weight range of our cases has been 1·5 to 3·7 kg and the age range 3 hours to 6 days. Occasionally it has been impossible to catheterize one artery, but in only 2 cases has it been impossible to introduce the arterial catheter; in one neither artery could be identified and in the other there was only one very tortuous umbilical artery Arterial spasm is frequently a problem in babies

under 12 hours old. In 8 babies the method has been used more than once; twice in 6, and 3 and 4 times in one each. It has been found usually that once used an artery cannot be used a second time, for it tends to retract and cannot be found again, but this is not always so and we have used the same artery twice on 5 occasions (including the baby who needed 4 exchange transfusions and in whom both arteries were used twice). There appear to be risks associated with leaving the arterial catheter *in situ* to allow the artery to be used again (see discussion). We have experienced no risk of haemorrhage whatever from the umbilical vessels, with or without heparinization of the baby.

Discussion

The method described appears to be a logical development.

The 2 deaths doubtless were caused, in part at least, by the transfusions being undertaken too fast, though we have done transfusions as fast as 500 ml in 45 minutes without any upset whatever. Though there are no volume changes in this method, rapid absorption of blood diluent by the tissues might theoretically be a danger if the transfusion is made too quickly. We use quarter or half packed blood, and there may be advantages in using fully packed blood.

A continuous flow of cool blood to the heart could well be injurious and contribute to sudden cardiac arrest, especially in diseased infants such as our 2 deaths. Some warming of the blood is probably a wise precaution, but we have not gone to the extreme of passing the blood through a thermostatically controlled coil. So long as the transfusions are not undertaken too fast, and the blood is allowed to come up to room temperature before use there appears to be no danger.

Another advantage, albeit theoretical, in undertaking the transfusion slowly is to allow more time for diffusion of bilirubin from the tissues, thereby making the procedure more effective. We have done too few bilirubin estimations on the waste blood from exchanges done at different rates to prove this point, but our few figures do suggest that this is more than a theoretical advantage in undertaking the procedure as slowly as possible. It has been found in our series also that the more thorough the exchange, the less likely is the need for subsequent topping up transfusions, though the statistics are too scant to prove the point.

The 2 babies with hyperbilirubinaemia who caused concern during transfusion show the necessity for very slow exchanges in ill and premature infants. Any problem baby should be transfused in an incubator with oxygen and in all other cases we use an Air Shields infant-warmer to prevent chilling of the baby.

None of the problems occurring with catheterization of umbilical arteries described by Egan and Eitzman (1971) has been encountered. It is probable that most dangers result from leaving the catheter *in situ*. In one case in which we left the catheter in the artery anticipating a need to repeat the process, after 24 hours the baby developed circulatory disturbances in both legs, including some oedema. The catheter was promptly removed and the signs resolved within the following 24 hours, with no sequelae.

The advantages of the method may be summarized as follows. (1) Maintenance of constant blood volume in the baby, and accurate matching of the input and output volumes; (2) elimination of dead space blood shunt; (3) automation, allowing time for other duties and thus saving medical man-hours; (4) ability to make full exchanges in very ill and/or premature babies; (5) elimination of a manually tiring and boring procedure; and thus (6) ability to exchange larger volumes than used traditionally.

Summary

A method for exchange transfusions is described being based on the method of Ata and Holman utilizing both umbilical artery and vein, and refined by the use of a two-channel blood impeller. The technique is simple and safe, eliminating most of the difficulties and dangers of older methods, and provides several major advantages. It is time saving for medical and nursing staffs and is far less laborious.

We thank Dr. R. J. Pugh for allowing us to use our method on babies admitted under his care, and Dr. A. G. Hocken for technical advice.

The purchase of equipment became possible primarily because of a bequest by Miss Veronica French, a member of our nursing staff who was dedicated to her work on the Special Baby Unit; she insisted that her savings be used for obtaining equipment for the Unit. We wish to thank the Hull and Humberside Ladies Circle who made additional monies available to us.

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Automated method for exchange transfusion.

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Notes