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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REFERENCES

Bevis, D. C. A. (1956). *J. Obstet. Gynaec. Brit. Emp.*, **63**, 68.
Liley, A. W. (1961). *Amer. J. Obstet. Gynec.*, **82**, 1359.
—— (1963). Ibid., **86**, 485.
Macdougall, L. G. (1958). *Brit. med. J.*, **1**, 139.
Mackay, E. V. (1961). *Aust. N.Z. J. Obstet. Gynaec.*, **1**, 78.
Mollison, P. L. (1961). *Blood Transfusion in Clinical Medicine*, 3rd ed. Blackwell, Oxford.
Ponder, E., and Levine, P. (1949). *Blood*, **4**, 1264.
Scopes, J. W. (1963). *Lancet*, **1**, 1027.
Singer, K., Chernoff, A. I., and Singer, L. (1951). *Blood*, **6**, 413.
Walker, A. H. C. (1957). *Brit. med. J.*, **2**, 376.

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

previously. He had been investigated for urinary symptoms; ureteric calculi were discovered in 1932 and also a large stag-horn calculus of the left renal pelvis in 1959, when his blood urea was 64 mg./100 ml.

Clinical examination in 1962 showed little of note except anaemia. Haemoglobin was 50%. A barium enema demonstrated diverticulosis, but sigmoidoscopy revealed no cause for the bleeding. Serum calcium was 3.9 mEq/l. and serum inorganic phosphate 2.5 mg./100 ml. The Sulkowitch test was negative. Bleeding continued from the bowel, requiring transfusion. Five bottles of blood were given over the nine days before operation. Laparotomy with a view to partial colectomy was decided upon and oral neomycin was started, a total of 6 g. being given over the 16 hours prior to operation.

Operation.—After atropine 0.65 mg. (1/100 gr.) anaesthesia was induced with nitrous oxide, oxygen, and halothane, the trachea intubated with a cuffed tube, and the halothane discontinued. Relaxation was achieved with minimal amounts of gallamine—80 mg. initially and 100 mg. in divided doses over two and a half hours, each dose being prompted by signs of returning respiration. Intermittent positive pressure ventilation was performed with a 25% mixture of O_2 in N_2O, using a mechanical ventilator with a circle absorber in a semiclosed circuit. Two bottles of blood were given and the patient's condition throughout was satisfactory. Partial colectomy was performed, and towards the end of the operation two long "bursts" of "polybactrin" were made into the peritoneal cavity.

Atropine 1.3 mg. (1/50 gr.) and neostigmine 2.5 mg. were given intravenously at the end of the operation, but the patient failed to breathe adequately. Artificial ventilation was reinstituted. A further 1 mg. of neostigmine had no effect. Electromyography confirmed the presence of a typical curare-like block as described by Churchill-Davidson and Christie (1959). Serum electrolytes were: sodium 162 mEq/l.; chloride 109 mEq/l.; potassium 4.6 mEq/l.; blood urea 90 mg./100 ml. Two hours later a further 1.3 mg. of atropine and 2.5 mg. of neostigmine were given and there followed an improvement in the electromyographic tracing. Respiratory efforts were being made and the ventilation was discontinued. Soon afterwards the clinical picture deteriorated, respiration became inadequate, and electromyography showed reversion to a more complete curare-like block. At this time P_{CO_2} was 91, *p*H 7.064, and standard bicarbonate 26.5 mEq/l. Sodium bicarbonate 100 mEq was given and the ventilation continued. Two hours later P_{CO_2} was 71 and *p*H 7.21. A further 200 mEq of sodium bicarbonate was given, and about one hour later—that is, some six hours after operation—the patient was able to maintain adequate spontaneous respiration.

COMMENT

A curare-like block was confirmed by electromyography. The only agents used known to produce this block were gallamine and neomycin. Gallamine was given in small doses, as the anaesthetist realized that renal function was impaired and gallamine is eliminated via the kidneys (Wylie and Churchill-Davidson, 1960). It should be emphasized that the increments of gallamine, after the first 80 mg., were given only when signs of returning respiration were evident. It seems unlikely, therefore, that the prolonged respiratory insufficiency was entirely due to gallamine. However, the persistence of any form of curare-like block is not easy to explain. Churchill-Davidson (1963) states: "Neostigmine-resistant curarization still remains a mystery, for to date there is no authenticated case in the literature demonstrating, first, that neuromuscular block was present and, secondly, that neostigmine had failed to improve neuromuscular transmission. The matter must await further investigation."

In the above case neuromuscular block of a curare-like nature persisted after the administration of neostigmine, and further doses produced only a transient change in the electromyographic picture. In animal experiments, neomycin-induced block is usually reversed by neostigmine, but this has not always been so in reported cases (Emery, 1963). Consideration, in retrospect, suggests that the following features were significant: (1) neomycin was administered orally in the presence of renal impairment; (2) neomycin, probably less than 150 mg., was introduced into the peritoneal cavity; (3) prior to operation serum calcium was 3.9 mEq/l. (normal range, 4.7 to 5.3); and (4) gallamine, a non-depolarizing muscle relaxant, was used.

All reported cases of respiratory insufficiency following intraperitoneal neomycin in adults have resulted from doses between 1 and 10 g. Bush (1962) reported a case in which apnoea resulted from the use of about 165 mg. of neomycin from a polybactrin spray in a young baby, but it seems unlikely that such a dose, by itself, could produce apnoea in an adult.

Prevention and Treatment.—(1) Renal function should be estimated. (2) Neomycin, orally or otherwise, should be kept to a minimum. (3) Choice of anaesthetic technique should be made in the light of possible potentiation by ether and the non-depolarizing relaxants. If respiratory insufficiency occurs electromyography is useful in determining the cause. Artificial ventilation should be maintained until adequate spontaneous respiration returns. Atropine 0.65 to 1.35 mg. followed by neostigmine 1 to 2.5 mg. should be given, and can be repeated later, but with due consideration of the possible dangers of these drugs. Intravenous calcium gluconate up to 1 g. is recommended. Estimations of electrolytes, *p*H, and P_{CO_2} should be made. Respiratory insufficiency is not likely to be detrimental if adequate ventilation is provided and the circulatory status of the patient is maintained.

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REFERENCES

Bodley, P. O., and Brett, J. E. (1962). *Anaesthesia*, **17**, 438.
Bush, G. H. (1962). *Brit. med. J.*, **2**, 1062.
Churchill-Davidson, H. C. (1963). In *Recent Advances in Anaesthesia and Analgesia*, edited by C. Langton Hewer, p. 98. Churchill, London.
—— and Christie, T. H. (1959). *Brit. J. Anaesth.*, **31**, 290.
Corrado, A. P., and Ramos, A. O. (1958). *Rev. bras. Biol.*, **18**, 81.
—— —— De Escobar, C. T. (1959). *Arch. int. Pharmacodyn.*, **121**, 380.
Emery, E. R. J. (1963). *Anaesthesia*, **18**, 57.
Hoffman, E. (1960). *Amer. Surg.*, **25**, 170.
Kownacki, V. P., and Serlin, O. (1960). *Arch. Surg.*, **81**, 838.
Kunin, C. M., Chalmers, T. C., Leevy, C. M., Sebastyen, S. C., Lieber, C. S., and Finland, M. (1960). *New Engl. J. Med.*, **262**, 380.
Last, P. M., and Sherlock, S. (1960). Ibid., **262**, 385.
Mann, L. S., and Levin, M. J. (1960). *Arch. Surg.*, **81**, 690.
Pittinger, C. B., and Long, J. P. (1958). *Antibiot. and Chemother.*, **8**, 198.
Poth, E. J. (1960). *Surgery*, **47**, 1018.
—— Fromm, S. M., Wise, R. I., and Chinn Min Hsiang (1950). *Tex. Rep. Biol. Med.*, **8**, 353.
Pridgen, J. E. (1956). *Surgery*, **40**, 571.
Short, W. B., Hartley, J. L., and Martin, J. D., jun. (1959). *J. med. Ass. Ga*, **48**, 453.
Waisbren, B. A., and Spink, W. W. (1950). *Ann. intern. Med.*, **33**, 1099.
Wylie, W. D., and Churchill-Davidson, H. C. (1960). *A Practice of Anaesthesia*, pp. 598 and 288. Lloyd-Luke, London.