these alternatives, but it makes clear that in one way or another nicotine stimulates the atria by liberating noradrenaline and adrenaline, since the stimulant action disappears when the rabbit is treated with reserpine and these amines are no longer there.

The presence of noradrenaline and adrenaline in the atria has been known for some time, but, so far as we are aware, there has been no previous evidence suggesting that they play a part in cardiac contraction. Not only is the action of nicotine due to release of these amines, but the spontaneous rate of the isolated atria is modified by them, for in their absence the mean rate was found to fall from 146 to 112.

FIG. 2.—Contractions of isolated atria from rabbit treated with reserpine. All observations were made in the presence of atropine. *a* and *c* show that nicotine failed to cause stimulation when 1.6 mg. and 3.2 mg. nicotine acid tartrate were injected. *b* Shows that 50 µg. histamine caused the usual stimulation.

Our evidence has a clear bearing on the question whether a patient who has some cardiac abnormality should smoke. Many doctors, even those who are cardiologists, have been reluctant to tell a patient suffering from cardiac arrhythmias or another disorder that he must not smoke. This reluctance has been due to lack of definite evidence that smoking may do harm. Previous work (Burn, 1951) showed that during smoking the antidiuretic hormone is released from the pituitary posterior lobe, and, since this hormone constricts the coronary vessels, smoking can diminish the coronary blood flow. The present work shows that smoking may liberate noradrenaline and adrenaline from stores within the heart so that they produce acceleration and may cause or exaggerate ventricular arrhythmias.

Summary

Nicotine not only has an inhibitory action on the rate of the isolated heart (as would be expected, since it is a ganglionic stimulant) but it also has a stimulant action which is readily seen when the atria are dissected from other tissue and suspended in a bath which contains atropine to exclude the inhibition.

This stimulant action is shown to be due to nicotine releasing noradrenaline and adrenaline from stores within the heart. These stores can be depleted by giving the rabbit reserpine, and the atria of hearts depleted in this way are not stimulated by nicotine.

The stores of noradrenaline and adrenaline in the heart normally exert some effect and accelerate the spontaneous rate. The mean rate of isolated atria from control animals was 142 per minute, while the mean rate of atria from animals treated with reserpine was 112. The effect of smoking on the heart is discussed.

REFERENCES

- Bertler, A., Carlsson, A., and Rosengren, E. (1956). *Naturwissenschaften*, 43, 521.
 Burn, J. H. (1951). *Brit. med. J.*, 2, 199.
 Cannon, W. B., and Lissák, K. (1939). *Amer. J. Physiol.*, 125, 765.
 von Euler, U. S. (1946). *J. Physiol. (Lond.)*, 105, 38.
 Goodall, McC. (1951). *Acta physiol. scand.*, 24, Suppl. 85.
 Kottegoda, S. R. (1953). *Brit. J. Pharmacol.*, 8, 83.
 McEwen, L. M. (1956). *J. Physiol. (Lond.)*, 131, 678.
 Raab, W. (1943). *Exp. Med. Surg.*, 1, 188.
 Shaw, F. H. (1938). *Biochem. J.*, 32, 19.

INTRAPERITONEAL BLOOD TRANSFUSIONS IN CHILDREN

BY

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The use of the intraperitoneal route for giving blood transfusions is usually mentioned only to be condemned, and most modern textbooks, while describing the technique of intravenous, bone-marrow, and corpus cavernosum transfusions, fail to mention the intraperitoneal route at all. However, the introduction of sterile citrated blood into a healthy peritoneal cavity has been found by previous workers to be of distinct value in raising the haemoglobin and red-cell content of the circulating blood (Siperstein and Sansby, 1923; Cole and Montgomery, 1929; Courtice *et al.*, 1953).

The major advantage of such a transfusion is the ease of administration, a point of considerable importance when dealing with infants and young children. In countries where medical services are as yet incomplete high standards are often impossible, and without skilled medical and nursing supervision intravenous transfusions in infants can be fatal rather than life-saving procedures, overloading of the circulation being the rule rather than the exception.

In an effort to prevent such tragedies with saline infusions, the intraperitoneal route was adopted in the children's wards of King George VI Hospital, Nairobi, three years ago with considerable success (Carter, 1953).

The work of Courtice *et al.* (1953) in investigating the rate of absorption of blood from the peritoneal cavity of cats leaves no doubt whatever that such blood is absorbed intact and constitutes a true transfusion. Earlier workers (Florey and Witts, 1928; Hahn *et al.*, 1944) demonstrated that blood from the peritoneal cavity was absorbed into the thoracic duct, but Courtice *et al.* (1953) have since proved by the simultaneous introduction of cannulae into the thoracic and right lymphatic ducts that there is a greater concentration of absorbed blood in the latter.

A more rapid rate of peritoneal absorption could be obtained by increasing the rate of diaphragmatic movement with the inhalation of 5% carbon dioxide in oxygen (Courtice *et al.*, 1953; Morris, 1953). It was also demonstrated by Courtice and Steinbeck (1951) that the rate of absorption was increased if the pelvis was raised, but that even if the pelvis was in the lowered position injected material was still drawn towards the diaphragm against gravity. These results confirm the earlier investigation of Siperstein and Sansby (1923). It is essential that the same precautions regarding grouping and cross-matching be undertaken as in the case of intravenous transfusions (Wiener, 1943a).

Clinical Trials in the Literature

Following his experimental work on animals, Siperstein (1923) undertook a clinical trial involving five cases. Results were considered favourable in three, one patient died, and one required repeated intraperitoneal and intravenous transfusions before showing improvement. In a further series of four cases (Sansby and Siperstein, 1923) good results were obtained in three.

Cole and Montgomery (1929) reported a series of 237 intraperitoneal blood transfusions in 117 cases. A more recent report by Waite *et al.* (1956) comments on the value of intraperitoneal blood transfusions in the treatment of a case of thalassaemia where multiple transfusions were required and the technique of intravenous transfusion was becoming increasingly difficult.

Mengert *et al.* (1951) reported a series of 19 cases in which blood, saline, plasma, and washed red cells were introduced into the peritoneal cavity of women to undergo laparotomy.

Present Trial

In this series 23 anaemic children, aged from 1 month to 4 years, were selected for intraperitoneal transfusions of whole citrated blood. The causes of the anaemic conditions were: nutritional anaemia in 2 cases, nutritional anaemia with superadded infection in 6, chronic infection in 2, sickle-cell anaemia in 2, sickle-cell anaemia with acute superadded infection in 5, malaria in 5, and ankylostomiasis in 1.

The blood of the donor and that of the recipient were grouped and cross-matched for compatibility in all cases. The standard M.R.C.-type bottle and giving-set were used with a short-bevelled wide bore needle. Preliminary sedation was not given as a routine as many of the children were moribund and collapsed at the time of transfusion. In less severe cases where the child was apprehensive or irritable, chloral hydrate in doses appropriate to body weight was given one hour before transfusion.

The method used was that described by Carter (1953) in which the injection was made 1 in. (2.5 cm.) above the umbilicus after careful cleansing of the abdominal skin. To control the depth of penetration of the needle the skin was grasped between thumb and forefinger of the left hand and traction exerted on it while the needle was pushed slowly and firmly into the peritoneal cavity with the right hand. Immediately the needle had penetrated the skin the control clip on the giving-set was opened fully and the blood (previously warmed) allowed to run in a steady stream. In all cases the transfusion was completed within 10-20 minutes. The amount of blood transfused at any one time varied from 60 to 300 ml., the average being approximately 23 ml. per kg. body weight—slightly more than the recommended intravenous amount of 15-20 ml. per kg. (Wiener, 1943b). At the completion of the transfusion the foot of the child's cot was raised on blocks to encourage drainage of the blood towards the diaphragm. Breast-fed babies were lifted for feeding and returned to this position.

The haemoglobin (Sahli) was estimated immediately before transfusion in all cases except four in which it was estimated the day before. Wherever possible it was checked again 24 hours later and thereafter at intervals of one to three days. Owing to constant pressure on beds it was impossible to keep these children in hospital until the haemoglobin had reached the 100% (14.8 g./100 ml.) level. The majority were discharged with a haemoglobin of 10.4-11.8 g./100 ml. and continued with oral iron as out-patients.

Results

Of the 23 cases under observation, 14 survived. The accompanying Table gives an outline of the response obtained in the 11 cases in which uninterrupted improvement occurred. As can be seen, the rate of haemoglobin response varied considerably irrespective of the amount of

Response to Treatment in 11 Cases

Case No.	Cause of Anaemia	Age in Years	Initial Hb. (g./100 ml.)	Total Amount of Blood Given (ml.)	No. of Transfusions	Total Rise in Hb. (g./100 ml.)	No. of Days
1	Nutritional anaemia; pneumonia	1½	4.14	540	2	5.33	12
3	Nutritional anaemia; salmonellosis	8/12	3.11	270	1	7.25	20
6	Subtertian malaria	7/12	3.11	270	1	7.25	7
9	" "	4/12	5.77	120	1	6.07	2
11	" "	9/12	8.14	150	1	3.11	6
14	Nutritional anaemia; pneumonia; bac. dysentery	10/12	6.22	140	1	5.62	7
16	Nutritional anaemia; pneumonia	6/12	7.40	180	2	3.70	13
17	Subtertian malaria	9/12	6.66	100	1	5.70	6
20	Ankylostomiasis*	4	2.66	410	3	9.18	24
22	Sickle-cell anaemia	1	6.36	150	1	2.23	15
23	Nutritional anaemia†	1	5.48	120	1	5.18	7

* T. 100° F. (37.8° C.) each evening after transfusion. Abdominal discomfort after each transfusion. Vomited after first two transfusions.

† Small vomit at completion of transfusion.

blood given. Eight cases showed a steady rise in haemoglobin after a single transfusion, and there was no significantly better response in the three who received more than one transfusion. In all cases a rise in haemoglobin was obtained within 24 hours of receiving blood intraperitoneally.

FIG. 1.—Chart of Case 2.

FIG. 2.—Chart of Case 12.

FIG. 3.—Chart of Case 13.

The progress of Case 2 (subtertian malaria) and Case 13 (nutritional anaemia) was complicated by an intercurrent infection and Case 12 (sickle-cell anaemia) by further haemolytic incidents. Their response to treatment is shown in Figs. 1, 2, and 3. In each of these cases the intraperitoneal transfusion was supplemented by an intravenous transfusion. In Cases 12 and 13 the patients were moribund on admission and received 80 ml. and 60 ml. of blood respectively. This was given slowly by syringe into the internal jugular vein and was immediately followed by an intraperitoneal transfusion. A good haemoglobin response was obtained in both cases.

In Case 2 there was an immediate but unsustained response to the first intraperitoneal transfusion, and, despite a similar rise after the second transfusion, the child's condition remained so critical that an intravenous transfusion was given. The immediate clinical and haematological response to this was no better, and it was not until the child's febrile illness was subsiding that the haemoglobin started to rise steadily. The reason for this febrile reaction was never determined, and although it followed immediately after the first intraperitoneal transfusion there was nothing clinically to suggest an intraperitoneal infection, or any clinical or laboratory evidence of incompatibility.

Details of the Fatal Cases

The haemoglobin responses, causes of death, and necropsy findings of the nine patients who died are shown below.

Cases 4, 7, 10, and 19.—These children, aged 9, 6, 5, and 18 months respectively, died from sickle-cell anaemia and lobar pneumonia within 24–48 hours, an intraperitoneal transfusion having been given on admission to hospital. The haemoglobin levels of these cases were 3, 5.3, 2.4, and 4.4 g./100 ml. respectively, and in none of them was a rise in haemoglobin detected in the time between transfusion and death. The amount of blood given varied from 140 to 270 ml. in the four cases, and at necropsy the amount of liquid blood recovered varied from 0 to 80 ml. In all cases there was a thin layer of viscid blood spread evenly over the visceral and parietal peritoneum, and in one case a notable thickness of this layer over the diaphragmatic peritoneum. In none of these cases was there any evidence of injury to abdominal viscera or of clots, bands, or adhesions.

Case 8.—A child aged 1 month with marasmus due to congenital syphilis died four days after receiving 60 ml. of blood and having shown a rise in haemoglobin from 4.7 to 7.4 g./100 ml. in the first three days. Necropsy was refused.

Case 15.—A child aged 5 months with sickle-cell anaemia and enteritis died four days after receiving 120 ml. of blood, the haemoglobin having risen from 5.15 to 6.7 g./100 ml. before death. Necropsy was refused.

Case 5.—A child aged 6 months convalescing from bacillary dysentery died two weeks after receiving 200 ml. of blood. The haemoglobin level rose from 7 to 10.36 g./100 ml. within three days, but later fell again to 7.46 g./100 ml. owing to a relapse of dysentery, from which the child died. At necropsy there was no blood in the peritoneal cavity or any evidence of inflammation, bands, or adhesions. The diagnosis of bacillary dysentery was confirmed.

Case 21.—A child aged 1 year recovering from malaria died as the result of bacillary dysentery and pneumonia 21 days after an intraperitoneal transfusion. The haemoglobin on admission was 2.7 g./100 ml.; it rose to 4.4 g./100 ml. two days after transfusing 80 ml. of blood. A further 140 ml. was given on the third day, and the haemoglobin rose to 8.9 g./100 ml. by the thirteenth day, remaining at this level until the patient's death. At necropsy there was no sign of blood in the peritoneal cavity and no inflammation, bands, and adhesions. The diagnosis of left lobar pneumonia and bacillary dysentery was confirmed.

Case 18.—A child aged 2 years suffering from tuberculous bronchopneumonia died 11 days after the administration of 120 ml. of blood. The haemoglobin level rose from 4.4 to 8.3 g./100 ml. within five days, then fell to 4.4 g./100 ml. during the succeeding six days; no further blood could be obtained. At necropsy no blood was present in the peritoneal cavity and there was no evidence of inflammation, bands, or adhesions. Extensive tuberculous cavitation of both lungs was present.

From these nine cases it can be seen that a fulminating acute or chronic infection complicating the anaemia was responsible for death in each instance. Although necropsy was not carried out in two cases there was nothing to suggest that the transfusion had in any way been responsible for the fatal outcome.

Reactions

Of the 23 cases, 4 showed a mild reaction attributable to the intraperitoneal transfusion. This consisted of restlessness and abdominal discomfort after receiving amounts of blood in excess of 100 ml. Two of these patients vomited at the completion of the transfusion, one (Case 20) had a temporary febrile reaction of 100° F. (37.8° C.) following each transfusion, and one (Case 2) had the prolonged febrile illness recorded above, the origin of which remains obscure.

Conclusions

From the results obtained in this series it is concluded that intraperitoneal blood transfusions have a definite value in the treatment of children's anaemias. In cases of haemorrhage the necessity for rapid replacement still calls for the intravenous route.

It is possible that the haemolytic crises of sickle-cell anaemia would also benefit more from an intravenous transfusion, but as four such cases in this series were also suffering from an acute lobar pneumonia, the danger of overloading the circulation by an inadequately supervised intravenous transfusion was thought to outweigh the advantages. Although all four patients died, they were *in extremis* on admission, and it is extremely problematical if they could have been saved by any form of treatment.

If sudden blood loss or blood destruction is excluded, intraperitoneal transfusions have a very definite value in cases of more chronic blood loss or inadequate blood formation associated with nutritional defects or infections.

The ease of administration both for the operator and for the patient is a factor of great practical importance, not only in the circumstances described above where medical services are as yet incomplete, but also in hospitals with adequate medical and nursing personnel confronted with

aplastic or chronic haemolytic anaemia in children who require repeated small transfusions over a period of years. Under such circumstances the transfusion could be given in the out-patient department and the child spared the necessity of repeated admissions to hospital.

In no case in the present series was death directly attributable to the administration of intraperitoneal blood, and, provided a stringent aseptic technique is employed and there is no evidence of intra-abdominal disease or injury, there is no reason to anticipate a greater risk of infection from this route than from the intravenous one. As no record of an acute peritonitis or abscess formation following intraperitoneal transfusion can be traced in the literature or the present series, it is felt that this "potential danger" is not a real one. Intra-abdominal injury has been recorded in three cases (Ravenel, 1933), but again it is felt that, with care and the correct choice of site for insertion of the needle, these accidents might have been avoided.

In the case of a collapsed infant with a lax abdomen the danger of a direct and uncontrolled puncture through the abdominal wall is very real, and for this reason the necessity to control the depth of penetration by countertraction on the skin has been stressed by Carter (1953). Similarly, to avoid possible puncture of unobliterated hypogastric arteries or a full bladder in small infants the site chosen for injection was $\frac{1}{2}$ –1 in. (1.3 to 2.5 cm.) above the umbilicus. In the course of several thousand intraperitoneal saline infusions and the present series of blood transfusions, no damage to an intra-abdominal organ or blood vessel has been encountered.

From experimental and post-mortem findings there is no doubt whatever that such blood is absorbed; and in all cases, except the four patients who died within 24–48 hours, a rise in haemoglobin the day after transfusion was recorded.

From the present series it has been impossible to arrive at a conclusion regarding the optimum amount of blood to give intraperitoneally, as results have varied considerably, from a good initial haemoglobin response to 60 ml. (Case 8) to a poor response with 270 ml. (Case 2). From the purely mechanical point of view, however, it has been found that the majority of children between 3 months and 4 years can tolerate 100–270 ml. without discomfort.

It is felt that this therapy deserves more recognition, and a knowledge of the technique would prove a valuable adjunct to the more orthodox training of students, housemen, and general practitioners, who may not always have the facilities of a fully equipped paediatric hospital behind them when confronted with an anaemic infant requiring blood transfusion.

Summary

Of 23 cases of anaemia in childhood treated by intraperitoneal blood transfusion, 11 showed an uninterrupted haemoglobin response and improvement, three were complicated by intercurrent infection or acute haemolysis requiring a supplement of intravenous blood, and nine patients died.

Of the nine deaths, none was directly attributable to intraperitoneal transfusion, and post-mortem examination in seven cases showed complete or partial absorption of the blood with no sign of intra-abdominal injury, sepsis, or adhesions.

The intraperitoneal route is recommended as a technically simple and effective means of giving blood in low-grade or severe chronic anaemias in children where repeated transfusions may be required or a single slow blood transfusion indicated.

REFERENCES

- Carter, F. S. (1953). *E. Afr. med. J.*, 30, 499.
 Cole, W. C. C., and Montgomery, J. C. (1929). *Amer. J. Dis. Child.*, 37, 497.
 Courtice, F. C., Harding, J., and Steinbeck, A. W. (1953). *Aust. J. exp. Biol. med. Sci.*, 31, 215.
 — and Steinbeck, A. W. (1951). *Ibid.*, 29, 451.

- Florey, H., and Witts, L. J. (1928). *Lancet*, 1, 1323.
 Hahn, P. F., Miller, L. L., Robschtein-Robbins, F. S., Bale, W. F., and Whipple, G. H. (1944). *J. exp. Med.*, 80, 77.
 Mengert, W. F., Cobb, S. W., and Brown, W. W. (1951). *J. Amer. med. Ass.*, 147, 34.
 Morris, B. (1953). *Aust. J. exp. Biol. med. Sci.*, 31, 239.
 Ravenel, S. F. (1933). *J. Amer. med. Ass.*, 100, 473.
 Sansby, J. M., and Siperstein, D. M. (1923). *Ibid.*, 80, 1763.
 Siperstein, D. M. (1923). *Amer. J. Dis. Child.*, 25, 202.
 — and Sansby, J. M. (1923). *Ibid.*, 25, 107.
 Waite, M. E., Colucci, D. D., and Glaser, J. (1956). *Ibid.*, 91, 561.
 Wiener, A. S. (1943a). *Blood Groups and Transfusion*, 3rd ed., p. 70. Thomas, Springfield, Illinois.
 — (1943b). *Ibid.*, p. 112.

VALVOTOMY IN MITRAL STENOSIS COMPLICATED BY PREGNANCY

BY

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The aim of valvotomy in mitral stenosis complicated by pregnancy is the relief of the mechanical obstruction so that the heart can handle with ease the physiological increase in the blood volume during the term of gestation. The pioneer work on rheumatic heart disease and pregnancy was done by Mackenzie, Bramwell, and Jones during the second quarter of this century, but it was not until 1952 that the newly acquired art of mitral valvotomy was successfully applied to these cases by Brock (1952) and Logan and Turner (1952) in this country and by Cooley and Chapman (1952) in the United States. Till then the attitude had been one of "termination of pregnancy and sterilization" (Laubry and Routier, 1947)—a totally frustrating attitude, the impact of which can never be gauged objectively. Mitral valvotomy in pregnancy is still a controversial subject, and we are presenting our short series of 11 cases not so much to answer the question as to raise the problem.

Analysis of Cases

Since May, 1954, 11 pregnant women with mitral stenosis have been submitted to surgery. The oldest was 39 and the youngest 18; and six were in their twenties. Seven were multigravidae and four primiparae. At the time of valvotomy the duration of pregnancy was 19 weeks at the earliest and 31 weeks at the latest.

Status Before Admission.—A history of rheumatic fever and/or chorea was available in five, of scarlet fever in two, and of tonsillitis in another. The symptoms of mitral stenosis were first noticed during pregnancy in five, and in the other six the symptoms had rapidly worsened during the present pregnancy; four of these latter had gone through one or more pregnancies before the present one. There was an earlier history of cardiac failure in one, and in another of an embolic episode involving vision in the right eye two years earlier.

Symptoms.—All 11 complained of progressive dyspnoea on exertion restricting activity to less than 100 yards (91 m.) on the flat. Ten had cough and six had haemoptysis; of these six, five were seen because of a recent episode of pulmonary oedema.

Findings on Admission.—Ten were in sinus rhythm and one had supraventricular tachycardia controlled by digitalis and quinidine before operation. A clinical diagnosis of pure mitral stenosis was made in seven, a mild degree of