INCOMPATIBLE BLOOD TRANSFUSIONS DURING OPERATION

BY

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Recognition of haemolytic transfusion reactions in conscious patients is usually not difficult. Shortly after the onset of an incompatible blood transfusion, the conscious patient generally develops a variety of symptoms (Wiener, 1943), such as a sensation of fullness in the head, generalized tingling, precordial oppression and sudden sharp pain in the lumbar region. He becomes anxious, restless and dyspnoeic. His face is suffused and the neck veins are distended. Nausea and vomiting are not uncommon. These initial signs and symptoms may be followed by circulatory collapse, marked by hypotension, a rapid feeble pulse, and cold clammy skin; more rarely, pilo-erection and cyanosis appear. About an hour later, the patient commonly has a shaking chill and an elevation in temperature. Occasionally, chills and fever alone or in combination are the presenting signs of haemolytic reaction, the initial symptoms being unrecognized or absent. A haemorrhagic tendency can develop during or immediately after transfusion, and blood may ooze from the transfusion site, from the gums, uterus (in postpartum patients), or from any incised tissue. The appearance of this clinical complex makes recognition of haemolytic transfusion reactions in the conscious patient relatively simple.

The unconscious patient or one undergoing operation, however, is unable to manifest the initial group of symptoms (fullness in the head, precordial oppression, etc.), and the only signs indicating that a haemolytic reaction has been taking place are those which tend to develop as the reaction becomes more advanced, i.e., sudden hypotension and/or oozing. During operation, diagnosis becomes still more difficult and uncertain, because even when present, hypotension and oozing are easily attributed to events incident to anaesthesia, operation, or both. Thus haemolytic transfusion reactions occurring during operation are generally not recognized early and their ambiguous clinical manifestations are too often treated with additional incompatible blood. For example, a recent analysis of incompatible transfusions (Binder, Ginsberg and Harmel, 1959) showed that those patients who underwent operation received the larger volumes of incompatible blood and sustained the majority of fatal reactions. These findings indicate that earlier recognition and treatment of haemolytic transfusion reactions during operation is of utmost importance. The following case reports are therefore presented to detail the subtle manner with which haemolytic reactions appear during operation in the hope that this experience will lead to earlier recognition and more effective treatment.

Ten patients were given incompatible blood during operation. The case reports are summarized in table I and presented below. In addition, one patient is discussed who had been successfully treated for a severe haemolytic transfusion reaction and then subjected to emergency operation.

Since hypotension is by far the most common and frequently the only sign of a haemolytic reaction, the cases are presented according to the following classification:

(A) No hypotension.
(B) Hypotension.
   (1) Preceding and continuing after the incompatible transfusion.
   (2) Appearing only after the incompatible transfusion.
CASE REPORTS

(A) No Hypotension.

Case I.

A girl of 11 years was admitted because of a congenitally dislocated hip for reconstruction of the acetabulum. The history was otherwise of no consequence and the pertinent physical findings were limited to the hip. The blood pressure was 110/70 mm Hg; pulse rate 72/minute; haemoglobin 14 grams per cent; urine normal. The blood group was reported as AB positive.

Pre-anaesthetic medication: pethidine 25 mg and atropine 0.4 mg, was given 1 hour before operation. In the operating room, the blood pressure was 100/40 mm Hg, the pulse rate 126/minute.

Anaesthesia was induced with thiopentone 75 mg and maintained with cyclopropane using a closed circuit and assisted respiration. In anticipation of excessive blood loss, a transfusion of blood was begun early in the operation. The blood loss was an estimated 400 ml; the blood pressure and pulse rate remained constant during the 13-hour procedure.

The immediate postoperative course was uneventful. The patient regained consciousness rapidly and experienced neither hypotension nor tachycardia afterwards. The next day the temperature was normal, but the abdomen was slightly distended and the patient vomited several times. As she had not urinated, the bladder was catheterized and 450 ml of grossly blood-stained fluid was obtained. The haemolytic reaction was confirmed when the blood was regrouped and stained fluid was obtained. The haemolytic reaction apparently was not suspected until 2 hours after the haemorrhagic diathesis had been recognized; for only at this time was a specimen of venous blood finally taken for study. It was grossly haemolysed and did not clot.

The persistent bleeding was treated with 5 grams of fibrinogen, after which the wound was reopened and packed. The blood was also regrouped, and when it was found to be B positive and not A positive, a litre of correctly grouped blood was administered. One and a half hours after they had been directed to the clotting effect, i.e., 4 hours after the haemorrhagic diathesis was recognized, the bleeding had essentially stopped. The patient who had been anaesthetized during this entire period, was finally allowed to awaken.

Although the blood pressure and pulse rate had remained at his normal level throughout this episode, he became completely anemic. In addition, his postoperative course was complicated by a progressively severe intractable ileus. The patient died with ileus and renal failure on the fifth postoperative day. An autopsy was not granted.

Case III.

A man aged 71 was to have a partial cystectomy for carcinoma of the urinary bladder. Pertinent physical findings included: signs consistent with a moderate, obstructive emphysema; e.g., indicating an uncomplicated sinus tachycardia; blood pressure 145/85 mm Hg; haemoglobin 14 grams per cent; and one-plus haematuria. The blood group was reported to be A positive.

Pre-operative medication: pethidine 35 mg and atropine 0.4 mg, was given 14 hours before operation, but the patient appeared apprehensive and the effect of the drugs was considered unsatisfactory. Eleven mg of an amethocaine-dextrose solution with 0.1 mg of adrenaline was prepared (a total volume of 2.4 ml) and injected intrathecally. The initial sensory level was at T10; 15 minutes later it had ascended to T6.

 Apparently because the patient was restless and garrulous, the spinal analgesia was supplemented with intravenous pethidine and in the next 2 hours 100 mg were given intermittently. During this interval the blood pressure gradually fell from 160/80 to 120/80 mm Hg, but the pulse rate remained at 76 to 80 per minute and the patient appeared in no distress.

In spite of minimal blood loss, a transfusion with A positive blood was begun. Ten minutes later the patient began to complain of epigastric pain. Because the anaesthetic level was believed to be inadequate, general anaesthesia was induced with cyclopropane. The patient was then intubated, and surgical anaesthesia was maintained with a light ether-oxygen mixture employing a semiclosed circuit.

Twenty minutes later, immediately following closure of the peritoneum and removal of skin drapes, an increased ooze was seen issuing from the cut surfaces. Attempts to secure haemostasis were unsuccessful. Nevertheless the wound was closed, but bleeding became so profuse that 1,000 ml of citrated blood, cross-matched from the patient’s original specimen, was pumped in rapidly under pressure. A haemolytic reaction apparently was not suspected until 2 hours after the haemorrhagic diathesis had been recognized; for only at this time was a specimen of venous blood finally taken for study. It was grossly haemolysed and did not clot.

The persistent bleeding was treated with 5 grams of fibrinogen, after which the wound was reopened and packed. The blood was also regrouped, and when it was found to be B positive and not A positive, a litre of correctly grouped blood was administered. One and a half hours after therapy had been directed to the clotting effect, i.e., 4 hours after the haemorrhagic diathesis was recognized, the bleeding had essentially stopped. The patient who had been anaesthetized during this entire period, was finally allowed to awaken.

Although the blood pressure and pulse rate had remained at his normal level throughout this episode, he became completely anemic. In addition, his postoperative course was complicated by a progressively severe intractable ileus. The patient died with ileus and renal failure on the fifth postoperative day. An autopsy was not granted.
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L TETRAL. HEMO

3. INTUBATION

4. RAPID BLEEDING

5. BLOOD B + A. BLOOD TAKEN FOR X-MATCH

6. NOTIFIED BY BLOOD BANK PATIENT A + TRANSFUSION STOPPED.

7. BLOOD B + A.

8. BLOOD STOUFFED.

PLASMA HEMO

LYZED

9. TRACHEAL TOILET, DHY. EUTRAB

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FIG. 1

Anaesthetic record of patient described as case no. III. The illustration shows the hypertension which followed an incompatible blood transfusion.

bated with a no. 10 cuffed tube, and surgical anaesthesia was maintained with intermittent cyclopropane in a closed circuit. The gall bladder, densely adherent to liver, stomach, omentum and abdominal wall, made dissection very difficult, and bleeding was brisk. The blood pressure soon fell from 160/100 to 100/60 mm Hg, and the first of two transfusions with B positive blood was begun. Incidentally, a sample of venous blood was withdrawn in order to cross-match additional blood. After 700 ml of incompatible blood had been transfused, the blood bank reported that this second sample was A positive, not B positive.

The patient's blood pressure had not fallen with the incompatible transfusion. Instead, it was returned to its pre-operative level (140/80 mm Hg) with the first bottle of blood, the pulse rate remaining at 40 to 50 per minute. With the beginning of the second transfusion less than a half-hour later, the patient became hypertensive. At first the blood pressure was elevated to 170/100 mm Hg, but at the close of the procedure 1 hour later, it had ascended to 240/120 mm Hg. The pulse rate still remained at 50 to 60 per minute. The marked hypertension (230/120 to 180/100 mm Hg) lasted for 7 hours, then gradually decreased during the next 9 hours to its usual range, 140/90 mm Hg. Nevertheless, the 24-hour urine output was 300 ml. The oliguria persisted for 4 days. His course thereafter was relatively uncomplicated and he was discharged a month later.

Discussion.

The absence of hypotension makes the diagnosis of haemolytic transfusion reaction inordinately difficult. In a certain number of reactions, cardiocirculatory and bleeding disturbances may be completely lacking; and in common with "silent" transfusion reactions in conscious patients, the first inkling of their occurrence is the appearance of oliguria several days later. Case I typifies the silent reaction. Infrequently, a haemorrhagic diathesis may be the only significant sign, hypotension being completely absent. This is illustrated in case II. Also of interest in
this case was the development of epigastric pain shortly after the incompatible transfusion was begun. In retrospect, this symptom may have signalled the onset of the haemolytic reaction, but unfortunately, it was thought to be the result of an ineffective level of spinal analgesia. Therefore, inhalation anaesthesia was undertaken which effectively masked other possible symptoms, and incompatible blood was transfused until the coagulation defect became obvious. It is conceivable that had the transfusion been discontinued when epigastric pain appeared, the haemorrhagic diathesis would not have occurred.

Although sudden hypotension is the most common cardiocirculatory disturbance associated with haemolytic reactions, other aberrations in haemodynamics such as tachycardia and hypertension also occur. The difficulty has been that hypertension and tachycardia are often attributed to other causes. Indeed, the cause of the persistent hypertension in case III was not investigated. That it could have been related to a haemolytic reaction was not even considered, and only after the diagnosis had been made by accident was this relationship finally entertained.

**(B) Hypotension.**

**(1) Hypotension Preceding Incompatible Transfusion**

**Case IV.**

An obese female aged 40 years was admitted for hysterectomy with a diagnosis of fibroid uterus. The history and physical examination were otherwise non-contributory. The blood pressure was 150/70 mm Hg; pulse rate 64/minute; haemoglobin 9 grams per cent; urine normal. The blood group was reported as B positive.

The pre-anaesthetic medication, atropine 0.4 mg and pethidine 100 mg, was clinically satisfactory. A lumbar puncture was performed with ease and 16 mg of amethocaine in 1.6 mg of 10 per cent dextrose-water and 0.4 mg of adrenaline (total volume 2 ml) was injected intrathecally (fig. 2). Immediately preceding lumbar puncture, an injection of 20 mg of methamphetamine was given intramuscularly. The initial sensory level was said to be T6; the height of the sensory level was not further recorded. That it may have crept somewhat higher is suggested by the fact that the patient's blood pressure fell to 90/50 mm Hg, the pulse rate remaining at 64 per minute. A phenylephrine infusion (0.01 mg/ml) was begun and 1 mg was administered within 10 minutes. The blood pressure responded promptly, but because it fell again when administration of the vasopressor was halted, the infusion was continued for the major part of the procedure.

Fifteen minutes before the end of the operation the phenylephrine was again stopped. The blood pressure promptly fell to 60/40 mm Hg. Although an estimated 300 ml of blood had been lost, 500 ml of blood was transfused rapidly, but without effect on the blood pressure. The phenylephrine infusion was then restarted, and the blood pressure again was returned to the pre-operative level of 130/70 mm Hg.

The poor response to transfusion suggested the possibility of transfusion of an incompatible blood. The pressure of transfusion was then catheterized, but as the urine was macroscopically clear, a second transfusion was begun. When 100 ml had been administered the patient began to have shaking chills. The blood was discontinued and the vasopressor again restarted. At this time, venous blood was finally withdrawn for study. On centrifugation unmistakable haemolysis was revealed and the haemolytic transfusion reaction was confirmed when, on re-grouping, the patient's blood was O positive and not B positive as originally determined.

The operation having ended, the patient was sent to the ward. There, O positive blood was pumped in rapidly under pressure and noradrenaline substituted for the phenylephrine infusion. After 2,500 ml of blood had been administered, the blood pressure fell to 110/70 mm Hg, haemoglobin 11.5 grams per cent. Approximately 4½ hours after the first transfusions of incompatible blood had been begun, the patient suddenly and unexpectedly gasped and died. At that moment blood appeared at the mouth and rectum.

At necropsy, bleeding was demonstrated from all mucous and serous membranes. In addition, between 1 and 2 litres of unclothed blood was found in the abdominal cavity. The ligatures were secure.

**Case V.**

A man of 72 years was brought to surgery for suprapubic prostatectomy. Except for the present disease, physical findings and past history were non-contributory. The blood pressure on admission was 150/80 mm Hg; pulse rate 62/minute; haemoglobin 11.5 grams per cent; e.c.g. indicated sinus bradycardia. The blood group was reported as AB positive.

Pre-anaesthetic medication, pentobarbitone 100 mg and atropine 0.4 mg, was given ½ hours before operation. The blood pressure immediately before induction of anaesthesia was 120/80 mm Hg, the pulse rate 68 per minute. Spinal analgesia was initiated with 10 mg of amethocaine-dextrose solution. The initial sensory level was at T10; no later evaluations of the level were recorded. Twenty minutes later, the blood pressure fell to 100/80 mm Hg and the pulse rate to 56 per minute. When divided doses of intravenous methamphetamine failed to produce the desired response, 500 ml of AB positive blood was transfused rapidly. The blood pressure rose to 140/80 mm Hg where it remained for the next half-hour. The pulse rate also gradually climbed to 80 per minute.

Forty-five minutes after the start of the transfusion, the blood pressure suddenly fell to 80/60 mm Hg. At this time, the pressure of transfusion was increased, and the suprapubic catheter. Although the blood loss was thought to be small, the blood pressure could no longer be measured and the patient had become cold, clammy and disoriented. A second bottle of AB positive blood was transfused rapidly. The wound was reopened and a generalized ooze observed. Since no bleeding point could be found, the fossa was packed and the wound reclosed.

A transfusion reaction was then suspected. Venous blood was obtained which showed haemolysis and inability to clot. The blood was immediately re-
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Fig. 2

Anaesthetic record of patient described as case no. IV. The illustration shows the poor response of the blood pressure to transfusion with incompatible blood and the difficulty in distinguishing between the hypotension produced by the spinal anaesthetic and that associated with transfusion reaction.

grouped and found to be O positive, not AB positive. Massive transfusion with O positive blood was begun, and in the following 24 hours, 8,500 ml of blood, 750 ml of fibrinogen, and 1,000 ml of fresh-frozen plasma were administered without effect. Finally, in a vain attempt to secure better haemostasis the wound was reopened, but the bleeding could not be controlled and the procedure was abandoned.

The patient was returned to the ward. His blood pressure was 90/60 mm Hg, pulse rate 100 to 120 per minute. An infusion of phenylephrine was started. He continued to bleed and to receive citrated blood. Twelve hours after transfusion of the first bottle of incompatible blood, he had received a total of 17,500 ml of blood plus additional fibrinogen and fresh-frozen plasma; but the coagulation defect persisted. Only then was the patient returned to the operating room for direct transfusions. After 500 ml had been transfused, the patient died. Consent for necropsy was not obtained.

Case VI.

A man aged 36 was admitted to the hospital after having been struck by an automobile and sustaining a compound fracture of the left leg. Following admission, he became progressively drowsy and finally lost consciousness. A paraplegia developed on the left side and he lapsed deeper into coma. The patient was then brought to surgery for emergency craniotomy. The blood pressure was 130/80 mm Hg; pulse rate 60/minute; respirations, hyperpnoeic at 16/minute; haemoglobin 14.5 grams per cent; urine negative. The blood group was mistakenly reported as B positive.

No pre-operative medication was given. The scalp was infiltrated with 1 per cent procaine, and the craniotomy was performed. Both subdural and epidural haemorrhages were found; in addition, the brain was contused and lacerated. Although the operative blood loss was small, the patient's blood pressure fell to 100/70 mm Hg and the pulse rate increased to 120 or 130 per minute. Presuming these events to be signs of hidden haemorrhage at his leg fracture site, a transfusion of B positive blood was begun. Twenty-five minutes later, the pulse rate suddenly increased to 180 per minute. The blood pressure rose concomitantly from 110/70 to 140/90 mm Hg; but unlike the
pulse rate which remained elevated, it gradually fell in the next 45 minutes to 100/80 mm Hg. This minimal hypotension and persistent tachycardia prompted a second transfusion of incompatible blood. However, this transfusion did not affect his pulse rate and blood pressure.

The craniotomy was completed in 24 hours, and the patient was returned to the ward in critical condition. There he continued to receive incompatible blood until 6 hours after his return, when a fresh venous sample taken to cross-match additional blood was regrouped and shown to be A positive, not B positive.

In spite of vigorous treatment of the then recognized haemolytic reaction, the patient's condition deteriorated steadily. During the first 24 hours he excreted only 200 ml of muddy urine. The coma deepened and generalized spasticity became more and more prominent. A second craniotomy was undertaken to decompress the brain, but when the flap was reopened, the patient developed rapid Cheyne-Stokes respiration and the blood pressure fell precipitously to 70/40 mm Hg and the pulse rate increased to 140 per minute. The brain bulged out of the wound under marked pressure and the procedure was finally abandoned. No epidual or subdural bleeding was seen and haemostasis was normal. The patient continued to worsen and died 4 days later.

At necropsy, the positive findings were limited to the head and leg fracture.

Case VII.

An 18-year-old primigravida was admitted in the 36th week of gestation in active labour. Admission history and physical examination revealed: a blood pressure of 116/80 mm Hg; pulse rate 65/minute; haemoglobin 10 grams per cent, but the haematocrit taken 1 day later was 41 per cent and the plasma fraction was slightly icteric. X-ray pelvimetry revealed a borderline contracted pelvis. The blood group was A positive, not B positive.

Spinal analgesia was attempted with a hyperbaric amethocaine solution, but the amount of agent used was not recorded; nor was the indication for transfusion given. The order and time of their administration were not recorded. Both bottles of blood (O positive and AB positive) were used. The blood pressure of 120/70 mm Hg; pulse 80/minute; haemoglobin 14.5 grams per cent; and two-plus albuminuria. The blood group was erroneously reported as AB positive.

Labour was protracted and ineffective, and when hypotonic uterine dysfunction developed, the patient was scheduled for caesarean section under spinal anaesthesia. As only one bottle of AB positive blood was available, a unit of low titre O positive blood was also cross-matched.

Unfortunately, the anaesthetic record is inadequate. The pre-anaesthetic medication, if any, was not stated. Spinal analgesia was attempted with a hyperbaric amethocaine solution, but the amount of agent used and the anaesthetic level achieved were not recorded. However, inasmuch as the spinal analgesia was supplemented with nitrous oxide-ether, it was probably unsatisfactory. Both bottles of blood (O positive and AB positive) were used. The order and time of their administration was not recorded; nor was the indication for transfusion given.

Toward the end of the procedure, the blood pressure became imperceptible and the pulse rose to 170 per minute. The operation was completed rapidly and the patient returned to the ward still hypotensive. There, a noradrenaline infusion was started which elevated the blood pressure to 80/7 mm Hg. The haemacotocrit at this time was 32 per cent and the plasma fraction was deep yellow. On catheterization of the bladder, no urine was obtained.

Because of hypotension and icterus, liver failure was diagnosed. A transfusion reaction was not considered until 13 hours later, when 30 ml of mahogany-coloured urine finally was obtained. The patient's blood was then regrouped and shown to be B positive, not AB positive as originally reported.

In spite of supportive therapy including increasing doses of noradrenaline and transfusion with compatible blood, the patient died 44 hours after operation. At necropsy, the findings were consistent with both acute haemoglobinuric nephrosis and extensive liver necrosis.

Discussion.

Hypotension preceded incompatible blood transfusion in four patients. In two, hypotension was precipitated by high levels of spinal analgesia attempted in hypovolaemic patients; in the remainder, the patient's precarious surgical status rather than the anaesthetic management seemed to be the predisposing cause. In each instance, the blood transfusion (of incompatible blood) did not restore cardiocirculatory stability. This finding, although not invariable, may be of diagnostic significance when it does occur. Unfortunately, except when other manifestations of haemolysis (chills, increased bleeding) were also present, the correlation between haemolytic transfusion reaction and continuing or deepening hypotension was not made.

(2) Hypotension appearing only after incompatible transfusion

Case VIII.

A woman aged 40 was to have a radical vulvectomy and bilateral groin dissection for carcinoma of the vulva. Apart from pruritus, burning during micturition, and vulvar leukoplakia, the admission history and physical examination were not significant. The blood pressure was 120/70 mm Hg; pulse 80/minute; haemoglobin 14.5 grams per cent; and two-plus albuminuria. The blood group was erroneously reported as A positive.

The pre-anaesthetic medication, morphine 10 mg and atropine 0.4 mg, produced a satisfactory clinical effect. Anaesthesia was induced with cyclopropane-oxygen, the trachea intubated without difficulty, and surgical anaesthesia maintained with cyclopropane and "top ether" using a closed circuit (fig. 3). In anticipation of excessive blood loss, the first of three incompatible blood transfusions with A positive blood was begun. For 3 hours, the pulse rate remained stable at 90 per minute and the blood pressure at 140/80 mm Hg; but 25 minutes after the start of the third transfusion, the pulse rate gradually rose to 120-140 per minute and the blood pressure became unrecordable. Ten minutes later the blood pressure was 100/60 mm Hg by palpation. The gravimetrically estimated blood loss was 1,000 ml.

The operation having been completed, the patient was returned to the ward still unconscious. There, she remained unconscious for 6 hours, much longer than could be accounted for by the anaesthetic. In addition, the blood pressure fell again from 90/60 mm Hg to 50/7. The bladder was catheterized but...
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bleeding. Inspection of the blood bottles, however, revealed one to have contained A positive and not O positive blood.

The patient's blood pressure remained at 170/114 mm Hg and the pulse rate at 130 per minute until she arrived at the ward. There, she became hypotensive, necessitating the use of noradrenaline and additional transfusions of 1,000 ml of blood. After 3 hours the blood pressure became stable at her normal hypertensive level.

The subsequent postoperative course was very stormy, complicated by acute renal failure of 8 days duration, severe postpartum psychosis, convulsions, and a wound dehiscence. She was finally discharged 7 weeks after admission.

Case X.

A woman of 31 was admitted to the hospital with a 6-weeks history of threatened abortion. One hour prior to admission, she began to bleed profusely and claimed to have aborted. Physical examination was noncontributory. Haemoglobin was 13 grams per cent; urine normal. The blood group was O positive. The patient continued to bleed briskly and was brought to surgery for emergency curettage.

Pre-anaesthetic medication, pethidine 75 mg and atropine 0.4 mg, was given intramuscularly 15 minutes before operation. Its effect was satisfactory. The blood pressure immediately before operation was 110/80 mm Hg, pulse 96 per minute.

On induction of anaesthesia with cyclopropane, the pulse and blood pressure became unobtainable. The anaesthetic was immediately discontinued, the uterus rapidly evacuated of large amounts of clot and tissue, and a transfusion begun. The pulse and blood pressure quickly returned to normal. The patient regained consciousness and was returned to the ward in good condition.

Two hours later, the patient had received only 100 ml of blood. Suddenly she had a rigor. The bladder was catheterized and "dark amber" urine obtained. A haematocrit likewise revealed haemolysis. Rechecking her blood against that remaining in the bottle showed that the bottle had been mislabelled, and that the patient had been given A positive not O positive blood.
The blood pressure, 130/110 mm Hg immediately after transfusion, and then 140/90 mm Hg, gradually fell during the next hour to hypotensive levels. Treatment with noradrenaline and correctly grouped blood, however, soon restored normal blood pressure. The urine output remained normal and the patient was discharged 2 days later.

Discussion.

Hypotension following an incompatible transfusion is generally not an immediate finding. In contrast to the early subjective responses, it tends to appear 1 or 2 hours later, when it is more likely to be attributed to postanaesthetic hypotension or continued bleeding than to incompatible transfusion. An interesting manifestation of haemolytic reactions is a change in the patient's behaviour. This may present as drowsiness, lethargy, anxiety, and other aberrations in the state of consciousness or awareness. In case X, the patient remained unconscious postoperatively considerably longer than could be accounted for by the anaesthetic.

Case XI.

A primigravida of 43 years was brought to surgery for emergency hysterectomy. She had been admitted at term in active labour. The admission history and physical examination were noncontributory. The initial blood pressure was 140/80 mm Hg; pulse 80/minute; temperature 101.8°F. The blood group was reported as A positive.

She subsequently underwent an uneventful Caesarean section for amnionitis. Postoperatively, because of sepsis and an estimated 750 ml blood loss, a transfusion was begun. After 300 ml of A positive blood had been transfused, the patient was found sweating and irrational. The blood pressure was unobtainable. The uterus was flaccid and an estimated 1,500 ml of liquid blood was seen in the bed. Uterine atony was diagnosed. Thereupon, the remaining 200 ml of blood was pumped in under pressure followed by another bottle of A positive blood. At the same time, a new specimen was sent to be cross-matched against additional blood. This sample showed the patient to be O positive, not A positive. Meanwhile, the patient had received 1,000 ml of incompatible blood.

Energetic transfusion with O positive blood, fibrinogen and fresh-frozen plasma was begun. With transfusion, the blood pressure climbed to 90/60 mm Hg, but a tachycardia of 160 per minute persisted and the patient continued to bleed profusely from the nose, mouth, vagina and incision. Fourteen hours later, after she had received 15,000 ml of O positive whole blood, 22 grams of fibrinogen and 700 ml of fresh-frozen plasma, the bleeding apparently stopped. The coagulation mechanism seemed to be restored, as evidenced by a normal clotting time with good clot retraction and stability. The blood pressure at this time was 100/60 mm Hg, the pulse 140 per minute. The total urine output was 225 ml of bloody urine.

Four hours later, although the clotting mechanism remained good, bleeding per vagina started anew. The uterus was again flaccid and unresponsive, and the blood pressure was 70/40 mm Hg. A noradrenaline infusion was begun. In view of the uterine atony, an immediate subtotal hysterectomy was undertaken. Atropine 0.4 mg was given intravenously 5 minutes before operation.

Induction of anaesthesia was with thiopentone (125 mg), and endotracheal intubation was performed with the aid of 80 mg of suxamethonium. Anaesthesia was maintained with nitrous oxide-oxygen in a semiclosed circuit. Nine mg of d-tubocurarine was given at the time of incision.

When 2,000 ml of blood and clots were found in the abdominal cavity, the patient was transfused with an additional 1,500 ml of whole blood and, prophylactically, with 3 grams of fibrinogen. The blood pressure remained at 100/60 mm Hg throughout the 40-minute procedure, but the pulse rate was elevated from 90 per minute to 140 per minute. Haemostasis was adequate and the patient was returned to the ward, conscious but in critical condition.

Postoperatively, the patient's status continued to worsen. The blood pressure fell again. Noradrenaline effected only a transient and ineffectual response and the patient died 3½ hours later.

At necropsy, examination revealed several litres of blood and clots in the abdomen, lower nephron nephrosis, partial pulmonary atelectasis, and a gonadal vein thrombosis.

Discussion.

The case is presented to illustrate the difficulties in management of a patient subjected to operation after surviving a severe haemolytic reaction and prolonged haemorrhage. The clotting defect apparently manifested itself as uterine bleeding, but a haemolytic reaction was not suspected. The “uterine atony” was therefore treated with oxytocics and still more incompatible blood until the correct diagnosis was finally made by the blood bank.

EVALUATIONS AND CONCLUSIONS

Eleven case reports are presented in which haemolytic transfusion reaction are associated with operation. Six patients died, five recovered. Three deaths (case nos. IV, V, XI) were a direct result of incompatible blood transfusions. In each instance, the immediate cause of death was intractable, generalized, exsanguinating haemorrhage. The patients' ailment probably was the primary factor in the remaining three deaths (case nos. II, VI, VII); however, renal failure secondary to incompatible blood transfusion undoubtedly contributed to their eventual demise. Of the five patients who survived, four (case nos. I, III, VIII, IX) developed an oliguria which lasted from 36 hours to 8 days. The fifth (case no. X) received only 100 ml of incompatible blood before the transfusion reaction was discovered.
and this patient had no evidence of kidney dysfunction. Significantly, all but this patient received 500 ml of blood or more, and all but this patient had severe and, in several instances, fatal transfusion reactions. This finding supports the contention that the severity of incompatible blood transfusion reactions tends to increase with the volume of blood transfused.

Thus, to avoid excessive transfusion with incompatible blood, early diagnosis of transfusion reactions is of paramount importance. However, in this series of cases, it was not possible for either of the two cardinal signs of haemolytic transfusion reaction in the operated patient, intractable oozing or hypotension, to warn the surgeon or anaesthetist as to the possibility of transfusion reaction. Indeed, only two reactions (case nos. IV, X) were recognized early.

A haemorrhagic diathesis developed in four patients. In cases II and IX the increased bleeding was the only sign of incompatible transfusion, while in cases XI and V, bleeding and hypotension appeared together.

The significance of intractable oozing when present alone was not appreciated. In case II, the bleeding was assumed to be routine and consequently was treated with two more bottles of incompatible blood. In case IX, citrate intoxication was considered to be the cause of the coagulation defect and the incompatible transfusion was continued after intravenous calcium gluconate had been given. Only after inspection of the bottles of previously administered blood revealed one to have contained incompatible blood was the haemolytic reaction recognized and the blood taken down.

Not even when increased bleeding and hypotension appeared together was the diagnosis made. In case XI the haemorrhage was thought to be due to uterine atony (in retrospect, the reverse may have been true); while in case V a discrete bleeding point was first postulated to explain the haemorrhage. Only after much time had been spent in a fruitless search for a hypothetical bleeding point did the combination of bleeding and hypotension suggest the correct diagnosis.

This study indicates that the aetiology of a haemorrhagic diathesis secondary to transfusion reaction is not readily appreciated. Other causes often invoked are: citrate intoxication, vitamin K deficiency, congenital clotting defects, hypothermia, liver disease or usual surgical blood loss. Unfortunately, incompatible blood is usually continued while these causes are either treated empirically or ruled out.

Hypotension, too, may be ascribed to a great variety of causes. A partial list includes: pre-existing hypotension, chronic hypovolaemia, surgical blood loss, congestive failure and myocardial infarction, pre-anaesthetic medication, deep general anaesthesia, and a too-high level of spinal analgesia. Some of the problems of recognition of incompatible transfusion reactions in the face of hypotension are illustrated in these case presentations. It is significant that of the six patients in whom hypotension was observed relatively early, the only one in which the reaction was soon recognized was the patient in whom low blood pressure appeared in conjunction with a rigor (case no. IV).

An analysis of the record clearly shows that the responsible physician is often not sufficiently aware of the possibility of a haemolytic transfusion reaction. This is particularly distressing, because once it is considered, the diagnosis is extremely simple. When a transfusion reaction is suspected, the following course is suggested. The transfusion should be stopped at once. If volume replacement becomes necessary, a plasma-volume expander may be used. Dextran may not be the preferable expander because of its possible relation to late coagulation defects (Langdell, et al., 1958). An oxalated venous specimen is centrifuged for 3 to 5 minutes which is sufficient to reveal haemolysis. Urine haemoglobin determinations are not performed at this time as early urine samples are not readily obtainable or sufficiently reliable (see case nos. IV, VII).

If haemolysis is demonstrated or if a haemorrhagic diathesis is suspected, intensive study of the possible coagulation defect is instituted. However, since time is of the greatest importance, a sample of blood is immediately regrouped and cross-matched with fresh blood which was collected by gravity drainage into plastic containers. Transfusion of fresh blood should be begun without delay.

The use of fresh blood for all bleeding problems is suggested, because the deficient clotting
factor or factors are not predictable; nor can one afford the time to await their determination. Instead, while these tests are conducted, the patient is given the only substance which is known to have adequate quantities of all clotting factors, namely, fresh blood collected in the manner described or by direct transfusion. When the deficient factor(s) is identified, it is administered, when possible, to reinforce the effect of fresh blood.

However, even though recognition is prompt and treatment optimum, one must remember that in the natural course of a haemolytic reaction, hypotension and possibly bleeding are relatively late manifestations. One or two hours have often elapsed from the beginning of transfusion before these signs have appeared and one can begin to suspect its presence. During this interval, the incompatible transfusion is often continued and the severity of the reaction thereby increased.

Since the clinical circumstances peculiar to the anaesthetized surgical patient present such serious obstacles to the early recognition of haemolytic transfusion reactions, the indications for blood transfusion during operation must be carefully assessed. Attention should be directed toward restoration of blood volume pre-operatively whenever feasible. The need for relatively small amounts of blood (500 ml or less) during operation should be especially considered, and deferred whenever possible until the patient regains consciousness.

SUMMARY

Eleven case reports are presented which illustrate the circumstances surrounding the administration of incompatible blood and the development of incompatible transfusion reactions during anaesthesia. Unlike the clinical picture manifested by conscious patients, the signs of transfusion reaction in this group of patients were generally limited to hypotension, generalized oozing, or both; and incompatible transfusion reactions which develop during operation may be classified on this basis. Because the coagulation defect may be unrecognized, and because both hypotension and increased bleeding are commonly attributed to other causes, the incompatible transfusion reaction is not suspected until late and the patient therefore treated with still more incompatible blood.

The coagulation defects associated with incompatible transfusion reactions are not clearly defined. The authors suggest that fresh whole blood is the only substance which provides all clotting factors, and should therefore be the initial therapy of any acute coagulation defect.

Since diagnosis and treatment of incompatible transfusion reaction are uniquely difficult during operation and in the immediate postoperative period, the authors stress that the greater hope for decreasing the incidence of incompatible transfusion reactions in the surgical patient lies in more adequate preparation of the patient with regard to pre-operative blood volume replacement and more judicious use of blood during operation.

REFERENCES

