Studies on Cross Circulation in Man

I. Methods and Clinical Changes

By Howard R. Bierman, M.D., Ralph L. Byron, Jr., M.D.,
Keith H. Kelly, M.D.,* Kenneth S. Doh, M.D.,† and
Patrice M. Black, M.S.

The leukemias of man are commonly considered as diseases characterized by widespread proliferation of leukocytes and their precursors in the tissues of the body. This concept has greatly influenced thought and investigations concerning this group of diseases, although indisputable proof of hyperproduction of the white blood cells in leukemia is not recorded in the literature. More recently, attention has been focused upon the possible role of an impaired leukocyte removal mechanism in this condition. Further studies have demonstrated a removal site in the pulmonary circulation of man, capable of removing billions of white cells within the period of one circulation. Up to 143 billion leukocytes obtained from leukemic donors were rapidly infused intravenously into nonleukemic recipients. These cells were promptly and almost completely removed by the lungs of the recipients. These observations were so reproducible and arresting that investigations over more prolonged periods became desirable. A large reservoir of leukocytes with a means for rapid transfer of these cells from donor to recipient was required. It also became essential that manipulation of the blood be kept at a minimum to avoid introducing an unknown variable resulting from injury or deterioration of the blood elements to be transfused. The prerequisites for such a study would be satisfied if a successful method of cross circulation could be attained in man.

Nyiri described “crossed transfusions” in experimental uremia in dogs but the exchange of blood was slow and of short duration since no anticoagulant was used. Similar exchange transfusions have been performed on other animals for other purposes but none were as successful as those of Thalhimer, who used purified heparin as the anticoagulant of choice. By the use of a pump he was able to cross transfuse dogs continuously from artery to vein for twenty-seven consecutive hours.
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Direct transfusions and cross transfusions in man have been performed previously in an attempt to transmit circulatory pressor substances from patients with malignant hypertension to subjects with normal cardiovascular systems. The maximum amount of blood interchanged was 2000 cc.

Duncan, Tocantins and Cuttle succeeded in cross transfusing 2,520 cc., 7,020 cc. and 26,770 cc. in 3 patients with chronic uremia; normal donors were used in each case. Again a pump was employed, with heparin as the anticoagulant in a vein to vein exchange. No untoward reactions due to the procedure were observed.

There are three available methods for cross circulation in man: (1) vein to vein, (2) vein to artery or artery to vein and (3) artery to artery. All methods require constant observation. A pump of some design is necessary when the source of blood, e.g. vein, possesses a low pressure. The disadvantages of a pump reside mainly in the danger of hemolysis, damage to the leukocytes and platelets, and fibrin formation due to the mechanical agitation inherent in such devices. The advantage is essentially that of control and flexibility barring defects in the pump. A number of pumps for cross transfusion have been described, the most recent of which is that of Salisbury. We have had no experience with this device.

The eventual aim of such cross transfusions in this investigation, if results warrant, is to maintain a continuous parabiotic connection for days and perhaps weeks. Such a goal would demand freedom of movement, independently maintained head of pressure with automatic regulation and continuous flow of blood. A connection such as exists in the Siamese twin parabiosis would be ideal though difficult to maintain.

Vein to vein, artery to vein and artery to artery cross transfusions were tried and evaluated for the specific purpose of investigating the pulmonary leukocyte removal mechanism. This report deals with the relative success of these methods and the behavior of the patients during and after seven such cross transfusions.

METHOD AND SUBJECTS

All patients in these studies were suffering from hopelessly incurable neoplastic diseases. The details, risks and experimental nature of the procedure were thoroughly explained both to the patients and to their close relatives prior to obtaining their written consent. The possibilities of transmission of neoplastic diseases and fatality from the procedure were properly emphasized and fully discussed.

The participants of the cross transfusion were matched according to blood group, major Rh type and usually the blood volume. The latter varied, however, particularly when children were cross circulated, since an adult was the donor in such instances. Heparin was used as the anticoagulant in all procedures. A large room isolated from the routine traffic of the ward served admirably. Hospital beds or preferably narrow tables (30 inches wide) were employed, with the patients placed head to foot (fig. 1).

The first two cross transfusions were accomplished by a direct vein to vein connection employing clear rubber tubing and the blood was pumped manually by syringe. The veins were isolated and cannulated after cut-down. Twenty to 50 cc. of blood were removed from the veins of patients A and B and then given intravenously to each partner. Both patients were kept heparinized with 1 to 2 mg./Kg./hour. The syringes and tubing were frequently flushed with heparinized saline. The difficulties encountered with fibrin formation and coagulation prevented simultaneous withdrawal and administration at all times although this was the aim.
The third procedure was by direct artery to vein connection. The arteries and veins were isolated surgically and connected so that the arterial blood of higher pressure would run from patient A to the low pressure venous channel of patient B and vice versa. The major difficulty was technical since it was felt inadvisable to jeopardize both artery and vein in the same extremity for fear of diminished circulation following repair. Therefore, four separate cannulation sites were needed and although the blood flow was excellent, the dangers of pulmonary embolic phenomena remained present.

The remaining four cross circulations were artery to artery, and since this method was eventually selected in preference to the others for this study, it is described in detail. In

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**Fig. 1.**—Schematic representation of the artery to artery connection for cross transfusions.

Adult to adult interarterial cross circulation, the superficial femoral artery was chosen at an area just distal to the branching of the profunda. In the fourth cross transfusion the brachial artery of the adult was selected, since it approximated the size of the child’s superficial femoral artery.

**Surgical Procedure for Artery to Artery Cross Transfusion**

The femoral artery in Hunter’s canal below the profunda branch was used. A 6 cm. incision was made over the sartorius muscle roughly 10 cm. below the inguinal ligament, carrying out all of the usually aseptic surgical precautions. The incision was developed down through the subcutaneous fat to the fascia overlying the sartorius muscle. The fascia was divided parallel to the muscle, and the muscle was retracted either laterally or medially, whichever proved to be easier, exposing the neurovascular bundle. The artery was then dissected away from the vein and the nerve, over a distance of approximately 4 cm. A cotton tie was placed beneath the artery at both the proximal and distal portions and kept in readiness to anchor the cannula in place. Large bleeders were clamped and tied with cotton and the smaller bleeding points electrocoagulated to keep the wound as dry as possible. This surgery was then repeated on the other patient to be used in the cross transfusion,
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utilizing the leg closest to the artery already exposed. As soon as the artery had been well exposed in the second patient and all was in readiness, the patients were heparinized.

The artery was incised longitudinally and a large cannula 13-16 or polyethylene tubing with an internal diameter of 2 to 4 mm. was inserted proximally into the femoral artery of patient A and the other end of the tubing was likewise placed into the distal end of the artery of the recipient patient B (fig. 1). The procedure was then repeated in the other direction to complete the cycle. The cotton sutures were tied, constricting the artery around the cannulae and anchoring them in place. The ties about the arteries and cannulae effectively reduced the blood pressure in the distal segment of the artery, permitting flow from the high pressure proximal segment of patient A to the low pressure distal segment of patient B, and similarly from B to A. The wound was then covered with sterile towels. Maximal aseptic technic was maintained throughout the course of the procedure (fig. 2).

Fig. 2.—Patients after six hours of a twelve and one-half hour continuous cross transfusion artery to artery. The venturimeters, which record the rate of blood flow in each direction, can be seen in the center of the photograph.

Completion of the Procedure

When the experiment had been completed, the ties around the artery were cut. Rubber bands were placed beneath the artery to control the blood flow through the vessel. The cannulae were next withdrawn. Using 00000 arterial suture (DeKuetal), the defect in each artery was repaired with a running suture. The skin was closed with cotton sutures. No attempt was made to close the deeper layers of the wound as these wounds were considered potentially infected. Pressure dressings were applied and antibiotics used liberally. Inasmuch as the procedure was carried out well below the profunda branch of the femoral artery, ligation of the superficial femoral artery could be carried out if repair was impossible.

The initial dose of heparin was 2 mg./Kg. body weight and was given just before the cannulae were inserted into the arteries. Adequate heparinization early in the procedure was of extreme importance since it was very difficult to free the system once clotting started. Duplicate tubing and cannulae could then be substituted if the obstruction could not be cleared. A clotting time in excess of three hours was maintained by heparin administered every one to two hours.

In five of the cross transfusions (No. 3 to No. 7) two glass venturimeters were incorporated into the system to measure the flow of blood in each direction. Control of the flow by means of adjustable clamps was dictated by inequalities of rate of flow as read on the
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manometers. However, the vasomotor systems of both patients were sufficiently sensitive so that the flows soon approximated one another closely and rarely required mechanical manipulation of the flow after a few hours. An adjustable clamp permitted ready access of blood from one patient to another via the arterial route if any sign of hypotension appeared.

For the first six cross transfusions, clear rubber and plastic tubing were used. On the sixth cross transfusion fibrin formed in the venturimeters and caused emboli to the foot of one of the patients (see No. 6). On the seventh cross transfusion, the tubing and venturimeters were siliconed throughout, and there was no sign of fibrin or clot formation during the entire study which exceeded twenty-six hours.

The arterial blood flowing from each patient was sampled simultaneously at frequent intervals from a T tube incorporated in the connecting tubing for chemical and hematologic determinations. Heparin was used as additional anticoagulant for the samples and all determinations were run on fresh specimens insofar as possible.

**Table 1**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Type of Connection</th>
<th>Amount Blood Received</th>
<th>Duration of Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. S.</td>
<td>3</td>
<td>F</td>
<td>Acute lymphatic leukemia.</td>
<td>Vein to vein*</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>T. H.</td>
<td>34</td>
<td>M</td>
<td>Carcinoma, lung.</td>
<td>Vein to vein*</td>
<td>0.6</td>
<td>6</td>
</tr>
<tr>
<td>J. S.</td>
<td>3</td>
<td>F</td>
<td>Acute lymphatic leukemia.</td>
<td>Vein to vein*</td>
<td>4.3</td>
<td>6</td>
</tr>
<tr>
<td>D. C.</td>
<td>51</td>
<td>M</td>
<td>Carcinoma, mouth.</td>
<td>Vein to vein*</td>
<td>3.9</td>
<td>6</td>
</tr>
<tr>
<td>J. S.</td>
<td>3</td>
<td>F</td>
<td>Acute lymphatic leukemia.</td>
<td>Femoral vein and artery from brachial artery</td>
<td>2.0</td>
<td>4</td>
</tr>
<tr>
<td>T. H.</td>
<td>34</td>
<td>M</td>
<td>Carcinoma, lung.</td>
<td>Femoral artery to femoral artery</td>
<td>2.0</td>
<td>4.25</td>
</tr>
<tr>
<td>C. S.</td>
<td>34</td>
<td>F</td>
<td>Carcinoma, pelvis.</td>
<td>Femoral artery to femoral artery</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td>E. G.</td>
<td>57</td>
<td>M</td>
<td>Lymphatic leukemia.</td>
<td>Femoral artery to femoral artery</td>
<td>4.1</td>
<td>12.5</td>
</tr>
<tr>
<td>S. M.</td>
<td>32</td>
<td>M</td>
<td>Hodgkin's disease.</td>
<td>Femoral artery to femoral artery</td>
<td>80.0</td>
<td>12.5</td>
</tr>
<tr>
<td>H. D.</td>
<td>31</td>
<td>M</td>
<td>Carcinoma, testis.</td>
<td>Femoral artery to femoral artery</td>
<td>80.0</td>
<td>15.0</td>
</tr>
<tr>
<td>B. H.</td>
<td>2</td>
<td>M</td>
<td>Lymphatic leukemia.</td>
<td>Femoral artery to femoral artery</td>
<td>15.0</td>
<td>6</td>
</tr>
<tr>
<td>G. W.</td>
<td>57</td>
<td>M</td>
<td>Myelogenous leukemia.</td>
<td>Femoral artery to femoral artery</td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>E. W.</td>
<td>37</td>
<td>M</td>
<td>Melanoma.</td>
<td>Femoral artery to femoral artery</td>
<td>150.0</td>
<td>15.0</td>
</tr>
<tr>
<td>G. J.</td>
<td>51</td>
<td>M</td>
<td>Subleukemic lymphatic leukemia.</td>
<td>Femoral artery to femoral artery</td>
<td>150.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

* By means of manual syringe pump.

**Hematology**

All cell counts were done by the same individuals employing NBS certified Trenner automatic filling pipets and NBS certified hemocytometers. Eighteen squares on both chambers were counted after a ten minute period of shaking of the filled pipet to ensure uniform distribution. Fixed smears taken at the same time were prepared with Wright's stain and studied later. Fresh cover slip preparations with supravital staining were studied periodically as a check during the cross transfusion; hematocrits, platelet and reticulocyte counts were done by the routine accepted methods.

**Results**

Seven cross transfusions were attempted and completed (table 1). The shortest cross transfusion was for two hours with a flow of 900 cc. during this period. The longest cross transfusion consumed twenty-six hours and resulted in 150 liters of blood being exchanged (table 1).
Marked changes in the total leukocyte count of the leukemic individual occurred after the cross transfusion in four instances (Nos. 1 to 4). Disappearance of a leukemic skin infiltration occurred overnight in one individual (J. S.) and a moribund state was replaced by one of a transient remission for one month in this same individual (cross transfusion No. 1). Equilibration of the leukocyte counts occurred only in one case; that in a cross transfusion between 2 leukemic individuals (No. 6). The leukocyte levels failed to equal one another during a twenty-six hour cross transfusion of a patient with metastatic melanomarca and a patient with sub-leukemic lymphatic leukemia although over 150 liters of blood were exchanged (No. 7). The details of each cross transfusion are presented in their protocols.

Cross Transfusion No. 1 (fig. 3)

The subject J. S., female, age 3, lymphatic leukemia, was cross circulated with T. H., male, age 34, bronchogenic carcinoma on May 26, 1949. This procedure was vein to vein, using heparinized saline and mineral oil lubricated syringes to pump the blood. Only 1000 cc. of blood were crossed in two hours. At one hour, the leukocyte count of J. S. fell from 148,000 to 110,000 and, subsequently, returned to 144,000 at the conclusion of the procedure. This child was moribund at the start of the procedure and after the early minutes of the cross transfusion, she was observed to awaken, become alert and improve in color, activity and general status.
At the start of the procedure there was what appeared to be a well-defined 2 x 1 cm. hemorrhagic leukemic infiltration of the left nasolabial fold. The next morning, twelve hours after the end of the cross transfusion, this lesion had vanished and only slightly wrinkled skin remained in that area to mark the former site of the lesion. Observers who had not previously seen the infiltration were unable to detect the area of involvement. The procedure was discontinued at two hours because of pain about the cannula in patient T. H. with subsequent hypotension and the relatively slow exchange of blood.

The count fell from 144,000 immediately after completion of the procedure to 32,000, twelve hours after the cross transfusion and subsequently to 30,000, seven days later.

Cross Transfusions Nos. 2 and 3 (figs. 4 and 5)

This same child J. S. was cross transfused on two subsequent occasions. No. 2, J. S. with D. C., male, age 51, epidermoid carcinoma of lip, intervenous, on June 7, 1949, and No. 3,

Fig. 4.—Cross transfusion No. 2. Rise in leukocyte level in both patients, more in the leukemic individual. Again the marked decrease in leukocyte count to leukopenic levels after the procedure was discontinued.

J. S. with T. H. (same patient as in No. 1), artery to vein, on June 17, 1949. Following the second procedure she enjoyed a temporary improvement for three weeks during which time her general condition reverted toward normal with decrease in lymph node enlargement, hepatosplenomegaly and hemorrhagic manifestations. In each of the three cross transfusions, a marked decrease in the leukocyte count was observed after the procedure was discontinued. Following each period of transient improvement she again exhibited more evident signs of her leukemic process, and succumbed eleven days after the third cross transfusion.

Postmortem examination on J. S. on June 28, 1949, revealed complete bone marrow aplasia, widespread hemorrhage, reticular hyperplasia of lymph nodes and a few scattered immature cells in skin, breast, myometrium, renal cortex and lymph nodes.

Partner T. H. (No. 1 and No. 3) expired at home on October 26, 1949. Postmortem examination revealed characteristic bronchogenic carcinoma with widespread metastases. There was no evidence of any leukemic process.

Partner D. C. (No. 2) expired on June 23, 1949, sixteen days after the cross transfusion on June 7, 1949. Postmortem findings showed squamous cell carcinoma of buccal mucosa, floor of mouth with extensive local invasion of gingiva, tongue and skin. Bilateral bronchopneumonia was the terminating event. No evidence of lymphatic leukemia was detected.
Fig. 5.—Cross transfusion No. 3. Same participants as in figure 3. Fall in white cell count during and after the procedure. Rise from 4,000 to 9,000 in the nonleukemic participant during the exchange with return to original level thereafter.

Fig. 6.—Cross transfusion No. 4. Marked decrease of leukocytes below 2,000/cu. mm. in leukemic patient. Restlessness from relatively fixed position in patient C. S. forced cessation of procedure and may be responsible for rise in count at that time.
Four and one-tenth liters of blood were crossed in four hours and fifteen minutes on June 9, 1949 (C. S., female, age 34, epidermoid carcinoma of the pelvic wall, with E. G., male, age 57, lymphatic leukemia). A decrease in leukocytes from 16,600 to 7,800 in patient C. S. was noted twelve hours after the procedure was completed. However, it returned almost to its original level five days later. The marked drop from 7,800 to 1,500 white blood cells during the cross transfusion in the leukemic patient E. G. also showed a return to the original level six days after the cross transfusion.

Both patients withstood the procedure well and patient E. G. left the hospital seven days later, with his left lung and mediastinal infiltration improved but with fluid at the left base (figs. 7 and 8).

Patient E. G. expired on September 10, 1949, three months later. Postmortem findings revealed chronic lymphatic leukemia with lymph node and bone marrow infiltration and minimal involvement of other organs, including kidneys, prostate and parathyroid, and bronchopneumonia, left upper lobe (early organization) with empyema and an acute pericarditis.

Patient C. S. expired on September 3, 1949, with a widely metastatic anaplastic carcinoma, primary site undetermined at autopsy. There was no evidence of any leukemic process.
Fig. 8.—Chest film of patient E. G. four days after cross transfusion. Marked decrease in infiltration of left lung and mediastinum. Fluid at left base slightly more than before procedure.

Fig. 9.—Cross transfusion No. 5 (see fig. 2). No significant change in leukocyte count in leukopenic patient during a fall in leukocytes in the other partner.
Cross Transfusion No. 5 (fig. 9)

H. D., age 31, male, carcinoma of the testicle, and S. M., age 32, male, with Hodgkin's disease were cross transfused on June 23, 1949. The cross circulation was continued for twelve and one-half hours artery to artery during which time 80 liters of blood were crossed to and from each participant. Patient S. M. had a leucocyte count of 1,200 which did not change significantly during or following the procedure. During this period the leucocyte count of patient H. D. gradually decreased from 9,900 to 4,500 in 560 minutes with a return to 11,000 four days following the parabiosis.

H. D. expired on August 11, 1949. Postmortem findings were characteristic of a teratocarcinoma of the right testis (choriocarcinoma pattern) with metastases to lung, liver, pancreas, adrenals and lymph nodes.

S. M. expired on September 5, 1949. Hodgkin's granuloma with wide-spread dissemination was found at postmortem. There was also a generalized depletion of lymphoid tissue, bleeding tendency and bone marrow aplasia.

![Graph showing leukocyte counts](image)

Fig. 10.—Cross transfusion No. 6 between 2 leukemic patients. Note prompt increase of leukocytes in the circulation of the child, due exclusively to myeloid cells. Equilibrium of counts attained within four hours and maintained for the remaining two hours of the exchange and for the next thirty hours after the end of the procedure.

Cross Transfusion No. 6 (fig. 10)

The subjects were G. W., a 37 year old male with myelogenous leukemia, and B. H., a 2 year old boy with lymphoblastic leukemia; they were cross transfused on September 8, 1949.

A rapid infusion of 20 cc. of myeloid blood with 165,000 cells per cu. mm. was administered intravenously to B. H. just prior to the cross transfusion because it was feared that a large amount of white cells presented to a small pulmonary leukocyte removal bed might have serious consequences. There was no untoward response whatever in the recipient and many myeloid cells were noted immediately to be circulating in the lymphoid leukemic recipient during the next few hours. The intra-arterial cross transfusion was then undertaken.

There was a prompt rise in total leukocyte count in B. H. soon after the commencement of the exchange (fig. 10). Equilibrium of the white blood cell count occurred at four hours and persisted for the remaining two hours of the cross transfusion.

In this cross transfusion the discrepancies between the sizes of the femoral arteries of G. W. and B. H. were marked. Some difficulty was encountered in keeping the distal-facing
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needle patent and it had to be cleared three times during the procedure. Also, fibrin formed in the venturi tubes of both patients despite a clotting time in excess of six hours.

At the conclusion of the procedure, it was noted that the foot of the infused right extremity of B. H. was cold and there was a line of demarcation at the ankle. Similarly there was an equally cold area 2 x 3 cm. on the posterior aspect of the right calf. During the next three days the line of demarcation descended to the distal third of the foot beyond which it remained cyanotic and cadaveric. It spontaneously amputated forty-two days later without bleeding and the free end epithelialized over rapidly thereafter.

The venturi tubes and connecting tubing had not been siliconed for this cross transfusion. The peripheral white blood cell count in B. H. ten days after the cross transfusion was 4,000. The differential leukocyte count revealed a marked change from a pattern typical of lymphatic leukemia with 90 per cent lymphocytes to a normal hemogram with 70 per cent granulocytes. Bone marrow aspirations on September 12, 29 and October 3, 25, 1949, however, showed little change from the marrow aspiration on September 1, 1949.

FIG. 11.—Cross transfusion No. 7. Marked decrease in leukocyte level in patient E. W. with failure to equilibrate the counts despite twenty-six hours of continuous exchange of 150 liters in both directions. The rise in count in patient G. J. was due almost exclusively to myeloid cells.

B. H. expired on February 15, 1950, five months after cross transfusion. The findings at autopsy were those of acute lymphocytic leukemia with generalized lymphadenopathy, hepatomegaly (1,220 Gm.), and splenomegaly (240 Gm). There was lymphocytic infiltration of the epicardium, lungs, kidneys, adrenals and bone marrow.

The partner G. W. was still alive eleven months after the cross transfusion with essentially no change in his condition.

Cross Transfusion No. 7 (fig. 11)

The participants were E. W., male, age 37, with metastatic melanosarcoma, and G. J., male, age 51, with sub-leukemic lymphatic leukemia. They were cross transfused on November 29, 1949.

The nonleukemic patient (E. W.) had a leukocyte count of 19,000 to 24,000, and the leukemic patient (G. J.) had a white cell count of 1,000/cu. mm. Immediately after the cross transfusion commenced there was a prompt increase of myeloid cells in the sub-leukemic individual which persisted throughout the twenty-six hours of the procedure. The leukocyte count in the patient with melanomasarcoma showed a more gradual fall to an asymptotic level at ten hours. Despite the continuation of the cross transfusion for another sixteen hours, at no time did the leukocyte counts ever equalize or approximate one another closer than 1,500 cells/cu. mm.
Immediately after the cross transfusion was terminated, there was a return of each patient's leukocyte count toward their original levels. The peripheral blood and bone marrow studies of the patient C. J. showed a remarkable change from one predominantly lymphoid to that of an essentially normal picture with a myeloid preponderance.

E. W. expired on December 6, 1949. Findings at necropsy revealed a melanotic melanoma with widespread regional and distant metastases to the lymph nodes and entire gastrointestinal tract, including a recent perforation of the small intestine with peritonitis due to necrosis of a metastatic melanotic nodule. Additional metastases were found in muscle, heart, liver, adrenals, kidneys, bone marrow, spleen, pancreas and thyroid.

G. J. expired on December 12, 1949, thirteen days after the cross transfusion. Postmortem findings were those of aplastic anemia with lymphoid marrow with an atypical maturation of marrow with numerous lymphocyte-like cells, and reticular hyperplasia of lymph nodes with lymphoid atrophy. Additional findings were cellular atrophy of spleen with extreme congestion (1,740 Gm.) and chronic hepatitis with fatty infiltration of the liver (3,600 Gm.).

Complications

The most common complication was hypotension usually in one patient associated with a rise in pressure of the partner. This was promptly and effectively countered by decreasing the outflow and increasing the inflow of blood, and in 2 cases by adding blood to the hypotensive patient by intravenous transfusion.

Hypotension could be avoided if the inequality of blood flow to the participants was kept at a minimum. This necessitated a selection of vessels of approximately the same caliber and close observation. Clot formation could hinder the flow to or from a partner and cause hypotension because of inequality of blood exchanged. This was observed in the early procedures and was partially remedied by the use of siliconed venturi-flow meters. Some inequality of flow resulted during cross transfusion No. 1 from the development of hypotension in one partner due to prolonged pain about the needle site. There was some discomfort of both patients due to the immobility enforced by the indwelling arterial cannulae; occasionally some distress was noted about the cut-down site. Both could be relieved by sedation and local procaine infiltration. The use of polyethylene tubing as cannulae permitted more mobility than the metal needles employed in earlier cross transfusions.

Sterile technic throughout was necessary although admittedly difficult to maintain over such long periods. Penicillin, 400,000 units daily, was started with the cross transfusion and was discontinued only after the wound had healed per primam. Only two wound infections have occurred.

The most serious complication occurred in the 2 year old boy with lymphatic leukemia (B. H.) who was cross transfused with an adult with myelogenous leukemia (G. W.). A dry gangrene developed, resulting in spontaneous amputation of the distal third of the foot. This complication probably could have been avoided by the use of silicone in the tubing.

There was no evidence of hemoglobinuria, hepatic disturbance or visceral damage directly attributable to the procedure in the 11 patients observed. Although 10 of the 11 patients were followed for relatively short periods, there was no indication at postmortem of transmission of leukemia or any neoplastic processes to either partner in the cross transfusion. The eleventh patient survived with his myeloid leukemia unaltered at the time of writing.
Previous investigations demonstrated that infused leukocytes would traverse the peripheral capillary bed in the lower extremity and yet be removed by the pulmonary mechanism. The prior administration of heparin in large doses, 2 to 3 mg./Kg./hour, permitted more infused leukocytes to pass the pulmonary barrier than if the clotting time were normal. It must be emphasized that during these cross transfusions both patients were kept well heparinized so that the clotting times frequently exceeded six hours. As the time to end the procedure approached, no further heparin was administered (except in one instance, patient B. H.) so that excessive bleeding would not unduly influence satisfactory surgical closures of the wounds. Therefore, the lung removal mechanisms under observation in these studies may have been influenced by heparin and must be so interpreted.

Arterial blood counts have proven to be stable and closely approximate finger or ear blood samples. Assuming that there are no leukocyte delivery or removal areas between the left auricle and the femoral artery, and none have been demonstrated, leukocyte counts from the femoral artery are essentially equivalent to those leaving the pulmonary vein. Since the peripheral capillary bed of the lower extremity does not remove leukocytes, the blood samples obtained arterially from patient A represent essentially the blood in the femoral vein of B enroute to the lungs. Therefore, arterial samples under these circumstances represent an estimate of the blood before and after passage through the lungs, permitting a study of the pulmonary circulation with respect to the removal of formed blood elements.

The lung is a potent organ in the immunologic system. It contains the largest amount of histamine of any organ. Andrewes and Webb found the lungs of rabbits and guinea pigs overloaded with leukocytes following death from anaphylactic shock. Since the lung removal mechanism was under study, it was felt advisable to infuse the blood intra-arterially rather than intravenously and thus spare the pulmonary circulation from large amounts of concentrated blood from a heterogeneous donor.

One of the potential hazards and possible benefits of this procedure is the production of antibodies stimulated by the introduction and continued circulation of blood from a heterogeneous donor. Despite the precaution of careful cross-matching, there are undoubtedly many other substances in whole blood which may serve as antigens in both patients under such circumstances. These substances, which may serve as antigens in the other participant, circulate repeatedly in large quantities, thus creating a situation which is ideal for immunologic responses. These may act favorably or otherwise on either patient. The hypoplasia of hematopoietic tissue in 3 patients may have been the result of such an overwhelming hyperimmune response. One might speculate that if leukemic blood would serve as an antigen, a recipient of this blood might conceivably be immunized against this disease.

In earlier studies it became apparent that despite prolonged clotting times produced by massive repeated doses of heparin (2 to 3 mg. Kg./hour), fibrin occasionally would form in the glass sections of the connecting arrangement...
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(venturimeters, T-tubes). Most of these fibrin clots were cleared but in one case (B. H.) it was probable that some fibrin was carried into the leg and lodged in the distal third of the foot causing loss of circulation to that area. Siliconizing the connecting tubing eliminated this complication subsequently, but such a possibility must be considered as one of the hazards of cross transfusion.

During cross transfusions with dogs, fibrin formation was a constant threat, particularly when silicone was not used. It proved essential to have both animals well heparinized before the cannulae were inserted. Clot or thrombus formation also add to the possible dangers of the procedure. Embolic phenomena would probably have far more serious consequences if thrown into the pulmonary circulation than into a lower extremity. Although the carotid arteries are surgically accessible, the potential danger of embolic phenomena again makes them undesirable.

From cross transfusions Nos. 1, 2, 3 and 4 it was apparent that while relatively little change in the peripheral leukocyte count took place during the procedure, a marked decrease in the number of circulating leukocytes occurred in the twelve hours after the cross transfusion was discontinued. Whether this decrease was due to the blood exchanged per se, the loss of leukemic cells, a washing out process or the influence of heterogeneous blood on the recipient is difficult to determine at this time. Dreyfus has related remissions in acute leukemias to the amount of blood transfused. Bessis and Henstell et al., have also observed the beneficial effect by transfusion of large amounts of blood. While it has not been possible statistically to substantiate the clinical impression of the advantages of transfusion therapy in leukemias it must be realized that the usual blood transfusions are given intermittently and in relatively small amounts when compared to the amounts exchanged here.

As previously stated, evidence is accumulating that one of the basic disturbances in some of the leukemic states may be an imbalance between the delivery into and the removal of leukocytes from the circulation. It has been postulated that some leukemic individuals with elevated leukocyte counts have an impaired removal mechanism thus favoring an excess number of leukocytes by virtue of their lack of normal removal rather than by virtue of hyperproduction. That the leukemic individual B. H. had an impaired lung removal mechanism as compared with the nonleukemic individuals in the other cross transfusions, is further support for this theory but most certainly not conclusive. More evidence on other leukemic subjects is needed.

Cross circulation may have value in the investigation and possible treatment of various conditions, particularly acute anuria, hypertension, erythroblastosis fetalis, irradiation overdosage, overwhelming infections in which large amounts of immune blood are needed, and neoplastic diseases, including leukemia. The transfusion of leukemic leukocytes does not appear to be dangerous. Cross transfusions may be of use in operative procedures attended by shock or release of toxic substances, or as a shunting device to permit a more direct attack on the heart, lungs and other vital organs. It should, however, be properly emphasized that cross transfusion in man remains at present an experimental procedure which should be undertaken only with full appreciation of the attendant risks and hazards.
STUDIES ON CROSS CIRCULATION IN MAN

Summary

1. Methods for continuous intervenous, arterial venous, and interarterial cross transfusions in man have been developed and a total of seven procedures have been successfully performed.

2. The interarterial method was preferred for an investigation of the pulmonary leukocyte removal mechanism and has been carried on for as long as twenty-six hours exchanging 150 liters of whole blood both to and from each participant.

3. On three occasions within twelve hours after the cross transfusions were terminated, a marked decrease in the leukocyte count occurred in 1 leukemic participant. Marked generalized improvement in the leukemic status occurred after each drop in the leukocyte count.

4. By cross transfusing an adult with myelogenous leukemia and a child with lymphogenous leukemia it was possible to pass myeloid cells through the pulmonary leukocyte removal mechanism into the circulation of the patient with lymphogenous leukemia.

5. An excessive leukocyte removal mechanism was demonstrated during another cross transfusion by a patient with sub-leukemic lymphogenous leukemia.

6. Cross transfusion in man is experimental and offers a technic of value as an investigative method for the study of formed elements and chemical constituents of the blood under these circumstances.

7. Careful cross matching for compatibility of blood and Rh type is essential and the hazards and risks of the procedure have been emphasized.

References

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Studies on Cross Circulation in Man: I. Methods and Clinical Changes

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