

Symposium

Blood and Blood Replacement

The Philosophy of the Use of Blood and Blood Products

Blood as a therapeutic agent represents an ancient concept. Probably, prehistoric man when he made his kill, noticed the flow of blood and realized that this fluid carried life and was therefore important. Certainly, historic man, early on, regarded blood highly and used it in several ways, smearing himself with it, bathing in it, and even drinking it with the idea that it could benefit him directly. Only when physicians began to note and accumulate scientific facts about the blood, especially its circulation, did transfusion become a possible mode of therapy. It was just about 200 years ago that references to authentic transfusion began to appear, describing blood infused through hollow quills or silver tubes. At first blood transfer was tried between dogs but later from animal (the lamb) to man. The bold and fearless surgeons who performed these remarkable transfusions saw no ill-effects from such treatments and confidently claimed benefits which the presently-known laws of species immunologic specificity make impossible. Even when limited to human donors, serious hemolytic reactions in recipients made transfusions hazardous. For without regard for major blood compatibility, the likelihood of such a reaction is about 35 per cent. Only after the turn of the century and Landsteiner's epoch-making discovery of the ABO blood groups was this statistical risk avoidable. Thereafter, blood transfusion became a practical and often lifesaving measure to combat blood loss and profound

anemia. But it was no simple procedure, since without an anticoagulant transfusions had to be of the "direct" type, connecting donor to recipient. Transfusion required a skilled operator and usually a practiced team. So the specialty of the transfusionist developed—often a hematologist but sometimes a dermatologist or syphilologist who had developed skill in administering intravenous treatments. Young physicians were attracted to this specialty for transfusion therapy paid well.

A simple discovery made the transfer of blood a much less hurried and less dextrous operation. In 1915, sodium citrate was found to prevent clotting, and thereafter the indirect transfusion became popular—blood being stirred into the citrate solution and transferred more slowly into the recipient. Even the lowly intern could learn to do this efficiently. Furthermore, the citrated blood could be kept under refrigeration for about a week, so that stored blood became a useful commodity.

Logically attention turned next to better and longer preservation of blood and the philosophy of the blood bank caught the imagination. Merely one week's storage was wasteful since an appreciable percentage of the "banked blood" would remain unused and become unusable at the end of this period. Under the stimulus of the demands of World War II, acid-citrate-dextrose was developed as the diluent-preservative, permitting blood storage for three full weeks at 4°-6° F. with



Transfusion from lamb to man (seventeenth century). Surgeon at left lets blood to make room for incoming flow from lamb. (This illustration and the other historical pictures by courtesy of The Bettmann Archive Inc., New York City.)

The drawing of the circulation appearing on the JOURNAL cover is from the first complete textbook of human anatomy, *De Humani Corporis Fabrica* (1543) by Andreas Vesalius.

the desired 70 per cent survival of the red cells, *in vitro*. By this time, the Blood Bank had become an accepted and a useful part of a hospital service, a necessary adjuvant to good and extensive surgery and for rapid and better recovery of the bled-out or chronically anemic patient.

Meanwhile, a major development in immunoserology served to explain previously mysterious hemolytic transfusion reactions, to protect against their further occurrence, to uncover the cause of the hemolytic disease of the newborn (erythroblastosis fetalis) and re-awakened a widespread interest in identifying new blood group factors. Dr. Philip Levine deserves prime credit for discovering what has become known, somewhat illogically, as the "Rhesus (or Rh) factor." This opened the door to further serologic research, using new and more sensitive methods of detecting blood group antibodies and the agglutinogens they identi-

fied on the surface of the red cell. Whereas before 1941 there were three families (ABO, MN and P) of blood groups with a total of 10 types, now there are at least 11 independent families of blood groups and over 100 subtypes. Fortunately, most of these are poor antigenic stimuli and only half a dozen or so can sensitize a recipient of a transfusion or the mother of a blood-group incompatible infant to a blood factor which she lacks. The outstanding examples are the Rh types and subtypes which are so commonly the cause of hemolytic disorders in newborns, or erythroblastosis fetalis. Other than the five most common Rh subtypes, only the Kell factor is strongly antigenic, and since this occurs relatively rarely (only about 10 per cent) in the general population, it does not represent a serious hazard in transfusion nor is it a common cause of transfusion reactions.

The next step in improvement of transfusion



Early type of transfusion was practiced by Johann Elsholtz (seventeenth century), who injected donor's blood into open vein.



First animal transfusion was staged by Richard Lower in 1665. Blood was passed through silver tube from artery of one dog to vein of another. Animal receiving blood survived.

therapy was the recognition that blood as a therapeutic measure is akin to a shot-gun medication in that it contains three different cellular elements and dozens of different chemical fractions. Since in most instances, whole blood usually was given only for its red cell content, all the other ingredients were unnecessary, wasted and dangerous because of the possibility of producing sensitization or reactions. Even as early as the mid-1930's, it was realized that blood plasma could be used advantageously to combat hypovolemic shock, to raise serum protein levels, and to provide certain antibodies. Moreover, plasma could be processed and stored for years. Obviously, in such cases, the red cells were in the way, and possibly harmful if incompatibility were present. Understandably, plasma was used more extensively, in fact too widely, as when it was given to

bleeding or bled-out persons in shock. The plasma further diluted the already depleted red-cell mass and the resulting increased anemia could cause anemic anoxia and death. The "swing" eventually was back to whole blood, or better still to sedimented or packed red cells to restore the hematocrit or treat anemia.

The philosophy of using specific blood components separately for specific replacement therapy—which is the basis for proper and efficient blood bank practice today—really began with attempts at the separation of albumin, the most stable of the plasma proteins. Not until the great Edwin J. Cohn perfected the method of fractionating and purifying the many components of plasma did specific replacement treatment become really possible. As Dr. Cohn emphasized repeatedly, it was



Erasmus Darwin (1731-1802) revived the practice of transfusion to sustain sufferers from cancer of the throat.

wasteful and inefficient to use whole blood or even plasma alone when a patient needed albumin for treatment of hypovolemic shock, or gamma globulin for specific antibodies, or fibrinogen for some clotting problems. Thanks to his foresight and vigorous championing of this principle, albumin and gamma globulin were produced, stockpiled and widely used, beginning more than 20 years ago, during the War. These plasma fractions are rightly credited with the protection and saving of thousands of lives. No longer is "shot-gun" medicine—the unit of whole blood—the only product available in the blood bank. With the introduction of modern plastics, single unit factory-sterilized blood bags and tubes with attached disposable needles now provide contamination-proof blood packs which minimize the danger of microbial infection, even with the dread homologous serum hepatitis virus. The non-wettable surfaces of the plastic equipment and siliconized needles permit better procurement of unclotted blood. It is then easier to separate by immediate centrifugation not

only the red cells but also fresh platelets. And the plasma can be processed at once in order to obtain unaltered some of the labile components such as antihemophilic globulin. The modern blood bank, therefore, should have available not just one or two products but more than a dozen, for many specific needs. A representative list would be: (1) whole blood, for treatment of acute bleeding; (2) fresh whole blood taken into heparin solution for exchange transfusion of the newborn infant or for massive transfusion; (3) packed red cells, for most cases of anemia, especially the chronic types; (4) fresh platelets for thrombopenic purpura in the bleeding phases or preoperatively; (5) fresh frozen or freshly-drawn plasma for hemophilic bleeding or other hemorrhagic states requiring labile clotting components; (6) stored plasma for bleeders, with Christmas disease (hemophilia B) and for ordinary plasmas replacement (hypovolemic shock and chronic malnutrition); (7) albumin for hypoalbuminemia; (8) gamma globulin for prophylaxis against measles, infectious hepatitis and hypo- or a-gamma globulinemia; (9) fibrinogen for treatment of hypo- or afibrinogenemia; (10) antihemophilic globulin concentrates for treatment of hemophilic bleeding; (11) prothrombin for hypoprothrombinemia, particularly in hepatic disease; and (12) finally, preserved blood of special rare types which are difficult to obtain at short notice (e.g., group AB, Rh negative, 0.75 per cent incidence, or even more rare, Rh negative, Kell negative, 0.03 per cent, etc.). Such blood is now available from a few special banks, in glycerinized units or rapidly frozen in liquid nitrogen, both stored at extremely low temperatures.

Such is the present philosophy of most scientists concerned with the use of blood and its component parts. We have almost come full circle (although by logical scientific steps we hope) to the seventeenth century concept that blood is a magic therapeutic substance which may transfer to its recipient not only the donor's vim and vigor but also his disposition and mental stability (? through endocrine factors).

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