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Blood transfusion : history, groups and reactions

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BLOOD TRANSFUSION;
HISTORY, GROUPS AND REACTIONS

By

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HISTORY OF BLOOD TRANSFUSION

The history blood transfusion is among the most fascinating, interesting, unusual and romantic part of medical history. There is probably no other therapeutical measure in the whole range of medical science which has waxed and waned with such extremes in medical usage. The idea that blood contained the vital essence of life is almost as old as medicine itself. There is abundant evidence in the ancient belief in the use of blood as a remedy, the idea being that healthy blood should be used as a potion for the treatment of various ills (70). And likewise the degrading effects of the abuse of blood in cases of perversion (20).

Historical beliefs regarding the effects of blood:

Pliny about 50 A.D. tells of the drinking of the blood of dying gladiators in the arena "as if out of living cups," for epilepsy; that "a man's own blood rubbed upon himself will relieve pain;" and that the Egyptian kings used baths of blood for the cure of elephantiasis. Galen about 200 A.D. advised the drinking of blood for the cure of various diseases, particularly epilepsy (20, 70).

One who drinks menstrual blood or the blood of a leper will act as a lunatic, will be sexually uncontrollable and generally evil. The antidote is to eat serpents whose heads and tails have been removed in the proper

manner. There were numerous, many not without humor, of the uses of cats, doves, turtles and other animals' blood in various mixtures for treatment, especially of epilepsy. One girl, an epileptic, is mentioned, who after taking cat's blood acted like a cat. If a black cat's tail be cut off at the distal third, and the first three drops of blood given to an epileptic, it will act towards a cure; the blood from a wild cat should be even better. The blood from the ear of a black cat should be of value in the treatment of erysipelas. The drinking of blood of a weasel or of a dog for the bite of a rabid animal was well recommended. The mixed blood of turtles, seals and man was used for the treatment of epilepsy, fits and scurvy among the Norwegians, and that of the reindeer in Lapland. Mixed blood from kids, geese and ducks was used for diseases affecting the spirits. The flowing blood from the wounded soldiers was saved and drunk as a remedy. People would rush into the arena and drink the fresh flowing blood of the wounded and dying gladiators. Distillates from the blood were employed with other distillates of even very obnoxious substances as the human bowel excreta for the remedy of many diseases. The blood was thought to contain various spirits and so it was used to treat cases that were thought to be due to the maladjustment of these mythical factors in the hope that it would restore the derangement (20).

Venesection once a very common practice:

This historical comment would be incomplete and would leave a false impression if blood letting was not mentioned. Bleeding has a prehistoric origin and may have arisen from the relief afforded by menstruation, nose bleed, and bleeding from piles (135). The rationale was that bleeding with the copious forcing of water washed and cleansed the blood (45, 57). Hippocrates 460 B.C. advised it for hypochondria, gas dyspnea, pain in the chest, flushing of the face, apoplexy, epilepsy, and "diseases connected with collection of the humors", palpitation, livid sputa, quinsy, fever, and over filling of the stomach. Celsus about 25 A.D. recognized that a patient's strength should be considered; and that a patient with a high fever should not be bled. Galen about 200 A.D. recommended quantitative blood letting, from 200 to 500 cc in the average case. He increased the number of diseases for which blood letting was used. It was probably upon his authority that it was extended later to almost every ailment (45). Bleeding became the fashion, carried on without reason once a year. Not only by the medical profession, but by the barbers and the tenders of public bath houses. Excessive blood letting glasses were handed down from family to family as treasured heirlooms. Some of the physicians bled their patients moderately, others bled them severely and repeatedly; and then

because the patient felt faint and weak and his pulse was rapid and weak, he was still bled again (45, 57). The fact is the first human transfusion was performed on a boy who was exhausted from repeated venesection (158). A verse exaggerating the tendency to bleed with other procedures:

"When patients to me apply,
I purges, bleeds, and sweats 'em:
If after that they choose to die,
What's that to me? I let's em."

Our own General George Washington died from loss of blood at his physicians' hands (45).

Transfusion without authentic support:

The old Egyptian writings refer to blood transfusion as a procedure to be used as a means of medication for the kings and princes (54). Herophilus, the great Alexandrian anatomist speaks of blood transfusion. It was condemned by Pliny and Celsus (42). A Jewish physician in 1492 took blood from three boys for Pope Innocent VIII. There is some doubt as to whether the transfusion was done. It is thought that a drought was made for the Pontiff but he and the boys all died (34, 57). Cardemes in 1556 offered to redeem the unregenerate by transfusion of blood from the virtuous. Andreas Libavius describes a blood transfusion before Harvey's discovery of the circulation of the blood which was 1613 to 1616 (20, 70). In his description of the

procedure, he tells how the blood from a strong healthy robust young man may be transferred with two silver tubes to the vessels of a thin, emaciated, weakened old man hardly able to contain his own soul, giving him life and strength. Then he cautions that the young man be given good care and food so that he will not suffer. But writers refer to this reference as ironical and doubt if Libavius ever saw or ever did a transfusion (20, 70). The first blood transfusion has been accredited to Francesco Folli, a Florentine physician, in 1654. He used a silver tube in the artery of the donor and a cannula in the vein of the recipient, connected by a hollow pipe made from a blood vessel from an animal. About the same time, a monk of Cluny demonstrated the possibility of intravenous transfusion using two silver tubes connected by a leather ball and containing valves so that the quantity of blood could be measured (20, 70). But these do not have authenticated records (57).

The first authentic blood transfusions:

The first authenticated blood transfusion was performed in England by Richard Lower from dog to dog. In 1665 he gave a demonstration of the procedure before the Royal Society in London, uniting an artery of one dog to a vein of another by means of two quills or silver tubes (20, 70, 158).

Jean Baptiste Denys or Denis of Montpelliar, physician to King Louis XIV, is given the honor of the first transfusion to man (20, 70, 158). In 1667, he injected the blood of a calf or lamb into the veins of a youth, somnolent and listless from loss of blood by repeated venesection. The patient became greatly improved and recovered. About this time, he transfused a well man with 20 ounces of blood from a lamb after having bled him of 10 ounces. The man suffered no bad results. Denys performed the procedure a third time; this time on a moribund patient who died a few hours later. His fourth transfusion was performed on an insane person and repeated twice. Following the second transfusion "his arm became hot, the pulse rose, sweat burst out over his forehead, he complained of pain in his kidneys and was sick to his stomach. The next day, the urine was very dark, in fact black." Following the third transfusion which was given at his wife's request, he died. Denys was tried for murder but exonerated. But was withstrained from further transfusions on humans except by the approval of the faculty of medicine of Paris, who were in opposition to blood transfusion. (158)

Lower in November 1667 transfused a sick man, Cogo, from a sheep; he died probably from complete hemolysis (20, 70). According to Zimmerman & Howell, the trans-

fusion performed by Lower in November 1667 was successful and was also repeated successfully on the same patient (158). Due to the fatalities following blood transfusion, public opinion became against the procedure and as a result the law of France and England prohibited it on humans; and the Pope in 1678 gave an edict prohibiting it. So the practice fell into oblivion for about the next century and a half (20, 70, 158). Germany and Italy both had their experimenters, but the procedure likewise was discontinued in both places (158).

About 150 years later, interest was again aroused in blood transfusion. In 1792 at Eye in Suffolk a Dr. Russell transfused the blood of two lambs into a boy suffering from hydrophobia and the recovery of the boy was attributed to the transfusion. In 1796 Erasmus Darwin advised transfusion for "putrid fever", cancer of the esophagus and cases of malnutrition. He suggested the use of goose quills connected by a short chicken's gut. There is no record that he followed his own advice (70).

James Blundell, an Englishman, in 1818 published his successful experiments on transfusion following hemorrhage by the use of syringe with a three way stop-cock; and of air injection in dogs - it required five drams of air in a very small dog to even cause any effect (14). He was the first to transfuse blood from human to

human and to show the value of this procedure in hemorrhage (158). In 1820, he stated "'that transfusion by syringe is a feasible and useful operation, and that after undergoing the usual ordeal of neglect, opposition and ridicule, it will hereafter be admitted into general practice.'" (70) The great difficulty in the use of the operation was the coagulation of the blood. Bischoff in 1835 tried to overcome this by the use of defibrinated blood as did others (70).

Martin of Berlin 1859 published records of 57 transfusions, 43 of which were successful. The fatalities were thought to be due to air embolism, but were more likely the result of incompatibility. Many and varied apparatuses were devised. Higginson 1857 added the rubber syringe with ball valves (70). Braxton Hicks in 1868 attempted to prevent blood coagulation with sodium phosphate (158). A summary made by the obstetrical society of London 1873-74 showed the results on the whole discouraging. Blood transfusion was used when the patient was "in extremis" and animal transfusion which was still used hampered asepsis. Karst and Highmore 1874 proposed the subcutaneous injection of defibrinated blood (70 & 158).

Discovery of the blood groups:

Landois observed agglutination and hemolysis 1875 and explained hemoglobinuria on that basis following

blood transfusion (57).

Probably the most outstanding work contributed toward blood transfusion was the work of Landsteiner in 1900, and of Shattock independently, demonstrating the presence of iso-agglutinins and iso-agglutinable substances in the human red blood corpuscles. The next great step was made by Jansky in 1907. He showed that all human blood falls into four groups. Hektoen in 1907 pointed out the danger of iso-agglutination in the transfusion of blood. Moss 1910 confirmed Jansky's work and added that iso-hemolysis of red cells follows previous agglutination, but that agglutination may occur without hemolysis (70, 158). Ottenberg in 1908 developed clinical tests for blood typing and applied clinical tests to human blood transfusion (158).

The development of technic:

The injection of normal saline solution in 1875 to 1880 almost completely replaced blood transfusion. Blood vessel surgery was improved; and petrolatum and paraffin coated vessels and syringes to prevent coagulation decreasing the danger of blood transfusion about 1900 (158).

Curtis and David in 1911 used paraffin coated Y-tube and syringe. Two years later Kimpton and Brown introduced the Kimpton-Brown paraffin coated tube. The same year, 1913, Lindeman revived the multiple syringe method

of Ziemessen 1892. The Blundell method of 1818 was revived. Unger in 1915 devised a four-way valve syringe attachment, in which the outlets to the donor and recipient were alternately connected with the syringe and with a reservoir of saline or citrate solution. Many modifications have been made of these instruments, notably are those of Bernheim, Janes and Scanell (70, 158).
The use of anticoagulants:

The blood clotting in the instruments still caused trouble. Defibrinated blood had been tried and abandoned. Braxton Hicks 1868 had tried unsuccessfully to use sodium phosphate to prevent coagulation; Landois in 1892 recommended the use of hirudin, but the narrow range between the toxic and the effective dose prevented the adoption of it. Hustin of Belgium in 1913 introduced the use of sodium citrate as an anticoagulant. The first transfusion with it was done by Agote of Buenos Aires November, 1914. Lewisolin improved the sodium citrate technic of blood transfusion. The knowledge of blood transfusion became universal following its introduction and use in the great wars in 1917 by America. (20, 70, 158)

THE FOUR BLOOD GROUPS AND ISO-AGGLUTINATION

The normal human red blood cells form an even suspension when mixed with normal saline. Mixing the serum of the same individual or that of a person of the same blood group has no reaction on the suspension, but if serum of an incompatible blood is mixed with this suspension clumping of the cells or agglutination results. Upon this phenomenon is based the division of humans into four main blood groups and into a few subgroups. This agglutination is a specific reaction and depends upon two substances, one in the red blood cells, called agglutigen; and one in the serum, called agglutinin. This reaction is of the same order as the Widal and other specific agglutination reactions (151).

Landsteiner (151) has described two agglutinogens A and B; and two agglutinins Alpha (or anti-A) and Beta (or anti-B). Several nomenclatures of the Landsteiner blood groups showing the respective agglutigen and agglutinin are given in table I. The International Nomenclature was officially recognized by the Health Community of the League of Nations. The Moss and Jansky numberings are confusing. The International Nomenclature corresponds to the agglutigen content in the red blood cells. It is possible for an individual's

TABLE I (151)

Classification & composition of the Ladsteiner blood groups:

Inter-national Nomenclature	Jansky	Moss	Cells	Serum
	Numbering	Numbering	Agglutigen	Agglutinin
O	I	IV		Alpha & Beta
A	II	II	A	Beta
B	III	III	B	Alpha
A B	IV	I	A & B	

serum to lose or change its specific iso-agglutinins but cell receptors or iso-agglutinogens are constant, and since the blood groups are named by the type of iso-agglutigen present in the cells, the blood groups do not change. They are inherited and last through life. The blood group specificity if not present at birth, which it usually is, appears within three months (54, 115). During embryonic development and the first three months of life, the human being does not possess specific agglutination power in the blood (40). The results of the sera of each group mixed with the red blood cells of each other group is shown in Table II and as can be seen, from the table, the blood group of any individual may be determined by testing his red blood cells with the sera of A and B groups. Group O red blood cells will not agglutinate with either serum. The cells of group A B agglutinate with each serum.

Group A cells will agglutinate with B serum and group B cells will agglutinate with A serum.

TABLE II (151)

Serum of Group	. Aggluti- nogen in cells	. Aggluti- nin in serum	Red Blood cells of group			
			. O	. A	. B	. A B
O	.	. Alpha & Beta	. -	. #	. #	. #
A	. A	. Beta	. -	. -	. #	. #
B	. B	. Alpha	. -	. #	. -	. #
A B	. A & B	.	. -	. -	. -	. -

signifies agglutination

- signifies absence of agglutination

Should there be any case of doubt following the reaction of unknown cells with known serum, the unknown serum may be tested with a known cell group suspension. Only those agglutinins are present in the serum for which there are no agglutinogens in the red blood cells. As: Red cells of group A have agglutinogen A in them, their serum has anti-B or Beta agglutinin in it; red cells of group B have agglutinogen B in them, their serum anti-A or Alpha agglutinin in it; red cells of group A B have in them agglutinogen A and B, their serum has no agglutinin in it; red cells of group O have no agglutinogen in them, their serum has both Alpha and Beta or anti-A and Anti-B agglutinins in it. Because group A B has no agglutinin in its serum and cannot agglutinate any red blood cells, it has been called the universal recipient. Group O because there are no

agglutinogens in its red blood cells and they cannot be agglutinated by any serum has been called the universal donor (54, 56, 151). Some men advise using universal donors for transfusions always and of giving any type of blood to universal recipients (113, 114) but this is dangerous without satisfactory cross-matching, for it often causes reactions (54, 106, 108). It should only be used when it is impossible to get the proper type of blood

The Technic of Blood Grouping:

In blood grouping we must consider the sera, the red blood cell suspension, and the various grouping tests. Only sera of A and B groups are necessary as already explained. Sera of high titer should be used to prevent errors, as blood cells vary in their sensitivity. Serum from certain pathological conditioned patients may show pseudoagglutination and autoagglutination which may be mistaken for isoagglutination. The sera of very young and very old individuals usually shows low agglutinin titer - therefore, sera of healthy middle aged individuals should be used for testing sera. The blood is collected in small test-tubes, allowed to clot, the clot is rimmed with a stirring rod, and the serum is separated by centrifuging or standing in the ice box over night. The serum is transferred by pipettes to small sterile vials capacity of about two cc each.

Sterile technic is used throughout the entire procedure. The serum is stored in an ice box; preservatives are unnecessary, but phenol one part of five per cent in normal saline to nine parts of serum has been used (151). Different colored preservatives (118) have been recommended and used to differentiate the sera by color. To A serum per cc is added 0.01 cc each of one per cent aqueous solution of neutral acriflavine and 0.5 per cent aqueous solution of basic fuchsin. To B serum per cc is added 0.01 cc of per cent aqueous solution of brilliant green. Commercial sera has been found not always reliable (120).

The red blood cell suspension should be fresh. Blood maybe gotten by stilet puncture of the lobe of the ear or end of a finger as for a blood count. Two drops of the blood are suspended in 5 cc of normal saline (151) or in 5 cc of one per cent sodium citrate in normal saline solution (54). The suspension should be washed if there is the tendency of pseudoagglutination or rouleaux formation (54 & 56). This is done by centrifuging, pouring off the supernatant fluid and resuspending in normal saline making a two to five per cent suspension. If the serum is to be tested also, venepuncture is preferable, using a few drops for the red cell suspension and the serum prepared as already described. Known cell suspension may be pre-

served (see blood preservation) then washed and resuspended when needed for testing unknown sera (151).

The blood grouping tests may be done macroscopically or microscopically. Landsteiner's macroscopic or microscopic technic (151): A drop of each of the unknown cell suspension, of saline, and of testing serum are mixed in a small test tube, inside diameter 7 mm. Upon standing, the reaction can be seen with the naked eye after a few minutes but should stand an hour. If desired a drop of the mixture may be transferred to a slide with a stirring rod and looked at with a microscope low power. A control should be run with this procedure. The reaction can be facilitated by centrifuging at 2000 revolutions per minute for three minutes. The tubes are then shaken until the control is evenly suspended and then read with the naked eye. The usual method used (151): One drop of A serum is put on the left end of a slide and one drop of B serum put on the right end of the slide, and one drop of the unknown cell suspension is mixed with each. The slide is tilted back and forth for 5 to 10 minutes, then the drops are covered with cover clips to facilitate microscopic examination. Examination is completed after an hour. Pseudo agglutination is possible in this last test (151).

Young (155) states that typing and cross matching by covering the serum and red blood cell suspensions with a cover glass is very dangerous, for that prevents agglutination or hemolysis. And he cites cases in his own experience to prove this. The hanging drop method observed for 45 minutes to an hour makes the procedure safe when done at 37 degrees centigrade or room temperature (54, 56, 155).

SOURCES OF ERROR IN BLOOD GROUPING

False negative reactions:

Weak sera or sera of low titer and old sera may not have any affect upon the red blood suspensions. Therefore, it is well to use controls. If the mixture of cell suspension and serum are not observed for a long enough period of time a positive reaction may be missed. Very concentrated red blood cells delay and weaken the reaction. This may be avoided by making a two to five per cent suspension of the red blood cells. The agglutinin in some red blood cells is very insensitive and may be the source of error. Such a patient of A B group was transfused 18 times with B blood before the error was detected. Hemolysis some times appears with fresh serum and masks agglutination, for the blood cells are hemolyzed as fast as they are agglutinated, but the scarcity of cells in the suspension should indicate hemolysis. The solution will also have a tendency to take on a pink color, but this is hard to detect in poor or artificial light. Hemolysis has the same significance as agglutination and never takes place without agglutination. Serum that has been kept in the ice box over night will not show this sudden hemolysis action (106, 108, 151).

False positive reactions:

Pseudoagglutination is the rapid settling out of red blood cells in acute infections. The cells settle out in piles like coins known as rouleaux-formation. When the rouleaux are very marked, the clumps become more irregular and simulate true agglutination; but the rouleaux are always present and result from the action of the acutely infected person's serum upon its own cells as well as the action of that same serum upon any red blood cell suspension. This phenomenon is used in clinical medicine in the sedimentation rate tests (32). Other factors which favor its occurrence are high concentration of serum and high temperature. It very rarely occurs in Landsteiner's test-tube test. On the slide, it can be distinguished from isoagglutination by a drop of saline or by pressing down on the cover slip over the preparation, either of which breaks up the clumps in false agglutination but will not affect true agglutination (29, 54, 106, 108, 151, 158).

Autoagglutination:

Cold or autoagglutination takes place with many sera mixed with red blood cells at low temperatures, as zero to five degrees centigrade. They are specific or non-specific (81). In some pathological conditions

autoagglutination takes place even at room temperature. This can be overcome by making a two to five per cent suspension of the cells in normal saline. Among the conditions causing it are: Paroxysmal hemoglobinuria, syphilis, syphilitic or hypertrophic cirrhosis of the liver, hemolytic icterus, pneumonia, Raymonds disease, trypanosomiasis, and severe anemias and cachexia. Autoagglutination is in some cases inherited (29, 30, 54, 106, 108, 140, 151).

Panagglutination:

Some saline red blood cells suspensions after having been kept a long time will be agglutinated by any serum, even their own, and by the serum of A B which has no agglutinins in it. Friedenreich says this is due to bacterial contamination (15, 29). Panagglutination may also occur in bacteremia and in chronic suppurations (29).

Anomalous agglutinins:

Anomalous agglutinins were found in about three per cent of sera according to Lansteiner and Levine (82). These rarely act at room temperature and the red blood cells of such sera show normal grouping reactions. These may be specific cold agglutinins (106, 108, 151).

Various tissue extracts cause false agglutinins as Wharton's jelly from the umbilical cord (106).

REACTIONS FOLLOWING TRANSFUSION

Reactions following blood transfusion vary with the different clinics and the different operators all the way from one half of one per cent to twenty per cent, if reports can be depended upon (84, 86, 104). According to Lewisohn (84, 86) the reactions in one hospital when done by him were only one half of one per cent, but when left to the hospital staff ranged from 10 to 20 per cent. The operator and his technic must be an important factor.

Incompatibility reactions:

Incompatibility between the donors and the recipients blood may be due to the one of the following causes: (a) Errors in grouping which is itself due to the following in order of greatest frequency: Poor technic for which there is no justification; the use of low titer or contaminated test sera; weak agglutinins or agglutinogens in the recipients blood; pseudoagglutination, cold agglutination and the subgroups; contamination of recipients blood by bacteria, anomalous or atypical agglutination (29, 106, 108). (See chapter on errors of blood grouping) (b) Indiscriminate use of the universal is dangerous because incompatibilities do occur from the use of such (41,

106, 108). (c) Immune isoanti-bodies and hemoly-sins may cause incompatibility (106, 108). For a discussion of symptoms, treatment and results of incompatibility see the chapter on transfusion nephretides. (d) Incompatibility of white cells have been found by experimentation. Such incompatibility though not common do give reactions. (84, 86, 104).

Citrate Reaction:

Mild reactions which occur so commonly following transfusion with some operators and so rarely with other operators have been blamed on the toxicity of the sodium citrate solution used by the advocates of unmodified blood, and upon the incipient coagulative changes in the transfused blood by the citrate advocates. But Lewisohn (84, 86) blames them to improperly prepared citrate, to unclean apparatus, and to poor technic. His citrate solution must be prepared with triple distilled water and made up with normal sodium chloride. Refer to separate discussion. These reactions are characterized by mild rigors with transitory rise in temperature following a mild chill, and are as often present when citrate is not used (16, 67). Some claim that citrate reactions are not harmful but beneficial. It would be better to use other methods of chill and fever, which can be con-

trolled and controlled independantly of the transfusion (10, 138).

Allergic Phemomena:

If there is a history of allergy in the recipient, a fast donor should be used and if a reaction still occurs it can be relieved with adrenaline and morphine (163, 101a). Allergic donors should not be used (29, 112). If the recipient has had former transfusion or serum administration, there is danger of an anaphylactic reaction. The greatest danger of this is between three to six weeks after the administration of blood or serum. Therefore, upon repeated transfusion even from the same donor, the blood of the recipient and donor should be cross-matched (16, 29, 106, 108). The allergic symptoms may take the form of urticaria, asthma, localized edema, or severe shock. Edema and urticaria are dangerous if they hit the glotis. If such occurs, intubation or tracheotomy may become necessary. Epinephrine is used in the allergic reactions. (16, 1-25) One death from anaphylaxis has been reported (25).

Systemic or constitutional reactions:

Reactions seen after the transfusion of certain pathological conditions in which there is a very active hemolytic agent at work. The latter may appear

in purpura, hemolytic jaundice, leucemia and sepsis. Reactions of this type can neither be foreseen nor avoided, but the possibility of their occurrence should be kept in mind so that prompt measures may be instituted to counteract them if they should occur (16, 84, 104, 116)

Heart failure and pulmonary edema may result from the transfusion, depending, of course, upon the condition of the patients circulatory apparatus. It is made more possible in a patient with a weakened heart condition due to a long standing anemia, previous failing heart to whatever cause, valvular disease, and arterial sclerosis and hypertension (12, 105). Rapid administration increases the danger of acute cardiac dilatation, especially when the myocardium is all ready weakened. Crile pointed out that the hearts work increases in geometric ration to the volume of blood. (147) It can be prevented by giving the blood slowly. If it occurs venesection must be performed at once (12). The amount of blood administered should not exceed $1/6$ to $1/5$ of the calculated circulating blood of the recipient because of the danger of overloading the circulatory system (29).

"Multiple emboli appear occasionally, usually in patients with endocarditis, or a blood stream

infection" (105). A thrombocyte crisis can be induced in cases of thrombocytopenia purpura by blood transfusion (142). "Retinal hemorrhage probably occurs more frequently than is thought" (105). Transfusional fatalities are more frequent in diseases of the blood and during sepsis than in acute hemorrhage (29).

Transmission of disease:

The transmission of disease from the donor to the recipient is a real danger and must always be guarded against. The recipient may also be endangered by blood from a person whose hemopoetic apparatus is not functioning properly (29). (Refer to separate discussion)

Embolism and thrombosis:

The danger of embolism and thrombosis is small, especially if faultless technic is used (29); except in endocarditis and blood stream infections (125). Air embolism, the greatest fear of distorical transfusion and accepted cause of many deaths is of no danger with proper technic, "The amount of air which may be accidentally injected into humans during an ordinary intravenous injection should occasion no clinical manifestations" (146).

The use of clean apparatus:

Any debris in the transfusion apparatus, whether from former transfusion or tubing, even though minute

causing reactions, some times alarming reactions (84, 86, 106, 108). Therefore, transfusing apparatus must be meticulously clean. It is easier to clean right after using. It is washed with running water several times after the water running through it is clear. After it is clean it is dried with compressed air, wrapped in towels and sterilized thoroughly. If there should be may particles of blood remaining in it, they will probably cause a reaction in the next recipient. New rubber tubing causes serious reactions from the sulfur compounds and powder washed from the tubing. The tubing is soaked for several hours and then boiled in five per cent sodium hydroxide solution for ten minutes. It is then treated in the same manner in a two per cent hydrochloric acid solution and washed over night in running water and sterilized for 30 minutes at 20 pounds pressure in the autoclave (109, 111). Lewisohn's technic (85) is much more thorough, it follows:

The apparatus is thoroughly washed with cold water after each transfusion, then with dilute solution of green soap to which has been added compound solution of cresol to make about 1% solution, and then thoroughly rinsed in tap water. All parts are then put in a large pan containing sodium hydroxide

in 0.1% solution and boiled five minutes and then rinsed in distilled water to remove the hydroxide, rewashed with triple distilled water for the glass ware and the rubber tubing, then assembled and sterilized in metal boxes or special bundles in the autoclave.

The glassware and rubber tubing are boiled separately. The needles are sharpened before being treated and are boiled for 3 minutes in 0.1% solution of sodium hydroxide. The recipient and donor bundles are done up and labelled separately for autoclaving, containing: Donor: Two pyrex cylinders 500 and 10 cc, respectively, one glass rod, two tourniquets, two needles gauge 13 and 15, Leur adapter and rubber tubing, one ampule of 30% sodium citrate. Recipient: A metal box containing glassware, rubber tubing and cannulas (85).

Coagulative and temperature changes in the blood:

It has been demonstrated that blood is toxic in direct proportion to the chemical alterations toward coagulation. This is particularly dangerous because the change invisible undetectable in the preclot state (54, 106, 108).

Warmed blood that is heated above body temperature whether given while above body temperature or not, hemolyzes due to the effect of the heat upon the

erythrocytes. The symptoms, treatment and effect are the same as for incompatibility (12, 105).

Blood may be chilled or even kept in the ice box without deleterious effects if it is warmed to body temperature when given. But if it is given cold, it is said to cause a reaction. This may account for some of the reactions that have been blamed on to citrate (10). However, Lewisohn (85, 86) maintains that injected cold blood does not give any reaction. But it does sound reasonable that cold blood might give a chill.

Death from blood transfusion:

Death from blood transfusion is mainly due to elimination of foreign substances overtaxing certain organs as the kidneys, liver and heart causing insufficiency of those organs, as in the post renal nephritides from incompatibility. Fatalities are more frequent in transfusion in diseases of the blood and in sepsis than in acute hemorrhage (29). The death rate from blood transfusion was figured by Tiber (141) in 1930 to be 0.39 per 1000. A much greater ratio than this of transfused persons die, but it is figured that they die of the disease for which they were transfused.

POST TRANSFUSION NEPHRITIDES

The post transfusion nephritides are, due to their clinical aspect, physiopathological characteristics, modes of appearance, related to the acute chemical nephritides. The treatment is not satisfactory but prophylaxis is. The prophylaxis is ensuring compatibility of blood before the transfusion; not warming the blood above body temperature; and stopping the transfusion with the first signs of distress. The prognosis is guarded to favorable with exceptions (16, 116, 143).

The four clinical phases:

Clinically, there are four phases of the transfusion nephritis:

First: The alarm period with precocious subjective symptoms, and the transfusion is discontinued with a minimum of 20 to 30 cc of blood having been injected. Therefore, there may be normal complication. The symptoms are: tingling pains shooting over the body, a fullness in the head to a headache, cardiac consciousness with a feeling of tightness and constriction over the precordium and chest; an excruciating throbbing pain in the lumbar region; slowly the face becomes prematurely colored

a dark red to a cyanotic line; respiration becomes somewhat labored and the pulse rate slow, dropping suddenly to 20 or 30 beats a minute; vomiting, more or less violent rigor; unconsciousness may be present for a few minutes; urticarial eruptions appear in about half the cases; sudden palor followed by cyanosis; the pulse becomes very rapid, weak and thready; the skin becomes cold and clammy; in fifteen minutes to an hour a chill occurs followed by a high fever, temperature ranging from 102 to 106 degrees; the patient may become delirious (5, 16, 104, 121, 143, 147). The patient may rarely die immediately (113, 115, 147).

A reaction described by DeGowin is interesting, "When 125 cc of blood had been given, the patient complained of a feeling of constriction in the chest and severe shortness of breath. The administration of blood was promptly discontinued. She became intensely cyanotic and dyspneic. A marked chill occurred and the oral temperature rapidly rose to 106.2 degrees F. The pulse rate was 140 and the respiration rate 44 per minute." The next day the patient was feeling better.

The delayed reaction:

However, these symptoms may not appear until 200

to 300 cc of blood have been given, or they may not appear until the transfusion has been completed and thus be completely skipped. The following precautions should always be taken to protect the patient against reactions and to show the doctor the reaction before too much blood has been administered if there is going to be a reaction. 1. No morphine should be given before the blood transfusion, for this would mask the cardiac consciousness, lumbar pain and headache. 2. Every precaution for proved compatibility should be taken. 3. The blood should not be heated above body temperature. 4. The transfusion should be begun slowly. 5. Every sign of discomfort on the part of the patient should be minded and watched. However, there may be seemingly reactions that are psychic, or comatose and sleeping patients may not show reaction (16, 143).

Second: Anuria and oliguria start about and between six to twenty-four hours after the transfusion with or without a phase of alarm. The condition and the taking of a urine specimen is suggested by hematuria or because no urine has been passed. The bladder is found to be practically empty, albumen, erythrocytes with various amounts of alteration, diminished urea and chlorides, and granular cast in the sediment

are found. An interval of improvement may appear, lasting for two to six days with or without jaundice and always with continued oliguria or anuria. Then any variety of evolution may be observed: complete anuria to the end reaching a uremic-like condition and death in 8 to 12 days; or on the third to fourth day poor concentration of urine followed by oliguria or anuria; or a permanently poor concentration diuresis; or else a better concentration with less water eliminated. The general condition with regard to the underlying disease for which the blood transfusion was given is usually undisturbed in its course. Pains are absent, pulse and tension usually unchanged. Consecutive blood examination shows a steady increase in azotemia and non protein nitrogen and a decrease in alkali reserve and carbon dioxide combining power with slight variation in the chlorides. The blood pressure may or may not be increased. The kidney function tests are reduced. Edema is always present. The condition resembles experimental uranium nitrate poisoning or bichloride of mercury poisoning. The entire phase lasts about ten days (16, 143).

Third: The hydric crisis phase is often skipped. In this phase large amounts of water are eliminated, 1800 cc within 24 hours. The urine is poor in urea and chlorides, azotemia, increased non protein intro-

gen, decreased alkali reserve and carbondioxide of the blood are found. The kidney function tests are reduced. There is always edema. The amount of urea in the urine and the amount of urine excreted are better prognostic signs than the amount of hemoglobin excreted. The toxemia lags behind the elimination.

Fourth: The last or terminal period is 8 to 12 days or even 15 to 25 days after the transfusion was given. There may be two possibilities, either favorable or unfavorable with all the range between. The favorable cases after a few days of crisis have normal diuresis with chloruria and ozoturia and the patient begins convalescence. Permanent sequelae have never been observed. In the unfavorable cases power of kidney concentration remains very low and death results in coma with uremic manifestations. (16, 143).

The symptoms of unfavorable cases:

The unfavorable cases result from incompatible transfusion, and there is always the precocious aggravation. Digestive disturbances are always present, beginning with a loss of appetite and then vomiting and diarrhea appear and eventually urea and chlorides appear in both the vomitus and stools. There are pulmonary symptoms of Cheyne-Stokes syndrome, which may be related to the acidotic condition; nervous

symptoms of a progressive torpor from fatigue to somnolence and coma interrupted by spasmodic movements or convulsions. Death usually results two to three days after coma appears. The entire time of the nephritis is usually about ten days and very rarely 25 days (16, 143).

Other associated clinical symptoms:

Other associated clinical symptoms of post transfusion nephritides are: eruptions, petechial or urticarial, jaundice, edema, mild hematurias with albumenuria, cylindric granules, increase of urea and slight decrease of alkali reserve, and with erythema, urticaria, fungacious edema and articular pains. There are the benign or reflex nephritides, some lumbar pain, anuria of a varying duration, then diuresis and disappearance of the disturbance without sequelae (143).

Strange, but there seems to be no simple relationship between the amount of blood injected and the severity of the reaction nephritis (143).

Explanation of Post transfusion nephritides:

The explanation of post transfusion nephritides is that the blood is hemolyzed in vivo from incompatibility; or from heating the blood too much, slightly above body temperature; or from blood peculiarities; or the condition may be due to metabolic disturbances.

The hemoglobin from the destroyed red blood cells is excreted by the kidneys with one of the following possibilities occurring: (a) If the reaction of the urine is above pH 6.0 the hemoglobin will be excreted as oxyhemoglobin with no ill effects resulting. (b) But if the reaction of the urine is below pH 6.0 and there be sufficient concentration of Na Cl (about 1%), brown pigment will be precipitated in the kidney tubules (5).

It is reasoned that the hemoglobin passes through Bowman's capsule in the dilute transudate at about the pH of the blood. In the tubules reabsorption concentrates and increases the acidity of the urine. The hemoglobin is precipitated, probably as hematin. The tubules are occluded and renal function is impaired (5).

The mechanism or explanation by which incompatible blood damages the kidneys has four possibilities according to Bordley (16). 1. The mechanical blockage of the tubules renders the kidney functionless as an excretory organ. 2. There are or may be certain bodies in the injected blood to which the kidneys are sensitive, and functional decline results from a local reaction of the nature of anaphylactic shock. 3. "The immediate transfusion reaction

brings about a metabolic disturbance that affects the renal function. 4. By the action of toxic substances set free in the blood at the time of transfusion, the functioning renal tissue is so severely damaged that it is unable to perform its functions" (16).

Renal pathology and autopsy findings:

The renal pathology seems to be the obstruction of the tubular lumens with masses of pigment derived from the hemoglobin (41a, 105). The autopsy findings of the kidneys are: "edema and cellular infiltration of the interstitial tissue, dilatation of the intercapular spaces of the glomeruli, dilatation of the convoluted tubules, advanced necrotic changes in the tubular epithelium, especially of the collecting tubules, with deposits of pigmented droplets in many of the cells and finally, the appearance in the tubular hemina of leucocytes, large phagocytic wandering cells, desquamated epithelium and peculiar pigments globules of various sizes" (16). This pigment is suggestive of hemoglobin, and except for it the kidneys are much like the kidneys following death from mercuric chloride poisoning. There is central necrosis of the liver. Findings in the other organs vary (16, 41a, 105).

Experimentation and treatment:

Experimentation study on dogs following the intravenous injection of dog hemoglobin showed that if the urine was alkaline, the injection was without harmful effects; but when the urine was acid, renal insufficiency resulted, there was increased urea nitrogen (120 to 362.6 mg percent) and creatinine (4.5 to 15 mg percent), coma and death in 4 to 10 days resulted. The experimentation indicates the line of treatment in hemoglobinuria whether it be due to transfusions, paroxysmal hemoglobinuria, or blackwater fever. Any type of therapy tending to reduce the precipitative factors - that is acidity and sodinnchloride concentration - should prove of value. The alkaline diuretics are transfusion of sodium bicarbonate as soon as possible should tend to minimize the precipitation in the tubules (5, 41a).

The treatment is prophylaxis by proper blood grouping before the transfusion is given ensuring compatibility; not over working the blood; and close observation of the patient during the injection, especially early; the injection being given slow; and discontinuing it if there are any signs of reaction. The treatment consists of adrenaline 5 to 10 minums (0.3 to 0.6 cc), atropine 1/600 to 1/150 grains,

with morphine 1/8 to 1/4 grains (121, 125) and intravenous solution of sodium bicarbonate 10.7:1000 given right away. A compatible blood transfusion is very helpful (143). If vomiting and diarrhea are present injections of normal saline with glucose should be used. The rest of the treatment is as in any acute nephritis (104, 121, 125, 143). In extreme cases radical experimental procedures have been tried as kidney decapsulation or de-inervation by the injection of the proper dorsal nerve roots or by high spinal anesthesia. Immediate transfusion of compatible blood has been recommended (143).

THE USE OF CITRATE BLOOD

In the controversy of the whole or the unmodified method of blood transfusion versus the citrated or the modified method of blood transfusion consideration has been given: The citrate itself; the effect of calcium immobilization; disturbances in the hydrogen ion concentration of the blood; injury of platelets; changes in fragility of the red blood cells; alterations in the hemostatic powers of the blood; immobilization of the white cells; changes in the opsonic index; the development of the anticomplementary properties of the serum; alterations in the immunologic reactions of the serum in respect to antitoxic, virucidal, bactericidal, and other antibody properties (43, 58, 95, 144, 145).

The citrate reaction:

Citrate itself can hardly seem a cause for post transfusion reactions. But "citrate reactions" has been mentioned by many writers as being caused by the citrate (17, 79). It is "characterized by an unexplained slightly delayed febrile response; it is a common enough reaction even when the blood is given without the citrate, and it fortunately seems harm-

less." (16 & 67) Lewisohn (85, 86) thinks that the reactions with citrated and uncitrated blood are about equal in frequency of occurrence. He blames the mild post transfusion reactions upon unclean and contaminated apparatus (84). Sodium citrate is rapidly oxidized and disappears quickly from the circulation when given intravenously (54, 122). Hemorrhage does not effect this disappearance of the sodium citrate. Repeated doses disappear more slowly. Citrate given orally causes alkaline urine but there is only a small amount of the citrate in the urine. Intravenously 70 milligrams per kilogram of body weight, making over about five grams in the average adult, have given symptoms. The fatal dose is between 0.4 and 1.6 grams per kilogram of body weight, making the fatal dose about 70 grams in the adult. The toxicity of it depends upon the rapidity of injection, the faster it is injected the more toxic it becomes (122). In the average transfusion of 500 cc of blood, 1.25 grams of sodium citrate would be given. This is one-fourth the maximum safe dose (54, 101a).

Calcium immobilization:

"Some experimental work on citrate toxicity suggest that when the calcium content of the blood has been depleted as it often is in patients needing blood

transfusion, a smaller dose than five grams may be toxic. Possibly therein lies the reason that the citrate method gives more reactions than noted with the whole blood method." (101a) If the recipients are thought or found to be low in blood calcium, they can be given calcium gluconate intravenously, and the condition taken care of.

Sodium citrate effects have been studied both in experimental animals and in the various blood tests, and its injurious effects upon the platelets, red blood cells, opsonic index, anticomplimentary properties of serum and lowered phagocytic properties refuted (59, 122). There is no increase in the fragility of the white or red cells (84, 95). But there may be some effect upon pH and colloidal equilibrium which is theoretical as yet (95). The hemostatic power of citrated blood as compared to uncitrated blood in purpura hemorrhagica, hemophilia, and hemorrhagic disease of the new born cannot be definitely stated; but intravenous citrate solutions have been said to shorten the clotting time in hemorrhage except when due to platelet disturbance (99, 117). But according to Lewisohn (85, 86) and Jennings (73) citrate blood has been proved to be harmless and may be used in any disease where transfusion is indicated.

Effects of citrate upon immunotransfusion:

In the preparation of convalescent sera the preservatives used do not affect the potency of the immune bodies (eg ammonium sulfate, tricresol). And as far as our present knowledge, citrate would have no deliterious effect upon immune bloods (92, 102, 159, 160). However, Colebrook and Storer (32) showed that "the addition of decalcifying agents to normal blood considerably reduces its power to kill staphylococcus and streptococcus in some way interfering with the function of the leucocytes. But citrate did not affect the pneumococidal power of blood (27). However, it was found that the complement content of uncitrated blood was increased over that of citrated blood and hence the bactericidal power of the blood which is very closely related (109, 111). Okomoto (101) concludes that uncitrated blood has no advantages over citrated blood in transfusion of rabbits upon normal and immune agglutinins and normal and immune hemolysis.

Comparison of citrate blood with uncitrated blood:

It would seem that with a very sick patient "skill on the part of the operator and minimal disturbance to the patient are matters of far greater importance than the supposed merits of anyone method over those of another." (111) The citrate method:

minimizes the disturbance to the patient; veins need not be exposed; the blood may be given slowly; the skill is easily developed; and the equipment is simple, easy to handle and clean, and the donor is not directly exposed to the recipient. In infectious diseases and blood dyscrasias, the advantage may be with uncitrated blood, it would seem; but the evidence is incomplete (109, 111).

In any transfusion the delicate blood tissue is traumatized, perhaps as much in the rush method as in the anticoagulant method (109, 111).

Advantages of the citrate method:

The advantages of the citrate method are: First, its simplicity; second, speed is not necessary and so the blood can be given slowly enough to anticipate severe reaction and to minimize speed shock. It is true that slight febrile reactions (1 to 2 degrees F) occur more frequently following injection of citrated blood than of uncitrated blood, but these are of no serious moment. Third, the coagulation time is not prolonged as has been thought, but it is actually shortened. Therefore, there are no diseases in which the use of citrated blood is contraindicated.

The citrate method would seem the method of choice for the average practitioner who has only an occasional transfusion to perform. For the expert

who does many transfusions, one of the direct methods may be desirable (54).

Dangers of unmodified blood:

The dangers of unmodified blood are: First, the possibility of a clot forming in the apparatus and interrupting the procedure. This is avoided by the utmost speed and precision. Second, one cannot then inject a small amount of blood slowly to see whether a severe reaction is imminent. Third, the donor must be at the bedside of the recipient, this is objectionable to nervous or critically ill patients. Fourth, blood is increasingly toxic as the chemical changes preceding coagulation take place; so if the blood in the apparatus is on the verge of clotting, one is actually administering a toxic substance (54).

ACCIDENTAL TRANSMISSION OF DISEASES BY BLOOD TRANSFUSION

There have undoubtedly been many more diseases accidentally transmitted than have been reported. In a survey made by Hendrick (29) in 1935, he reported, "thirty-five cases of syphilis, thirty of malaria, three of measles, two of smallpox, one of typhus fever, three of allergy, and three of tuberculosis." transmitted by transfusion. There was a death two weeks following an accidental transfusion from a donor with acute myeloid leukemia (29).

Syphilis transmission:

The first accidental transmission of syphilis by transfusion was reported in 1915 (112a). There has been a total of 68 cases reported. (112a). One case in which two generations were given it directly by transfusion of an expectant mother. Both the mother and the unborn baby got syphilis.

The way such mistakes can be eliminated is for the physician to never do a blood transfusion without the written report of the laboratory regarding the prospective donor's serology. A verbal report should not be taken. A Kahn test can be performed in two hours. If the emergency cannot wait that long and there are no available tested and serological donors obtainable, the folks of the expected recipient after

having the situation explained may be asked to sign a written release, releasing the doctor if the patient should get syphilis following such an emergency blood transfusion. Such a transmitted syphilis has no chancre, but in about two and one half months the secondary rash may appear as in any case of syphilis and the other clinical symptoms usually resemble those of syphilis gotten in the usual manner (75).

Any one who has ever had syphilis should not be a donor for blood transfusion, although many physicians think there is no danger of using inactive cases for donors, except when it is a life saving procedure, and then having the patient or other responsible person sign a permit releasing the doctor in case the patient gets syphilis. The doctor may in the absence of a responsible person and with a patient that cannot give a rational consent, take this responsibility upon himself and be within his legal right of exercising a "reasonable care". It may be the means of saving the patients life in an exceptional case (75, 79).

Malaria transmission:

Malaria has been transmitted accidentally by transfusion to both donor and recipient. Of course, transmission to recipient is more common, and has been done even when the donor did not know he had malaria, or

when he had not had an attack for forty years (24). There have been reported four cases of malaria from one donor within two months and about thirty cases in all (29). The incubation period varies from one to fifty-six days with an average from one and one half to three weeks. Less than half of the donors had demonstrable malarial parasites in their blood smears, and less than half of them ever had symptoms of malaria. Protection can only be had by excluding all inhabitant of malarial regions from being donors (154).

Passive transfer of allergy:

Ramirez ⁽¹¹²⁾ (29) tells of a recipient several weeks following transfusion from a donor sensitive to horse dander, who was then himself sensitive to horses. Hendrick (29) tells of three transmissions of allergy accidentally by transfusion. Therefore, donors should always be questioned regarding allergy and asthma.

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