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Transfusion reaction

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TRANSFUSION REACTIONS

by

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INTRODUCTION

Since 1900 when Landsteiner pointed out the blood groups and their import, the use of transfusions has increased tremendously. Progress in preserving and storing blood as well as development of technique of withdrawing and administering the vital fluid have been important additional factors in the ever-increasing popularity of transfusions. The recent war emphasized still further the needs for plasma and blood in large quantities for innumerable transfusions. With these few facts in mind it is not difficult for one to realize that the problems of transfusion reactions are being multiplied in direct proportion to the increased utilization of this life-saving procedure.

Such problems must be met and solved in every hospital. To meet them one must be able to recognize them when they arise. To solve these barriers in the path of medical progress one must understand as well as possible the underlying mechanisms responsible for their occurrence.

It is the object of this paper to aid the average practitioner or clinician in understanding the fundamentals of transfusion procedures, in being able to recognize symptoms which indicate the reactions, and in forming an organized picture of the types of reactions to be expected. It is also the aim of this thesis to point

out the most desirable methods for coping with such reactions, and to make the reader realize that prophylactic measures will considerably reduce the incidence of the reactions.

HISTORY

How far back the history of transfusions can be dated is difficult to answer because of the vagueness of the literature and because of the confusion of terms. According to Zimmerman and Howell (1932) the discovery of transfusions could be traced to mythology and be attributed to Medea, wife of Jason. Jason begged his wife to restore youth to his aged father, so Medea gathered herbs from the world over and brewed a potent mixture. Following this, "Medea unsheathed her knife and cut the old man's throat; then, letting the old blood all run out, she filled his veins with her brew. When Aeson had drunk this in part through his lips and in part through the wound, his beard and hair lost their hoary grey and quickly became black again; went the pallor and look of neglect, the deep wrinkles were filled out with new flesh, his limbs had strength of youth. Aeson was filled with wonder and remembered that this was he forty years ago."

Transfusion of blood and taking of blood by mouth were phrases used interchangeably and to many had a common meaning. It is thus almost impossible to say that blood transfusions as we know them, i.e., passage of blood from one person's circulatory system to another's, and not through the stomach as an intermediary, started

on such and such a date. Among the first who used the term "transfusion" was Pasquale Villari in 1492 in discussing a stroke of Pope Innocent VIII. A young doctor, Abraham Meyre, on the scene using a new instrument decided to transfuse the blood of a young person to the pope; the story is told that the old Pope's blood was passed into the veins of ayouth and vice versa. Three boys died in this venture and the pope died in spite of it. Another version of this same event declares that the blood was administered by mouth rather than intravenously, and H.M. Brown (1917) doubts that any "new instrument" was on the scene. Brown also doubts the validity of any transfusions at this time.

Mention of blood transfusion is credited to Hieronymus Cardanus in the early 16th century. On the other hand, it is claimed that the idea of transfusions was first evolved by Magnus Pegel and that these ideas were printed in 1593 by Emperor Rudolphus II. Andreas Libavius is one to whom credit for the first description of the technique is given. Libavius wrote the details in 1615 and a quotation from his work is merited: "Let there be a young man, robust, full of spirited blood, and also an old man, thin, emaciated, his strength exhausted, hardly able to retain his own soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the old man, and put the

female tube into it, and then the two tubes being joined together, the hot and spirituous blood of the young man will pour into the old one, as ifit were from a fountain of life, and all of his weakness will be dispelled." (Kilduffe and DeBakey) Historians vary in their opinion of Libavius' attitude towards transfusions. Some (Garrson, 1924) believe he was a staunch supporter of the practice, others including H.M. Brown feel his extravagant claims reflect his contempt for the procedure.

In 1628 Jean de Colle of Padua suggested transfusion as a life-prolonging method. But, 1628 is more reknown for the announcement by William Harvey of the theory of blood circulation which theory he had professed twelve years earlier.

Dependable stories of blood transfusions start in the early 17th century. Francesco Folli, a physician from Florence, is another accredited with the first transfusion on August 13, 1654. Folli proposed the use of a silver tube inserted into the artery of the donor and a bone cannula inserted into the vein of the recipient. He connected the two with a hollow pipe made from an animal's blood vessel. This tube had a side branch to allow for escape of air as blood poured in from artery to vein. Brown gives Folli credit for being as well

He had but 20 s. for his suffering it, and is to have the same again tried upon him: the first sound man that ever had it tried on him in England, and but one that we hear of in France, which was a porter hired by the virtuosos."

In Paris, Jean Baptiste Denis, physician of Louis XIV was performing the first authentically recorded transfusion in human beings in June, 1667. A youth of fifteen with a fever made a rapid recovery after Denis administered nine ounces of lamb's blood. Denis repeated the procedure successfully on a healthy individual as a matter of experiment. By this time he was the object of jealous opposition. This opposition started to exert pressure when Denis' next two transfusions caused death probably due to incompatibility. So, Denis was on trial for his life. He was dismissed of the charges, but transfusions became prohibited by various and sundry Parliaments, Societies, etc. Denis described a reaction in a patient who later died:

"his arm became hot, the pulse rose, sweat burst out over his forehead, he complained of pain in the kidneys and was sick at the stomach. The next day the urine was very dark, in fact black."

Only the efforts of a few, Cantwell in 1749, Michel

Rosa in 1783, Harwood in 1792, and Scheel in 1802, spotted an interval of over a century in which progress had come to a standstill.

In 1818 James Blundell, an English obstetrician, stirred the interest in the now cold cauldron. He was stimulated to action by the previous helplessness in fighting puerperal hemorrhage. He experimented to see if any factor in the blood was lost by passage through instruments--he concluded that there was no loss. After four unsuccessful attempts he succeeded in three cases and finally had a batting average of .500 in a series of ten cases. (Jones, 1928) Blundell is to be given credit for arousing interest in a problem of long-standing. Much progress dates from his work. A few of Blundell's cases cited by Jones and Mackmull are quoted here:

"A woman with very severe hemorrhage during childbirth was transfused with four ounces of blood by syringe before respiration ceased, but being unable to secure more blood she died.

"Dr. Doubleday assisted Blundell in injecting with fourteen ounces of blood a woman dying of uterine hemorrhage. She is reported to have said after six ounces had been transfused that she felt as strong as a bull. She recovered."

Handicaps at this time were the frequent reactions due to incompatibility of blood, phlebitis, and coagulation of blood.

In 1835 Bischoff defibrinated blood to overcome the barrier of blood coagulation. At about this time the attempt was being made to add chemicals to blood to prevent coagulation; some of these were sodium bicarbonate, sodium phosphate, and ammonia. Hicks in 1868 suggested a solution of "phosphate soda mixed with blood of the supplier whilst flowing" to prevent coagulation. At this time he claimed success with the use of sodium phosphate in lower animals and in three cases of "human females during delivery."

Channing in 1828 was among the first in America to be influenced by Blundell. Channing felt that transfusions should be recommended to the profession.

In 1825 the statement was made by the editors of the Philadelphia Journal of Medical and Physiological Sciences that a Dr. Physci had performed the experiment of blood transfusion thirty years before. By 1859 the cases were accumulating; Edward Martin collected 57 of them in which transfusion was done for postpartum bleeding and in whcih 45 lived. By 1875 Landois reported a total of 347 human and 129 animal transfusions.

Methods of transfusion now appearing included the use of defibrinated blood, transfusion with pure blood, transfusion from vein to vein, and transfusion from artery to vein. Technique was complicated and the ability to practice transfusions was limited to a few.

A humorous sidelight was the suggestion of Thomas to use some vital animal fluid which would increase the quality and amount of blood and which would not give the difficulties encountered by coagulation. He suggested cow's milk. One firm believer in milk transfusion stated that the new operation would in a few years entirely supersede the transfusion of blood, which latter operation "is even now being rejected as at once dangerous and unavailing in many parts of the country." Hutchinson (1879) reported marked improvement in a patient after milk transfusions in 1878.

Gesselius in St. Petersburg promoted the use of lamb's blood. Fatal and severe reactions followed and its use died out. Cohnheim in 1882 discussed the danger of using serum of one species which is a poison for the corpuscles of another. Agglutination and hemolysis of heterologous blood corpuscles became a common demonstration by the end of the 19th century. The indiscriminate use of transfusions took its toll and again they began to be set aside.

The use of physiologic saline was demonstrated as a safe procedure in 1875, but was little tried.

The big milestone was reached in 1900 when Landsteiner demonstrated the blood groups and their significance. Landsteiner mentioned three groups; Decastello and Sturli added a fourth. Jansky and Moss contributed their classifications and transfusions reached the point where technique was the remaining problem. In 1907 Ludvic Hektoen first pointed out the possible danger in blood transfusions from iso-agglutination.

Ottenberg in 1908 developed clinical methods for typing human blood and he was the first to apply agglutination tests in human transfusions. He noted that accidents in transfusion due to occurrence of hemolysis or agglutination of donor's blood cells by the patient's serum or vice versa could be excluded with careful preliminary blood tests. Ottenberg gave clinical significance to and showed the practical application of Landsteiner's discovery of isoagglutination.

Early methods of preventing coagulation were by direct vessel-to-vessel continuity between parties so as to provide only an intimal wall to contact the blood and by use of paraffin-lined apparatus. Hirudin as an anticoagulant was suggested by Landois in 1892; toxicity

caused it to lose popularity. Hustin of Belgium in 1914 used sodium citrate and established the present-day method.

FUNDAMENTAL FACTS

In order to understand the discussion which will follow, it is essential to be acquainted with a few basic principles underlying transfusion reactions. These axioms will be stated briefly.

Two substances are responsible for the reactions which follow transfusions. One of these, termed an agglutinin is present in serum; the other, called an agglutinogen is present in the red blood cells. The reaction between agglutinin and agglutinogen results in agglutination or clumping of the red blood cells. The nature of the agglutinogen determines the blood groupings discovered by Landsteiner. The following table illustrates various nomenclatures used to signify the specific agglutinogens. The so-called "international nomenclature" seems to be the most commonly used.

International Nomenclature	Jansky Numbering	Moss Numbering	Cells (Agglutinogen)	Serum (Agglutinin
O	I	IV	--	a & b
A	II	II	A	b
B	III	III	B	a
AB	IV	I	A & B	--

The frequency of the blood groups in white people is 43% O, 40% A, 10% AB, 7% B.

Any given blood has present a specific agglutinogen in the red blood cells and a specific but not corresponding agglutinin in the serum. Exceptions to this

statement are that O type blood has no agglutinogen and AB type blood has no agglutinins. The presence together of an agglutinogen and its corresponding agglutinin (e.g. A agglutinogen and a agglutinin) results in clumping or agglutination. Thus, in an individual's blood stream there normally are present agglutinogens and agglutinins which do not correspond. Ordinarily only the agglutinogens need be considered in transfusing blood since the agglutinins in the serum are so diluted by the recipient's blood as not to be a factor in agglutination. The red blood cell retains its identity and integrity, and therefore cannot be diluted. When the agglutinogens of the donor are not the same as those of the recipient reactions necessarily follow.

Transfusion of group O blood can usually be given to any recipient regardless of blood group since the O type cells have no agglutinogens and thus cannot produce agglutination reactions. On the other hand, group AB can receive blood from anyone since group AB has no agglutinins and thus cannot be involved in agglutination reactions. The following table illustrates the theory of blood grouping; four unknown bloods are reacted with sera of groups A and B respectively (containing agglutinins b and a respectively) and depending upon the agglutinogens

present in the unknown blood, reaction will occur with one serum, both sera, or neither serum. As a result, the blood group of the unknown blood is determined, and is listed in the last column. For example, the first sample showed no agglutination with a or b agglutinins; consequently this sample must have no agglutinogens present and must belong to group O.

Blood Sample	Reaction with A serum (b agglutinins)	Reaction with B serum (a agglutinins)	Group
1.	--	--	O
2.	--	++	A
3.	++	++	AB
4.	++	--	B

Occasionally if a very high titer of agglutinins is present in the donor's blood, the dilution of them in the recipient will not be sufficient to prevent reactions. Thus it is important in typing blood to do a cross-matching test. This test involves mixing some of the donor's red blood cells with the serum of the recipient to see if the donor's agglutinogens correspond to the recipient's (if they correspond, there will be no agglutinins in the recipient's serum to agglutinate the donor's red blood cells); in addition, some of the donor's serum is mixed with the recipient's red blood cells to determine if the agglutinin titer in the donor's serum is unusually high and thus capable of agglutinating the re-

cipient's red blood cells. This test can be carried out on a glass slide and be examined microscopically or can be effected in a test tube and observed grossly. Details of this process will be found in the concluding section of this paper.

Mention should be made that in addition to the major groups aforedescribed, there are various other blood typings classified as subgroups. Though these are not common they are occasionally responsible for reactions between two samples of blood which are or appear to be of the same major grouping. Thus, on the basis of these subgroups, transfusion reactions may follow when, e.g., type A blood is transfused into a type A recipient. These are called intragroup reactions or intragroup incompatibilities since the major blood types of donor and recipient match, but subgroup agglutinogens do not.

The definition of a few terms is warranted. Isoagglutination refers to the reaction between bloods from animals of the same species. This term is used interchangeably with the less specific "agglutination." The same is true of isoagglutinins and agglutinins. Isoimmunization refers to the stimulation of agglutinin formation in one animal in response to a transfusion of agglutinogens from another animal of the same species..

THE REACTIONS

Before the reactions are discussed in detail, the etiological factors should be mentioned in outline form.

A. There are factors which might cause reactions on the basis of incompatibility, that is, the tendency towards agglutination between the donor's and the recipient's bloods.

a. Reactions may occur because the tests for compatibility are falsely negative. The laboratory methods used indicate that the matching is satisfactory, but for some reason the agglutination which should occur during the cross-match fails to do so. Then, when the supposedly safe donor's blood enters the actually incompatible surroundings of the recipient's blood stream, agglutination occurs. Low titer of testing sera, low sensitivity of agglutinogens, high concentration of red blood cell suspensions, and a temperature factor fit into this category.

b. On the basis of fallible technique or for other reasons to be considred it is possible to observe in vitro agglutinations between donor's and recipient's bloods which errongeously suggest certain blood groupings. Then, of course, when the the mismatched blood of the donor reaches the recipient, reactions occur.

Included in this group of false positive reactions are pseudoagglutination, autoagglutination, bacteriogenic agglutination, secondary coagulation, and false agglutination with umbilical cord sera.

c. Failure or neglect to properly test for unusual or irregular blood groupings or failure to detect these unusual blood groupings may be a further factor leading to incompatible blood transfusions. In other words, there may be compatibility as far as groups A, B, O, and AB are concerned, but consideration must be made also of subgroups A_1, A_2, A_1B, A_2B, and Rh. A donor and recipient may appear to be matched in that they are both, e.g., group A; however, proper testing for subgroups may demonstrate incompatibility. Such incompatibility occurring in bloods of the same major grouping is termed intragroup incompatibility.

d. Failure to realize that the so-called universal donor of the O type does not provide a safe transfusion in all cases may also give unfavorable if not disasterous results. Persons with type O blood have been considered "universal donors" because their cells contain no agglutinogens, and cannot take part in agglutination reactions. The basis for a "universal donor"

is that in transfusing blood the agglutinins in the serum are so diluted by the recipient's blood that they are an inconsequential factor in producing agglutination. On the other hand, agglutinogens cannot be diluted (the agglutinogen in the red cell retains its identity), and do promote agglutination reactions. Since O types contain only "harmless" agglutinins which "cannot" cause agglutination reactions, they have been called universal donors. The fallacy of this idea will be unfolded later.

B. There are factors which cause reactions of an allergic or anaphylactic nature in which a sensitivity present on the part of the recipient before transfusion is lighted up by substances contained in the donor's blood. Or, substances capable in themselves of causing reaction s of allergic nature may be passively transferred from donor to recipient only to become manifest in the recipient.

C. Substances may be present in the donor's blood or in the apparatus which cause febrile reactions in the recipients--these are the pyrogens.

D. Finally, there are the complications of transfusions. Some occur through poor foresight in the choice of a recipient for the transfusion. This is true in the case of a cardiac patient whose circulatory volume is increased by the transfusion beyond the

capabilities of the volume output of the heart. There are, too, the accidental type of complications which cannot be readily foreseen. These include embolus, retinal or intracranial hemorrhage, etc. Faulty technique may play a role in producing complications via disease transmission; the presence of such disease in a donor should seldom be overlooked.

REACTIONS DUE TO INCOMPATIBILITY

SYMPTOMS

The reaction occurs during or just following the transfusion. It may occur after a transfusion of as little as ten cc., but more usually after 50 cc.

Generalized tingling with great discomfort; anxiety; fullness in the head which makes the patient feel like his head will burst; feeling of constriction in the chest; difficulty getting breath; severe pain in the back of the neck, chest, and especially in the lumbar region are the early manifestations. Then, are noted signs of collapse with rapid, weak pulse; clammy, cold skin; flushed face; dyspnea; cyanosis; low blood pressure; dilated pupils; and nausea and vomiting. Urticaria may occur. A chill may be followed by a rise in temperature.

These symptoms occur in an hour and do not usually last over an hour. Still later manifestations are hemoglobinuria, anuria, and jaundice. The fever may last a few hours or a day and then subside. A week may pass during which the patient appears to be progressing; he sleeps well, eats well, and thinks in an oriented fashion. Oliguria may continue and jaundice may become more apparent along with a hemorrhagic tendency.

One to two weeks later is marked by the terminal or renal phase and includes restlessness, drowsiness, stupor

with evidence of renal failure, and anuria. The blood urea rise indicates nitrogenous retention. Uremia is ushured in by coma, muscle twitchings, and convulsions. Death in the fatal cases occurs in about one to two weeks after the transfusion. This one to two week interval is the time needed for the damaged kidneys to shove the patient into uremia.

Recovery is earmarked by profuse diuresis and increase in blood urea, both occurring before the uremic coma which would indicate a fatal prognosis.

Renal insufficiency, then, is the important feature of incompatible reactions. Bordley (1931) pointed out the renal pathology responsible for the symptoms. He described the kidneys as swollen and edematous with degenerative changes in the tubular epithelium. Tubules are filled with red blood cells, desquamated epithelium, blood pigment, and debris.

The mechanism of renal damage is in debate. Possibilities include (1) mechanical blocking of the tubules which renders them functionless as excretory passages; (2) kidneys are sensitized to injected blood and loss of function depends on a local anaphylactic reaction in the kidneys; (3) the immediate transfusion reaction

causes metabolic disturbance which upsets renal function; (4) transfusion reaction results in liberation of toxic substances set free in the blood causing damage to the kidneys. DeGowin (1937) cites the possibility that renal ischemia may lead to renal insufficiency. This is explained on the basis of constriction or spasm of renal vessels due to the presence of incompatible blood. It is noted that transfusions of compatible blood subsequently will relax the spastic renal vessels. DeGowin in this discussion is considering Herse's work in Leningrad; actually, he is not in favor of this theory, but rather believes the renal insufficiency to be on a basis of precipitation of hemoglobin in the tubules with subsequent obstruction. He showed also that if urine were made alkaline the possibility of hemoglobin precipitating was lessened as was the possibility of renal insufficiency and uremia. He demonstrated that when a dog's urine was made acid, nitrogenous retention immediately developed after the hemoglobin had been injected into the dog's blood stream whereas the same injection of hemoglobin was followed without consequence in the same dog if urine was alkalinized.

In 1938 DeGowin still believed that precipitation of hemoglobin was the chief cause of renal insufficiency;

however, he added the conclusion that tubular necrosis occurs and may be another factor in the mechanism of producing malfunctioning kidneys. The necrosis is probably on a toxic basis. DeGowin observed the two mechanisms he has propounded while doing autopsies on human beings; he suggests alkalinizing the urine as a preventative measure.

Polayes (1931) cites the work of Baker who experimentally showed that if the pH of a medium is six or less and the NaCl content is 1% or more, the hemoglobin is thrown out in solution from the glomerulus and after concentration in the tubules, pigment is precipitated in the form of hematin. He, too, suggests alkaline diuresis to combat hematin formation and subsequent urinary depression.

Generally there is no adequate therapy to care for a patient who has a reaction due to the transfusion of incompatible blood. Some of the practices pursued include alkalinization of urine, renal decapsulation, sympathectomy, subsequent compatible transfusions, etc. Strumia (1944) believes that only maintenance of fluid balance is of value. He has observed that the amount of blood administered determines the severity of symptoms to be expected. If 270 cc. are given the patient will likely recover from a first transfusion of incompatible

blood. If 500 cc. are administered once or if less is given on a second occasion, the prognosis is poor.

A case history (Bordley, 1931) will illustrate amply all the previous discussion:

"White woman aged 46 entered with complaint of weakness, weight loss, insomnia. (Past history, etc. are omitted because they are not pertinent to this discussion). Diagnosis of uterine pathology was considred with bleeding from uterus. Transfusions were decided upon as supportive treatment. During introduction of the first 200 cc. there was a fall in pulse rate from 90 to 70/' and pt. complained of creepy sensations all over her body. She said that her head felt full and tight as though it were going to burst. The subjective change seemed so definite that five minutes were allowed to pass before injection was continued. A second 20 cc. was introduced cautiously. Pulse rate had risen to 90 and the patient complained of a severe headache. Her face became suffused; there was fullness of veins of neck; respiration became shallow and labored; she became nauseated and vomited. The blood pressure at this stage was 120/60 where it had been the previous day. It was decided to discontinue the transfusion and the needle was removed from the vein. After interval of 20 minutes the

patient announced that she was feeling fine. Confidence in the blood matching stimulated resumption of the transfusion. Five minutes were spent injecting the third 20 cc. and during this period the pulse fell from 90 to 60, but without change in the blood pressure or other symptoms. After a pause of five minutes the fourth 20 cc. was injected and again the pulse dropped from 90-70, having returned to 90 in the previous five minute interval. There were no symptoms as the fifth 20 cc. were started. Scarcely had ten cc. been injected than the patient suddenly complained of lumbar backache, fullness of the head, nausea, faintness. She became short of breath, cyanotic; the pulse rose rapidly and beats could barely be detected at the wrist. The transfusion was discontinued after 90 cc. had been injected.

"Fifteen minutes later there was a violent chill and the patient had an involuntary stool. Temperature was 101.8, pulse was 128, respirations 26. Thirty minutes later the chill ended, but cyanosis was still marked and respiration was rapid and deep. There was considerable spontaneous bleeding from the venipuncture wounds in both arms which could be controlled only by the application of pressure bandages. Chill ended at 5:15. At 5:30 temperature was 105.6, pulse 142, respiration 38.

At 6:00 she said that she felt warm and sleepy; she was perspiring freely and temperature was 106. By 7:00, temperature was 104.6, pulse 118, respiration 28; cyanosis was gone and breathing was free. At this point moderate vaginal bleeding was first noted; menstrual period was not due for seven days. After a night's sleep, she felt fairly well. At 5:00 the next morning she voided 100 cc. of coffee-colored urine with much Hb, 3 plus albumin, a few RBC, no casts; this was on April 6. At 6:00 A.M. the temperature was 100.8, pulse was 98, respiration 22. At 8:00 A.M. she again voided 100 cc. of dark brown urine. She complained of anorexia and nausea and vomiting at noon. At 5:00 P.M. she passed 25 cc. of dark urine. In spite of the fact that temperature had risen to 102 she felt better in the evening and ate well.

"On April 7-9 patient seemed to be recovering satisfactorily from what was thought to be a hemolytic incompatible transfusion reaction. The hemoglobinuria, jaundice, and vomiting which had been striking features on the day after transfusion, subsided rapidly, and finally disappeared. Transfusions of 550 and 500 cc. of blood were given on April 7 and 9 followed by mild 'citrate' reactions without additional symptoms.

Urinary suppression which was marked on April 7-8 attracted little attention at the time. A single small voiding on each of these two occasions was not measured.

"In the afternnon of April 9, four days after the transfusion, though she seemed to be improving in every respect the patient displayed a peculiar apprehension. She said that she had a "funny feeling" in her head and that there were films before her eyes. She announced that she was going to die, and despite reassurance persisted in this opinion. On April 10, apprehension and agitation became more marked; that night she carried on a lengthy, rambling conversation with a neighboring patient which she did not remember on the following morning. She was continually talking of death. On the night of April 11, she talked irrationally, and her husband told us that she seemed to him entirely out of her head. On the morning of April 12 she decided that she did not wish to die in the hospital and insisted on being taken home. Aside from these queer and unexplained mental reactions, the patient appeared to be doing well. At 4:00 P.M. on April 12, eight days after the transfusion, she suddenly had a generalized convulsion lasting 15 minutes and passed into a state of semicoma. In the

evening she became completely comatose and had frequent generalized convulsions. At 7:00 P.M. large bruiselike purple spots appeared on both arms and a small, fresh hemorrhage was seen in the fundus of her left eye. A few hours later a fine petechial eruption was noted at the base of her neck. Studies of the blood at this point showed normal bleeding and clotting times. Platelets were down to 110,000, however. There had been a remarkable rise in blood NPN to 132 mg%. Early in the morning on April 13 she regained consciousness. At 9:00 A.M. she was oriented but drowsy and listless. The urine showed a trace of albumin and a few RBC. Together with symptomatic improvements on that day the urinary suppression gave way to diuresis which on the next day amounted to 5000 cc. of urine in 24 hours. As the diuresis progressed the patient cleared mentally and the blood NPN fell to normal. By April 25 the patient had completely recovered from the effects of the delayed transfusion reaction. On May 9 she seemed in fine condition for operation and was operated successfully. Discharged May 15 with NPN at 30 mg%, urine normal."

Thus, is presented a case in which a patient was transfused with incompatible blood and this was followed immediately with shock, chill, fever, vomiting, hemoglobinuria,

jaundice, urinary suppression. Acute symptoms subsided, but urinary suppression continued. Then, the delayed reaction occurred with the peak at the eighth post-transfusion day; this secondary reaction was characterized by agitation, psychosis, hypertension, reduced phthalein excretion, nitrogen retention, purpura, convulsions, and coma. Marked diuresis on the ninth post-transfusion day paralleled the beginning of recovery and in three months the patient was perfectly well. Had not the diuresis occurred and had anuria continued, death would have resulted as is often the case.

ETIOLOGICAL BASIS

FALSE NEGATIVE REACTIONS

The following group of reactions are based on wrong blood typing due to the failure of agglutination to occur.

If the titer of the testing serum is low--in other words, the concentration of agglutinins is low--no reaction of agglutinationwith the unknown red blood cells may result, and a false impression is left as to the type of the blood being dealt with.

On the other hand, highly concentrated red blood cell suspensions may weaken or delay the reaction between agglutinogens and agglutinins. The red blood cells absorb all agglutinins in the serum without agglutination

occurring. This is noted especially when blood is taken directly from the patient and mixed with the serum without diluting the red blood cells first.

Low sensitivity of agglutinogens in the blood of a newborn or in preserved blood suspensions provides a source of error in typing. Also, it is easy to mistake AB blood of subgroup A_2B for group B because of the weak activity of the A agglutinogen in A_2B. Sensitivity of agglutinogens is decreased by storage.

If the temperature of the blood cell suspension being tested is above 55° C. there is a good chance that no agglutination will occur, especially if such a temperature factor is combined with sera of low sensitivity. A better chance for agglutination to occur will be had at temperatures below body temperature.

FALSE POSITIVE REACTIONS

This group of conditions is responsible for false blood typing because agglutination occurs when it should not do so.

Pseudoagglutination is a process by which red blood cells settle rapidly and tend to do this in piles like coins--rouleaux formation. When marked, this simulates the clumping of true agglutination. This form of agglutination

occurs in acute infections. It is favored by highly concentrated serum and by high temperature and disappears on mild dilution of 1:2 or 1:3. The latter fact serves to differentiate pseudoagglutination from isoagglutination. Routine 1:3 dilution when test tube tests are made avoids pseudoagglutination. On slides rouleaux-formation is even more likely because the large surface area of the slides favors evaporation and concentration of the serum. Pseudo-clumps are destroyed by pressing them with a cover slip or by adding 1-2 drops of saline to the slide. Pseudoagglutination is due to the change in viscosity of the "sick" serum. Rouleaux formation and fast sedimentation occur concurrently with increase in plasma fibrinogen. Red blood cells do not absorb the agent responsible for this phenomenon whereas red blood cells do absorb true isoagglutinins. Pseudoagglutination will occur with any red blood cells combined with the serum with a fast sedimentation rate.

Since the patient's serum here causes rouleaux formation of patient's own red blood cells the process has been termed autohemagglutination; the term panagglutination has also been designated. A phenomenon related to pseudoagglutination is the agglutination caused by viscous things

like gum acacia, gum tragacanth, gelatin, etc. via change in serum protein concentration. Coca (1931) has summarized the main features of pseudoagglutination as including (1) clumping, (2) rouleaux formation especially notable at the periphery of the clumps, and (3) failure of the cells to coalesce as do clumped cells in true agglutination; the cells are not closely packed.

Wiltshire's observations as far back as in 1912 were complete in giving the characteristic description of rouleaux formation:

1. The viscosity of fluid medium in which the red blood cells are suspended exerts a slight influence. An increase in viscosity occurs concurrently with an increase in rouleaux formation.

2. Colloids as gum cause rouleaux formation.

3. Serum or pathological fluids which promote rouleaux formation lose said power with dilution.

4. Blood serum loses power of rouleaux formation with standing. The time of standing is quite variable.

5. Heating serum at 60° C. for 15 minutes increases its power of rouleaux formation. Heating it thus allows it to stand longer before losing said power. Once the power is lost, however, serum will not regain it even with heating.

6. Inflammatory exudates are powerful rouleaux formers. This power remains with standing.

7. Some bacteria enhance the power of a serum to produce rouleaux.

8. Red blood cells lose this power if exposed to temperatures as low as 38-45°.

9. A decrease in rouleaux formation in pernicious anemia is due to changes in red blood cells rather than in the serum.

10. Rouleaux formation is a constant occurrence in normal shed blood.

Wiltshire believes that surface tension appears to be responsible for rouleaux formation. Factors involving serum and corpuscles are present and these factors lose their power of action independently when blood stands. The serum body responsible for rouleaux formation is not present as such in normal circulating blood, but is formed immediately after blood is shed or in an area of inflammation. The loss of power of serum to promote rouleaux formation upon standing is due to the production of antibodies which form after blood is shed, and which are absent before the blood is shed.

Autoagglutination is agglutination of one's red blood cells by his own serum due to an absorbable agglutinin

in his serum and to a corresponding agglutinogen in his red blood cells. Some have shown that this is a common phenomenon, but occurs at low temperatures only. (Landsteiner and Levine, 1926) Sera with autoagglutinins act on red blood cells of all human beings regardless of the blood group. Thus, autoagglutinins are really panagglutinins; the latter term is avoided to prevent confusion with autohemagglutination or panhemagglutination already described. As mentioned the reaction here is enhanced by cooling and reversed by heating the serum. Autoagglutinins may be so increased in concentration in certain pathological conditions that agglutination will occur even at room temperature. Among these pathological conditions are paroxysmal hemoglobinuria, syphilitic or hypertrophic cirrhosis of the liver, hemolytic icterus, Raynaud's syndrome, trypanosomiasis, and severe anemias. More recently other diseases have been described in which autoagglutinin titers are present. A commission designated to study acute respiratory diseases at Fort Bragg, North Carolina (Am. J. M. Sc., 1944) noted such titers in primary atypical pneumonia, pneumococcal pneumonia, bronchitis simulating primary atypical pneumonia, tonsillitis, scarlet fever, and measles. Titers of autoagglutinins were most prominent among the cases of primary

atypical pneumonia and also tonsillitis with or without exudative pharyngitis. This commission observed increases in the titer of agglutinins as the disease became more severe. Meiklejohn (1943) observed such titers in influenza type A, lymphogranuloma venereum, and in coccidioidomycosis. The diagnostic value of autoagglutinins titers is in debate. (McCombs and McElroy, 1937)

Incorrect blood grouping occurs due to autoagglutinins which are active at room temperature. The error in grouping is directed towards calling the blood type AB because agglutination occurs with any serum. This error can be checked and eliminated by setting up a control using the patient's own cells and his own serum. Since one with type AB has no agglutinins, it can be concluded that the agglutination is due to "autoagglutinins and autoagglutinogens." Serum can be freed of autoagglutinins by separating it from the cells at about 0° C. At this temperature the red blood cells absorb the autoagglutinins and removal of the red blood cells necessarily removes the autoagglutinins. The following table adopted from A.S. Wiener (Blood Groups and Transfusions, 1943) serves to differentiate three types of agglutination:

	Pseudo-	Auto-	Iso-

		Agglutination	
	Pseudo-	Auto-	Iso-
Absorption of active principle	not absorbable	absorbable	absorbable
Affect of temperature	stronger at 37° C. than at low temp.	occurs just at low temperature	little affected by temp. from 0-37° C.
Affect of dilution	inactivated by slight dilution	stands much dilution	stands much dilution
Specificity	non-specific	non-specific	group specific

Wiener (1942) cites a case of autoagglutination in a patient 16 months old. This baby was well until August of 1941 when he developed fever, red throat, pallor, and a palpable spleen. The RBC was 1,200,000, Hb was 24%, WBC was 15,500, and a blood culture revealed Staph. aureus. The child was then transfused with the mother's blood of the same type. This was followed by chills, vomiting, and red urine which gave a positive test for blood. Re-check of the blood matching revealed no difference in blood groupings, but agglutination did occur between the mother's red blood cells and the child's serum. Further tests showed that the infant's serum agglutinated all red blood cells at hand, regardless of the group, including the patient's own red cells. Also, the titer was high enough in the baby's serum to agglutinate any

red blood cells even at 37° C.--unusual for the typical "cold agglutinins" apparently present in this case. Wiener knows of no other autoagglutination reaction which occurred at room temperature except one unpublished case of Dr. R. Kracke. What causes the autoantibody production is a mystery, but once such production occurs, survival of the patient is impossible.

Bacteriogenic agglutination is another cause of the false positive reactions. This has been called the "Hubener-Thomsen phenomenon." It consists of changes in serum and/or the red blood cells so as to cause agglutination. Wiener was one of the first to note that when blood is kept a number of days, e.g., menstrual blood and postmortem blood, the stored blood became panagglutinable;then, the stored red blood cells could be clumped by any serum, even that from the person who was the source of the red blood cells. Suspicion that bacteria were responsible was aroused when it was found that the property of panagglutinability could be transferred to fresh cell suspensions by adding a drop of panagglutinable blood to the fresh blood and waiting out an incubation period of 12-24 hours at about 37° C. Bacteria were isolated which were capable of producing this phenomenon in fresh blood. Friedenreich called the microorganisms

"M and J bacilli" due to their peculiar morphology; later other bacteria were studied and Corynebacterium and some of the vibrios were noted to have the same property. Davidson and Toharsky (1942) reported Corynebacterium as responsible for bacterial hemagglutination. This bacterium they have called Corynebacterium "H". The latter are responsible for the presence of "h" agglutinins in serum and for the subsequent panagglutinating property. Apparently the bacteria produce an enzyme which changes a "latent receptor" in the erythrocytes into an active agglutinogen called by Friedenreich the "T" agglutinogen. Almost all normal sera have "t" agglutinins with the exception of that in young infants. Thomsen states that all sera contain a "t" agglutinin capable of clumping the "transformed" red blood cells whereas "h" agglutinins are only present in sera containing the bacteria, Corynebacteria "H". Errors involved because of this phenomenon are due to stimulation of the AB group of red blood cells. If it is noted that bacterial-influenced cells also agglutinate in the presence of AB serum, this source of mistyping will be removed. By using only fresh red blood cell suspensions the bacterial activity is practically removed as a factor to upset normal agglutinating activity of red blood cells. Bacteria can act by another method to

cause red blood cell agglutination. This is by the production in the serum of bacterial substances which will of themselves agglutinate the red cells. Thus, the bacteria can change the nature of the serum as in the latter case or can alter the character of the red cell to bring about the agglutination. In one case the changed serum will agglutinate all red cells whereas in the second phenomenon the altered red blood cells will be agglutinated by all sera. The latter type of agglutination involving altered red cells has been termed "T" agglutination to differentiate from the other form of "H" agglutination. The transformation which occurs in the serum due to bacteria or their products can be prevented by the addition of formaldehyde 1:100,000, merthiolate 1:10,000, boric acid 1:100, acriflavine 0.1%, brilliant green 0.1%, gentian violet 0.1%, and sulfonamide drugs 0.08%. Vitamin B or yeast favors the development of the unknown substance. Heating plasma or serum at 65° C. for ten minutes destroys the ability of serum to form bacteriogenic hemagglutinins.

Secondary coagulation may simulate true agglutination. If unwashed cell suspensions are tested with fresh serum or plasma, secondary coagulation occurs. This happens when the unwashed red cells are taken directly from the finger as whole blood and used as such. Microscopic examination

reveals the clot and thus differentiates from the true clumping of agglutination. Prevention of such phenomena is by the use of washed cell suspensions or by use of stored or inactivated sera.

False agglutination by umbilical cord sera was discovered when such sera were tested against known red cells of groups A and B on open slides. Apparent agglutination occurred when the slide was tilted back and forth and the clumps resolved if the slide were at rest. This occurred between the serum from the umbilical cord and a suspension of any type red cells even those from the umbilical cord blood. It was eventually pointed out by Polayes et al. (1929) that Wharton's jelly from the umbilical cord was responsible for the phenomenon.

INTRAGROUP INCOMPATIBILITY

This classification includes the "irregular isoagglutinins" as well as the Rh factor.

Irregular or atypical isoagglutinins are uncommon isoagglutinins for factors (agglutinogens) other than A and B. Such isoagglutinins are weak and act only in the cold, thus the term "cold agglutinins." They are confused with autoagglutinins which also are active at low temperature, and often are present in the same sera. Distinction here is made in that autoagglutinins react with all human

bloods while cold isoagglutinins act on group specific bloods. Landsteiner and Levine found irregular isoagglutinins active at 15° C. in 3% of sera tested; Thomsen found less than 1% active when tests were made at room temperature.

Blood groups A and AB are subdivided into four groups depending on the qualitative differences in the A agglutinogen. The sensitivity of these agglutinogens are in order of least to greatest: A_1, A_1B, A_2, and A_2B. The a isoagglutinin will agglutinate all cells with A agglutinogen while the a_1 isoagglutinin agglutinates only A_1 agglutinogen. Now, a and a_1 isoagglutinins are found in sera of blood groups O and B and are present in varying concentrations. Thus, if such sera contain low concentrations of isoagglutinins and are combined with weakly sensitive cells of subgroups A_2 and A_2B, there may be no agglutination. Then, A_2 blood can be mistyped as group O (no agglutinogens) and A_2B mistyped as group B (agglutination having occurred just with b isoagglutinin). Herein is found a source of error in blood grouping and a possible source of some incompatible reactions. Wiener notes that although agglutinogens A_1 and A_2 can in each other's sera stimulate isoagglutinin production, seldom is the titer of such isoagglutinins high enough to cause a reaction. Also, these immune antibodies or isoagglutinins act like cold agglutinins,

reacting only at temperatures below 37° C.

O, too, is a poor antigen in animals and man. The anti-O agglutinins occurring in response to the presence of agglutinogen O do so in such low titer that the isoagglutinins can rarely be found either in man or in rabbits.

The four types of irregular isoagglutinins found in normal sera are

a. Irregular isoagglutinins reacting with the blood of subgroup A_1 and A_1B: these are called a_1 or anti-A_1 isoagglutinins. They are the most common of the irregular isoagglutinins and are found particularly in individuals with subgroups A_2 and A_2B.

b. Irregular isoagglutinins reacting with O groups and less so with A_2 are called a_2 or anti-O isoagglutinins. They are found in groups A_1B and A_1, but rarely in B.

c. Irregular isoagglutinins reacting with blood containing agglutinogen P are found in so-called "P-negative" individuals of all groups.

d. Unclassified irregular isoagglutinins.

Irregular isoagglutinins ordinarily do not interfere with grouping tests, but some which act at 37° C. may do so. Here again the reaction is weak and seldom a source of confusion.

Agglutinogens M and N are antigenic for rabbits and other animals, but not for man. No convincing report has been made where N blood in M individuals or vice versa was followed by the appearance of specific antibodies or irregular isoaggltuinins. Thus, M and N irregular agglutinogens as well as P have no clinical import in transfusion, but are of value from hereditary and medicolegal aspects for purposes of tracing blood. Landsteiner and Levine discovered M and N agglutinogens in 1926 and noted the following distribution of them: 30% have M, 20% have N, and the remainder have M and N. These figures concur with those of Grayden and Simmons (1945) in a series of 400 Japanese. Incidence of M and N in latter series was 28.5% (114) M, 20.5% (82) N, and 51% (204) MN.

The Rh factor is considered under intragroup incompatibility because it is responsible for reactions regardless of the fact that matching shows compatibility with reference to the major blood groupings. The Rh factor or Rhesus factor was first discovered in 1940 in the blood of Rhesus monkeys by Karl Landsteiner and Alexander Wiener. They injected blood from rhesus monkeys into rabbits; then, the serum from rabbit's blood was mixed with specimens of the red blood cells of the monkeys and clumping was noted. The same rabbit serum plus specimens of human red

cells resulted in clumping in 85% of the cases. It was thus concluded that a so-called Rh factor was present in 85% of human beings, the Rh positive group, and absent in 15%, the Rh negative group. Koucky (1943) asserts that there is no definite information yet available on the physical properties of the Rh factor. Presumably, it is, like A and B substances, a carbohydrate fixed to the protein of cells. In some Rh negative people the Rh substance is a powerful antigen and stimulates a high titer of antibodies. In others, little or no reaction occurs. Antibodies formed are in the serum and are contained in the globulin fraction. There are several types of antibodies formed, viz., agglutinins, hemolysins, precipitins, and cytotoxins. These have not been separated as yet.

The Rh factor is really a "mosaic composed of several antigenic factors." Not all anti-Rh sera give parallel reactions. The following table is the result of experiment with anti-Rh sera of three women and then the determination of the incidence of reactions of said sera when combined with various red blood cells.

Anti-Rh serum from patient	Incidence of Rh positive	Incidence of Rh negative
E.B.	87%	13%
M.F.	85	15
M.S.	73	27

Levine (1943) demonstrates by this table that the incidence of reactions of the various anti-Rh sera differs. Work with the three types of anti-Rh sera has resulted in the discovery of four types of bloods, viz., Rh_1, Rh_2, Rh', and Rh-. This classification was suggested by Wiener and Landsteiner. Levine compiled the following table of agglutination reactions between anti-Rh sera of mothers of erythroblastotic infants and the blood of 334 people picked at random:

Red blood cell type	Incidence	Anti-Rh M.F.	Anti-Rh_1 M.S.	Anti-Rh' E.B.
Rh_1	71%	+	+	+
Rh_2	14	+	-	+
Rh'	2	-	+	+
Rh-	13	-	-	-
Incidence of Rh- reactions in %		85	73	87
Incidence of Rh- reactions in %		15	27	13

From this table can be observed the fact that anti-Rh and anti-Rh_1 sera contain different agglutinins and that anti-Rh' serum contains both the anti-Rh and anti-Rh_1 agglutinins. Anti-Rh serum will detect most of the cases with the Rh factor in the red cells; anti-Rh_1 will detect

the exceptions. Apparently, anti-Rh serum is rare and is not commonly used. Often, even though no agglutinins for Rh are found in Rh negative serum, transfusions of Rh positive red cells subsequently cause reactions. To be certain that no incompatibility exists test the red cells of donor with anti-Rh serum. The safest policy is to use only Rh negative blood in transfusing Rh negative patients.

Wiener cites as peculiarities of Rh reactions the facts that Rh agglutination is easily reversed with shaking and that only 2% of Rh negative individuals respond to transfusions of Rh positive blood by producing isoantibodies.

In connection with Rh should be considered the Hr factor. Apparently certain Rh positive mothers are capable of being stimulated to produce immune agglutinins which then hemolyze the blood of the infant. These agglutinins react with all Rh negative and Rh_2 bloods. Levine (1941) termed the factor or agglutinogen responsible "Hr" because "it is probable that the blood factor described by this new agglutinin is genetically related to Rh." The Hr factor can be suspected when a mother of an erythroblastotic child is Rh positive and the father is Rh negative or Rh_2. (Levine, 1943)

The heredity of Rh can be described thus: there are two types, genetically, of Rh positive individuals, viz., RhRh or homozygous and Rhrh or heterozygous; there is one genetic type of Rh negative, rhrh. The incidence of the various genes has been noted by Potter (1944) to be 36.9% of the population RhRh, 47.7% Rhrh, and 15.4% rhrh. Two kinds of matings may occur genetically in which isoimmunization by the Rh factor can result. In one, the father is homozygous and the fetus must be Rh positive; pregnancy will then give the opportunity for immunization of the Rh negative mother's blood stream by the Rh positive fetal red blood cells. In the other mating a heterozygous father is involved, and 50% of offspring will be Rh positive and 50% will be Rh negative. In either type of mating the first one or two pregnancies with an Rh positive fetus may be required to produce a sufficient degree of immunization in the mother to result in erythroblastosis fetalis. Once the mother is immunized adequately, all subsequent Rh positive fetuses will be erythroblastotic. If one living child is Rh negative, the father is probably Rhrh or heterozygous. Since in such a case 50% of fetuses are expected to be Rh negative further pregnancy can be recommended. The following table is quoted from Levine (1943), and may

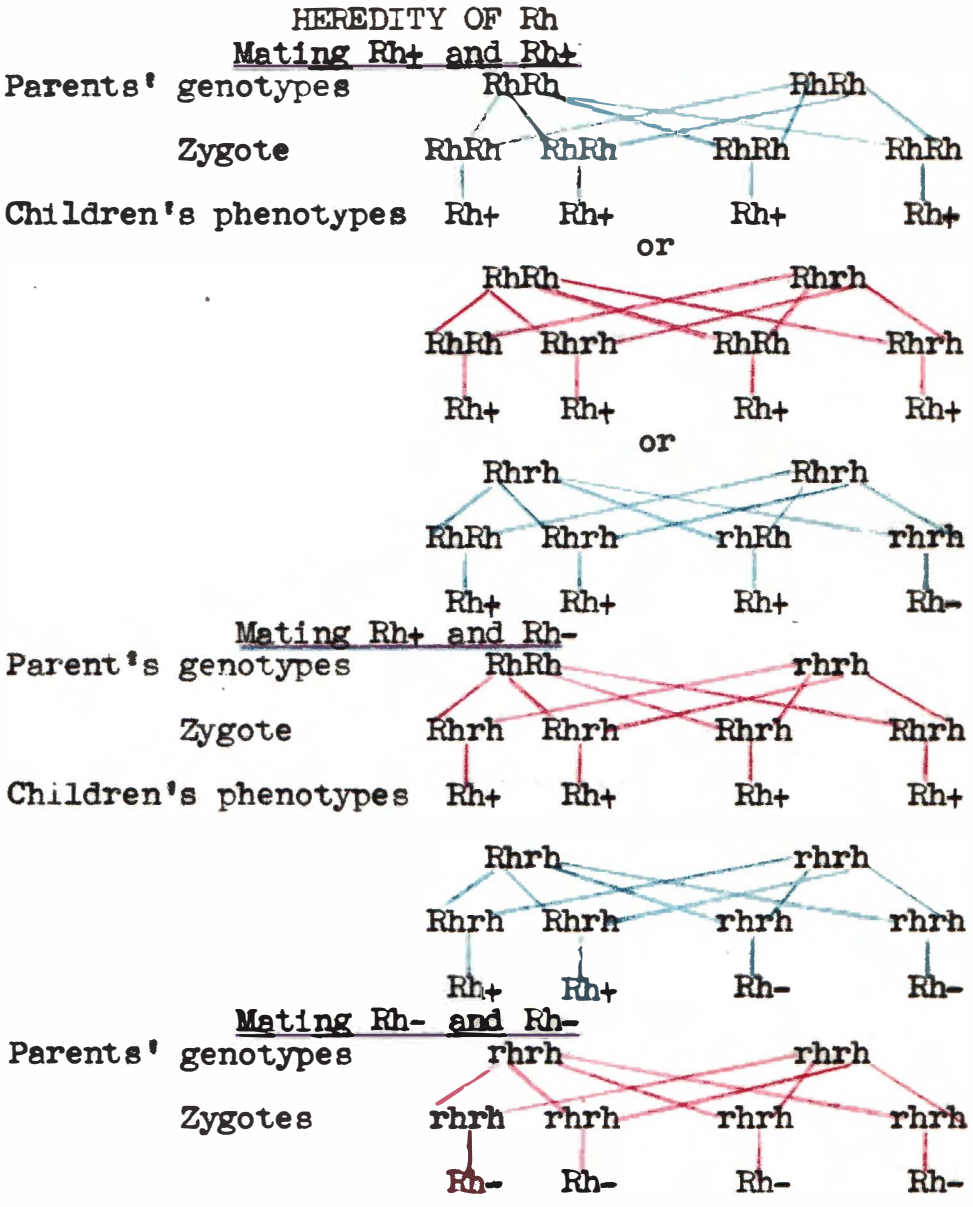
be enlightening to the previous discussion.

Phenotype	Genotype	Reactions with Anti-Rh	Anti-Rh_1	Anti-Hr
Rh_1	Rh_1Rh_1	+	+	0
	Rh_1Rh_2	+	+	±
	Rh_1rh	+	+	±
Rh_2	Rh_2Rh2	+	0	+
	Rh_2rh	+	0	+
Rh-	rhrh	0	0	+

Another system of nomenclature is given by Wiener (1944).

An accompanying chart illustrates the heredity of Rh. (Gradwohl, 1944)

Rh agglutinins act best at body temperature and lose their reactivity rapidly if the temperature changes in either direction. Thus at room temperature Rh agglutination would be difficult to detect and would be missed often. To determine if an Rh negative patient has been immunized by an Rh positive fetus or by repeated transfusions of Rh positive blood it is necessary to do agglutination tests. Always check the Rh status of a recipient before transfusing Rh positive cells. For example, you give a patient who is unknowingly Rh negative some Rh positive red blood cells. Then, suppose you decide on another transfusion and choose this time to do an Rh determination; the recently received Rh positive cells in the patient will, of course,


HEREDITY OF Rh
Mating Rh+ and Rh+
Parents' genotypes
RhRh
RhRh
Zygote
RhRh
RhRh
RhRh
RhRh
Children's phenotypes
Rh+
Rh+
Rh+
Rh+
or
RhRh
Rhrh
RhRh
Rhrh
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Rh+
Rh-
Mating Rh+ and Rh-
Parent's genotypes
RhRh
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Children's phenotypes
Rh+
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rhrh
Rh+
Rh+
Rh-
Rh-
Mating Rh- and Rh-
Parents' genotypes
rhrh
rhrh
Zygotes
rhrh
rhrh
rhrh
rhrh
Rh-
Rh-
Rh-
Rh-

agglutinate with the laboratory anti-Rh serum and give a false impression that the patient is Rh positive. Drummond et al. (1945) illustrate this situation well.

The relation of the Rh factor to erythroblastosis fetalis has been responsible in great part for elevating the Rh factor to a position of prominence. That some kind of antigen-antibody reaction between maternal and fetal bloods was responsible for icterus gravis and anemia of the newborn has been realized for some time. Now, since the presence of Rh can be determined, it has been found to be absent in 90% of mothers who deliver erythroblastotic infants. In other words, 90% of such mothers are Rh negative. The fetuses are Rh positive and are so because the Rh positive father has transmitted the factor as a mendelian dominant characteristic. The fetal Rh positive factor passes through the placenta into the mother's circulation and the mother becomes immunized to it. That is, the mother's Rh negative blood reacts to the presence of Rh positive factor by forming antibodies against the factor. These antibodies can then pass back through the placenta and hemolyze the fetal red cells which process is responsible for erythroblastosis. What about the other 10% of mothers who bear erythroblastotic infants and yet are Rh positive? Apparently some other isoagglutinins are present in these

mothers' sera which give an erythroblastotic reaction in the infant; such agglutinins are still undetermined. The manifestations of erythroblastosis may assume the form of hemolytic anemia, erythroblastemia (increase in nucleated red cells as a result of increased response of bone marrow due to hemolysis), icterus gravis, and congenital hydrops. Always check the mother's history of childbirth to see if any children were stillborn, neonatally died, were jaundiced, edematous, anemic, etc. Very likely these all indicate an erythroblastotic condition.

The principles of the troubles due to presence of the Rh factor can be summarized thus: 85% of all humans are Rh positive, that is, they possess the Rh agglutinogen. If blood from an Rh positive person is transfused into one with Rh negative blood, the latter is stimulated to form antibodies or Rh agglutinins. A first transfusion of Rh positive blood into an Rh negative blood stream will probably give no reaction, but will build up an antibody titer. The next transfusion of Rh positive blood into the Rh negative blood stream will likely give a severe hemolytic reaction because the previously formed agglutinins in the Rh negative serum will now agglutinate the Rh positive red cells.

If the child is the first and mother has not had any

previous transfusions, the chances are good that the reaction between Rh negative blood of mother and Rh positive blood of fetus will permit a live birth even though severe jaundice may occur in the infant. A second pregnancy under the same conditions, but with the added presence of antibodies in the mother's blood, is likely to result in a dead fetus. It is believed that 13 of every 100 marriages are between a father with Rh positive blood and a mother with Rh negative blood.

Rh negative blood can be transfused into anyone without reaction providing the major blood groupings have been checked. A danger, of course, is that the blood of an Rh negative person which you intend to use for transfusion may have been isoimmunized and contain anti-Rh agglutinins. These, when they enter an Rh positive blood stream, may cause a reaction. Rh negative blood from a donor not isoimmunized with Rh positive blood previously is the blood of choice for transfusing erythroblastotic infants. The mother's Rh negative blood could not be used just as could not anyone else's Rh negative blood which had been isoimmunized and contained Rh agglutinins. If no Rh negative blood is available, Levine suggests using the mother's blood after washing it, removing the plasma, rewashing the red cells twice more, and then

resuspending them in normal saline in volume equal to the original blood volume. Thus the Rh agglutinins present in the mother's serum will have been removed. Koucky advises transfusing of the infant early; he is opposed to long searches for Rh negative cells. Use Rh positive blood if need be, but check first with crossmatching. Of course, infant's tissues contain some of the Rh agglutinins which become fixed to the tissues and may be responsible for reactions even though a crossmatch shows compatibility. Harville (1945) suggests early transfusion into the umbilical cord as a desirable procedure for initiating therapy of an erythroblastotic infant.

Rh agglutinins were found by Fisk and Foord (1944) in breast milk samples of two mothers. In one case the milk was obtained on the third day postpartum and it still retained a potency of agglutinins equal to that of the serum. The other case showed a weaker titer in milk than in serum. Breast feeding of erythroblastotic infants is probably contraindicated. No proof is available, however, to indicate that this source of antibodies contributes to a hemolytic process.

The severity of erythroblastosis fetalis depends upon the amount of isoimmunization of the mother's blood and consequently upon the number of agglutinins formed. In

mild immune responses of mother's blood, the baby may have only a mild anemia; in others, a jaundiced or dead fetus may result. No proof of the means by which the red cells penetrate the placental barrier has been propounded. Levine has shown that only very minute amounts of fetal blood are needed to produce an immune response in the mother. It has been calculated that the agglutinin responses occur in the mother if as little as "0.0672 of red cell sediment" reaches her blood from the fetus--in a 120 pound woman. This is based on experiments wherein 14 daily injections of two cc. of 1:5000 human red cells (total volume of 0.0028 in terms of "sediment", Levine, 1942) into rabbits stimulated immune responses which were demonstrable. It is conceivable that some sediment of red cells makes an entrance into the placenta which has an average exposed surface area of 70square feet and a total length of villi of 11.4 miles--even without placental pathology.

Why the delayed response of newborn in becoming anemic and jaundiced? This has not been determined, but possibly the agglutinins are stored in fetus' tissues. Of course, if the baby is stillborn, there certainly was no delayed reaction, but rather, such reaction occurred in utero.

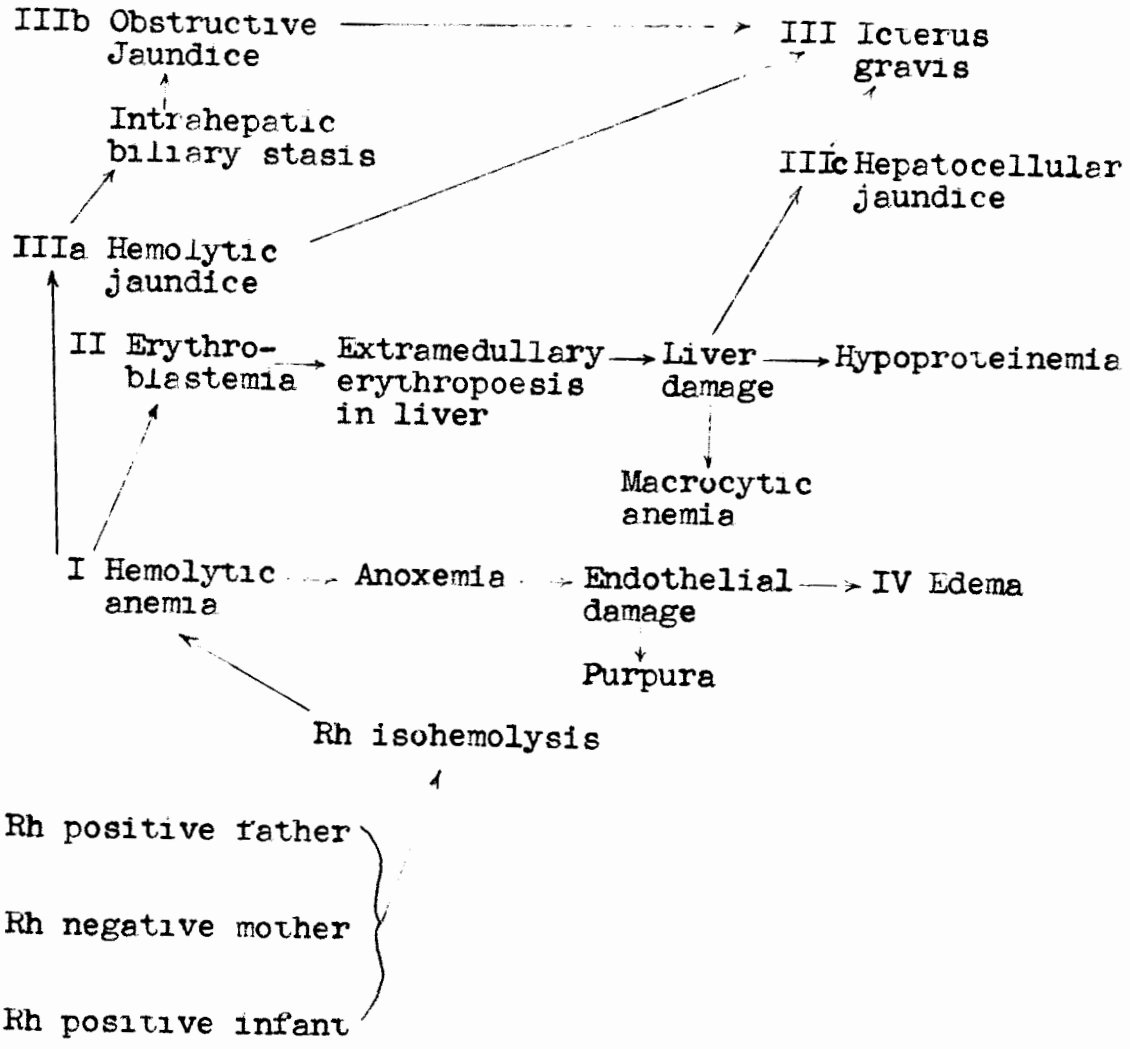
As previously mentioned 90% of mothers of erythroblastoti

infants are demonstrated as Rh negative. Potter (1944) believes that the majority of the other 10% are also Rh negative, but that poor technique or error in testing showed falsely that the mothers were Rh positive. Also, a few of the 10% may give birth to erythroblastotic infants for reasons other than Rh. Thus, erythroblastosis is considered as caused by Rh and other factors as well. Levine believes there are other isoimmune bodies in the 10% not noted to be Rh negative.

Potter emphasizes the need for accurate diagnosis of erythroblastosis on an Rh basis because in a series of 50 women whose fetuses died of erythroblastosis, 22 had 37 subsequent pregnancies and only three of said pregnancies yielded an infant which survived. If proper diagnosis is made, warnings against future pregnancies may prevent additional stillbirths. The accompanying diagram taken in toto from Davidsohn (1944) illustrates the events and consequences of the reaction of Rh agglutinins from mother on Rh positive red blood cells of infant.

Erythroblastosis fetalis occurs in one of every 200 pregnancies. An Rh positive father is mated with an Rh negative mother 14% of the time. It is, then, difficult to understand why only one case of erythroblastosis occurs in 200 pregnancies. One answer is the tendency

MANIFESTATIONS RESULTING FROM ACTION OF Rh AGGLUTININS FROM MOTHER ON Rh POSITIVE CELLS OF INFANT



towards small families so that the mother does not build up enough agglutinins in one or two pregnancies to do any harm to the fetus. Also, in the heterozygous matings, i.e., a father who is Rhrh, 50% of the offspring cannot immunize the mother since said number are Rh negative. Finally, it has been reported that only 2% of Rh negative individuals are readily sensitized to this Rh agglutinogen.

The racial incidence of erythroblastosis fetalis is directly proportional to the racial incidence of Rh negative individuals. Following is a table based on testing bloods of various races with anti-Rh serum as observed by Levine (1943):

Race	Number tested	%Rh+	%Rh-	Incidence of Eryth. fetalis
White	334	85	15	2.1%
Negro	264	95.5	4.5	0.7
American Indians	120	92.2	7.8	?
Chinese	150	99.3	0.7	very rare

Grayden and Simmons (1945) noted 99.75% Rh+ in 400 Japanese. A very recent survey of 283 negroes by Tisdall and Garland (1945) showed 9.89% to be Rh negative.

UNIVERSAL DONOR

Ottenberg first noted that injections of incompatible isoagglutinins rarely caused reactions. This served as a basis for "universal O donor", question of which has been debated back and forth in a maze of literature. It is true that the so-called universal donor is not always a safe one. The possibility exists that the agglutinins in the donor's serum may be of such high titer that the recipient's blood stream cannot dilute them enough and that reactions between the agglutinins of the donor and agglutinogens of recipient occur. Ordinarily the agglutinins contained in transfused blood are too few to affect the red cells of recipient. Shamov (1941) has made public his opinion that there are no great hazards in using a universal donor, but Kilduffe and DeBakey are firm in their opinion that serious and fatal reactions have occurred. The latter further believe that there is only one way to ascertain without any doubts the compatibility between donor and recipient. This one way is a grouping test of donor's cells and then a direct matching of donor's and recipient's cells and sera.

It has been shown that intravascular agglutination and hemolysis occur in a significant number of cases after transfusion of "universal O" blood into recipients

of group A in particular. Witebski et al (1942) have shown that the addition of group specific substances A and B lowers the isoagglutinin titer of O blood for transfusion and that in addition there are no untoward reactions attributable to these added substances. This fact was demonstrated with 147 cases. The same group of Witebski et al. (1941) has pointed out that the group-specific substances can be isolated in vitro and will combine rapidly with isoagglutinins. Conditioning of O blood supposedly permits universal donation thereof without first typing the recipient's blood and even without preliminary cross-matching. A series of 389 transfusions of O blood with the group specific substances added has been contrasted to a series of 1830 transfusions of homologous blood. (Klendshoj and Witebski, 1945) Five to ten cc. of a standard solution of these substances were added to each pint of blood just before transfusion or at the time the blood was placed in the blood bank. The 389 transfusions were used without selection of recipients and especially when emergencies arose where the time factor was important and saving of time by not doing cross-matches could be accomplished.

Klendshoj and Witebski classified the reactions in their series thus:

Reactions	Homologous blood		Conditioned O	
Pyrogenic grade 1 (rise 1-2°)	18	1.0%	0	0.0%
Pyrogenic grade 2 (rise 2-3°)	12	0.7	4	1
Pyrogenic grade 3 (over 3°)	50	2.7	10	2.6
Hemolytic	5	0.3	0	0
Allergic	28	1.5	5	1.3
Circulatory	3	0.2	0	0
Undetermined	3	0.2	0	0
	116	6.5%	19	4.9%
Total cases	1830		389	

Hemolytic reactions were accounted for by Rh, etc. The ideal universal blood should be Rh negative O type conditioned with blood group specific substances.

Isoagglutinin titers may be strong in some O individuals, e.g., because of previous transfusions into this O person with incompatible blood. It has been shown by Witebsky et al. (1942) that incompatible blood stimulates formation of isoagglutinins in the recipient raising the titer thereof. In fact, this method has been used to obtain typing serum of high isoagglutinin titer by injecting purified blood group specific agglutinogens into the individual. The question remains as to whether

or not sensitization of a person to "conditioned" universal blood could occur; it is not known what type of biologic response will be stimulated by the presence of the combination of agglutinins in O blood and the group specific substances added. In summary, Witebsky et al. (1942) believes the process of adding purified group specific substances A and B to O blood is a safe and desirable procedure.

Repeated transfusions from the same donor may eventually cause incompatible reactions. The repeated injection of donor's antigenic agglutinogens may sometime result in a high enough titer of antibodies in recipient so as to cause reactions. Such reaction can be prevented by firmly adhering to a crossmatching previous to every transfusion. The Rh factor is an example of a failure of the existence of a true universal donor. The presence of Rh agglutinogen in some so-called universal donors will by isoimmunization of the recipient's blood eventually cause a reaction. Here, repeated Rh positive red blood cell transfusions stimulates in an Rh negative recipient the formation of agglutinins or antibodies. These will eventually agglutinate the donor's red cells as they are received in the recipient's circulation. Other factors, the so-called irregular isoagglutinins

which are discussed elsewhere, are further reasons for the non-existence of a true universal donor. It was thought that the red cells of O donors were inagglutinable and that only the isoagglutinins of O serum were involved in reactions. However, it is now known that O red cells contain irregular agglutinogens for which an irregular agglutinin, anti-O, exists. Though rare, anti-O agglutinins occur in individuals of types A_1 and A_1B.

PROTEOLYTIC REACTIONS

These include a mild form with urticaria, small amount of angioneurotic edema, and eosinophilia; a more severe form with dyspnea, asthmatic rales, and incontinence due to spasm of smooth muscles; a very severe form which is immediately fatal. Such reactions are variously described as allergic, anaphylactic or the all-inclusive proteolytic.

The mild form is the common one and is relieved with 0.5-1.0 cc. of 1:1000 adrenalin. The incidence of proteolytic reactions is given as from 0.9 to 1.8% in series of cases ranging from 776 to 3077 cases respectively. Wiener observed such reactions in 1% of all transfusions.

The mechanism by which these reactions occur is undecided. Reactions are sometimes noted when a patient receives a transfusion and several weeks later has a repeated transfusion using the same blood. The reaction follows after the second transfusion due apparently to a hypersensitivity developed in the interval between the transfusions. However, the mechanism remains the object of many confusing discussions.

Gyorgy and Witebsky observed such a reaction in a child who received three consecutive transfusions, from father, mother, and again from father. The last transfusion was

accompanied by a thready pulse, transient generalized erythema of the skin, and edema of the face. This reaction could have been a developed hypersensitivity to a foreign "something" in the father's serum as previously suggested--or, perhaps, some foreign food product in the father's serum was responsible.

Colloid disturbances of blood and tissue may cause allergic phenomena, according to Hanzlik (1924). Another view is that reactions are due to protein alteration due in turn to increased cleavage power of the patient's serum by the addition of some such power from the donor's blood. The liver's malfunction in protein metabolism may be another factor responsible for some reactions. (Kordenat, 1925) The liver may permit split proteins to enter the blood stream and thus produce reactions.

Passive transfer of sensitivity apparently occurs. Sensitivity to strawberries has been transferred from donor to patient and lasted for three months in the recipient. (Holler and Diefenback, 1932) Garver (1939) has observed similar passive transfer of sensitivity via blood transfusions. Loveless (1941) demonstrated passive transfer of ragweed sensitivity which rapidly left the blood and was taken up by the skin, conjunctiva, and nasal mucosa. Ramirez (1919) cites a case in which

no history of bronchitis, asthma, urticaria, angioneurotic edema, hay fever could be elicited. Said patient was transfused with 600 cc. of blood. A few days later while riding in the park he developed a severe case of bronchial asthma which was relieved by epinephrine. The next day while the patient was walking in the park the same incident recurred. Ramirez checked the donor who had a definite history of bronchial asthma. Thus, an illustration is presented of passive transfer of sensitivity via blood transfusions. The sensitivity was to horse dandruff. Skin tests with this material gave a wheal of 1.5 cm. on the recipient and of 6 cm. on the donor.

A summary of the proposed mechanisms by which proteolytic reactions occur follows:

1. Donor may have eaten a food to which the recipient is sensitive. (Some have recommended the use of fasting donors.)

2. On the other hand, passive transfer of reagins from donor to recipient may occur. Then, the recipient eats certain foods causing reaction with the newly acquired reagins and resulting in urticaria, etc.

3. It has been further postulated that allergic reactions are due to individual differences in serum proteins. Thus, immune iso-precipitins may be produced

after repeated transfusions and cause reactions.

Neurological complications may follow administration of antisera for tetanus, diphtheria, scarlet fever, etc. This is not really a transfusion reaction, but if a donor very recently had been given some such antiserum and then, in turn, gave a transfusion, the recipient (if he were sensitive to such antiserum by previous contacts with it) might show signs of neurological complications. The reactions resulting would be similar to those allergic reactions occurring in the skin and joints, etc. The primary pathology is a vasodilatation causing a decrease in the amount of nutrition to the nerve tissue with the possible result of nerve cell death and neerosis. Edema may occur in the perineural sheaths or impaired blood supply to nerves or nerve roots may cause a neural or radicular syndrome. Briefly, the neurological syndromes are classified thus:

1. Cerebral, characterized by choked disk, meningeal irritation, positive Kernig's sign, aphasia, alexia, and visual symptoms. Paralysis of cranial nerves or of the medulla may occur.

2. Spinal, radicular, and neural types or combinations thereof.

The Erb-Duchenne type involving muscles supplied by

the fifth and sixth cervical roots is most commonly seen. One side is usually more involved than the other. The patient first complains of pain in the shoulder radiating down the chest wall under the axillae and lasting a week. Weakness of shoulder muscles is followed by paralysis. In seven to ten days muscles begin to waste. This wasting condition remains for three to eighteen months with progressive improvement eventually to complete cure. Occasionally, paresis or atrophy remain, especially in deltoid muscles. A case is mentioned in which the right deltoid muscle was paralyzed following a transfusion. Eight years later the same patient received a second transfusion in the opposite deltoid and the latter too became paralyzed.

Kraus and Chaney (1937) suggest the use of atropine, epinephrine, dehydration for edema, spinal punctures, use of caffeine and dextrose intravenously as measures of treatment in these neurological complications.

PYROGENIC REACTIONS

The cause of chills and fever following transfusions remained a problem for many years. The first thinking along this line placed the blame on chemical impurities in saline and glucose solutions or in solutions used to dissolve drugs such as arsenicals. Wechselmann in 1911 pointed out that the use of freshly distilled water prevented such reactions. He isolated from supposedly sterile solutions a gram-negative spore type of bacillus to which he accredited the pyrogenic reactions. Injecting distilled water immediately after distillation gives no reaction, but upon standing of the water pyrogens appear. They are not removed by Berkefeld filters as shown by Hart and Penfold (1911). The pyrogens were thought to be bacterial in origin although the centrifuged material of bacterial bodies did not verify this fact upon subsequent injection. At this time in 1911 the two above named Englishmen noted that the pyrogens gave rise to a late continuous fever in some cases and to an immediate fleeting febrile reaction in other cases.

Seibert did much work to bring pyrogens into the realm of understanding. She showed that ordinary distilled water gives febrile reactions and that such reactions are not due to impurities as silicates, particles of cork, etc. Also, she noted that the pyrogenic tap water occurred in

seasons, there being certain months when such pyrogens were apparently absent. Seibert found small gram-negative bacilli and was able to reproduce a febrile reaction with filtrates made from cultures of the above bacteria. Whatever the bacterial product is that is responsible for febrile reactions it was shown to be heatstable and removable by distillation of water. It remained for Fui and Schrift (1941) to determine that other organisms than those aforementioned could cause febrile reactions through pyrogenic products.

Thus far we have discussed the fever following the injection of solutions other than blood. However, the same principles apply in that the apparatus is cleansed with distilled water and the citrate and saline solutions used in conjunction with blood transfusions are prepared with distilled water. Reactions formerly ascribed to citrate are now believed to have etiology in the distilled water used to put citrate into solution. Bordley in 1931 noted a citrate reaction characterized by unexplained fever. He observed that the reaction is common enough even when blood is given without citrate. Wiener et al. noted that although the use of citrate transfusions was increasing tremendously after 1936, still the transfusion reactions of chills and fever remained at about a

12% incidence. This aroused suspicions that citrate was not to blame for the reactions. Finally, it was shown that using pure saline, purer than previously, and by taking greater care in cleaning equipment, chills and fever dropped to an incidence of 2-3%. If the chills are due to pyrogenic substances and not to incompatibility there will be excellent results as far as increase of the hemoglobin and red blood count is concerned.

Seibert devised an all-Pyrex glass distilling apparatus with a spray-catching trap. This water thus distilled should be combined with the pure reagents and then autoclaved within two hours. Flushing of the apparatus with pyrogen-free distilled water, drying in air, and later autoclaving should prevent pyrogens from occurring. If over several hours are permitted to pass between the flushing of the apparatus with distilled water and autoclaving, it is possible for pyrogens to be formed in a few droplets of distilled water remaining in the apparatus. New rubber tubing can be cleansed with alkali by soaking six hours or autoclaving in alkali for 15'. New glassware may be cleaned with sulfuric acid dichromate solution and then further cleaned as aforedescribed.

Kilduffe and DeBakey believe an incidence of pyrogenic reactions of over 5% indicates errors in technique

as well as in cleaning of apparatus.

Symptoms of reactions in this category include early chills followed by fever. Symptoms come on ¼-1 hour after transfusion. The patient may feel cold and shiver or may actually become rigorous. The chill lasts ¼-½ hour and precedes a rise in temperature which rise may reach 105-6°. It is possible also to have only a fever reaction without the chills. The temperature returns to normal within a few hours.

The patient should be kept warm during the chills and be given adrenalin 0.5 cc. 1:1000 subcutaneously in case any allergy is associated. Then, morphine grains¼, and atropine grains1/100 can be given subcutaneously.

It is important to determine if the chills and fever are due to pyrogens or to incompatible blood. First, recheck the cross-match; if no agglutination occurs the pyrogens are probably the villains. Also, check the icteric index and look for hemoglobin in the urine. If the icteric index is up or hemoglobin is found in the urine, it is likely that the reaction was hemolytic. If the patient and donor have the same blood types, check the M and N grouping. If M and N groupings are different in the two, the recipient's blood can be checked for the presence of donor's blood on basis of M-N typing.

If donor's blood is found yet in the recipient's circulation, hemolytic reaction can be ruled out. If no M-N agglutinogens corresponding to the donor's blood are present in the recipient, in all probability hemolysis has occurred. If M-N agglutinogens cannot be used due to similarity thereof in donor and recipient, the hemoglobin level can be determined. If the hemoglobin rises 8-10% with a 500 cc. transfusion and does not drop back to the pre-transfusion level in two days, no hemolysis has occurred. A drop in hemoglobin after a temproary rise indicates hemolysis.

MISCELLANEOUS REACTIONS

A type of reaction termed nitritoid follows administration of whole blood especially a fresh preparation or fresh serum which was kept in the frozen state. The reaction occurs during or immediately following administration. Symptoms include constriction of the chest, pain over the lumbar region, occasionally dills and/or fever, nausea and vomiting, and headache. The reaction lasts four to five hours and remits without permanent damage. Since the reactions do not occur in aged serum, it is presumed that an "x" factor is responsible and is present in fresh serum. Since fresh plasma gives the reactions less often than fresh whole blood, the substance given credit for the reaction is thought to be a product of blood clotting. Such reactions are rare. (Strumia, 1943)

Another miscellaneous consideration is the relation of temperature to transfusions. (DeGowin, 1940) Very careful clinical study was made by DeGowin of ten patients who received transfusions of blood varying at from 15-25° C. and administered at velocities varying from 6-42.8 cc. per minute. Rectal temperature fluctuated 0.2°C. at a maximum while blood pressure varied only a few points. The latter variation was attributed to the anxiety of the patients. No other clinical symptoms were manifest, not even a "cold" feeling as the blood below body temperature

entered the vein. Thus it is not necessary to heat the blood to body temperature preparatory to transfusion.

Blood is usually stored at around 5° C., and if this stands around a short time at room temperature it warms up to 15-20° C. without any external stimulus. In fact, it has been shown that deliberate heating of blood by various apparatuses which heat different portions of blood sample to different temperatures actually promotes hemolysis. At the Iowa University hospitals DeGowin observed 568 patients who received cold blood transfusions as given by different people at different times under varying conditions of temperature and of velocity of administration. The following table illustrates the results:

	Number	%
No symptoms or signs	520	91.5
Chills only	6	1.0
Chills and fever	31	5.4
Urticaria only	8	1.4
Hemoglobinuria	2	0.3
Abdominal pain	1	0.1

Since over 91.5% had no reactions, the reactions of the 8½% can be attributed in good measure to reasons other than the procedure used in transfusing, which procedure was quite standard with regard to equipment, cleansing of it,

etc. Hemoglobinuria was explained by other reasons. Urticaria remains unexplained. Pyrogens probably explain the chills and fever in 5.4% of cases. Thus, temperature is not an important factor in blood transfusions and it is not necessary to heat blood before transfusing. This method saves time and prevents reactions which occur in the heating process.

COMPLICATING REACTIONS

CARDIAC FAILURE

This is not a common occurrence, for only six of 45 deaths were shown to be due to cardiac failure in compilation of a series of 43,000 transfusions by Kilduffe and DeBakey. Cardiac failure usually occurs when a transfusion is given to a patient with myocardial disease. This results in overloading of the circulation and placing too great a load on a weakened heart. Occasionally, a chill or minor reaction may cause such constitutional disturbance as to further tax the heart. In patients with long-standing anemia the heart has had a decreased circulatory volume to pump as well as a deficient oxygen supply itself. Such myocardia are likely to be weakened and cannot respond to a suddenly increased blood volume.

Plummer and Pygott (1936 and 1937) have presented a series of cases in which cardiac failure has followed blood transfusions. In all cases cited it was pointed out that when anemia of long standing exists the myocardium suffers from lack of nutrition and becomes accustomed in it weakened condition to handle a given blood volume. When a transfusion increases this blood volume suddenly and the weakened myocardium does not respond fully enough, myocardial failure results. In contrast, acute blood loss occurring in a short time and depriving

the heart of adequate nutrition for a short time presents a different situation. Here, ymocardium is still in good shape and can handle adequately large and sudden increases in blood volume.

Pygott (1937) has noted a few symptoms occurring in conjunction with cardiac overloading. He has observed that after about 150 cc. of blood are given and the rate of administration is then speeded up, the patient enters a fit of severe coughing which ceases when the transfusion is stopped. Pygott ascribes this to overdistention of the right auricle. In one chronically anemic, myocardial dilatation is usually present and the stretched fibers do not contract to the fullest extent, having little capacity to stretch further. So, the right auricle cannot accommodate a large volume of blood suddenly introduced into the circulatory system. This is the mechanism, according to Drummond (1943), by which heart failure occurs. The extra volume of blood which the heart cannot handle goes into the blood vessels in the lungs and pulmonary edema results. Stretching of the right auricle causes precordial pain. As soon as the cardiac output increases, balance occurs in the amount of distention in the two auricles and all proceeds well. Backache of less severe nature than that occurring with

transfusions of incompatible blood plus restlessness have been observed after large transfusions quite commonly according to Pygott. The following case history illustrates cardiac inadequacy in a patient with a previously weakened myocardium: (Pygott, 1937)

"This was a case of pernicious anemia in which death followed five hours after the first transfusion. The patient was a male aged 50. He was a typical case of PA with early subacute combined degeneration of the spinal cord. He gave a history of increasing breathlessness on effort, tingling and numbness in hands and feet, and loss of energy, but no loss of weight.

"He was well nourished but anemic; his skin and conjunctivae had a subicteric tinge. Peripheral arteries were moderately sclerotic and his heart sounds were regular but of only fair quality. Blood pressure was 125/75. Examination of chest revealed mild generalized bronchitis. CNS showed some slight nystagmus, absent abdominal reflexes, bilateral extensor plantar responses, absent vibration sense in the legs.

"Laboratory:

Urine trace of albumin	RBC 1,250,000
Feces negative	Hb 25%
Achlorhydria	WBC 2500
Wasserman negative	

Evidence of definite renal damage by clearance tests.

"It was thought his improvement might be hastened by transfusion. On the fourth day after admission he was given 550 cc. of blood by the citrate method. The patient's and the donor's bloods were perfectly compatible when mixed directly before the transfusion.

"There was no immediate reaction of any kind, but one hour later the patient complained of feeling cold and had a rigor. He was given hot drinks, and he settled down again with no further complaints until four hours after the transfusion, when he suddenly collapsed and went into coma with cyanosis, dyspnea, and a feeble pulse. His chest was then full of bubbling rales, and he died an hour later.

"At necropsy the lungs were found to be edematous. The heart was slightly dilated and its muscle was very flabby and showed a typical thrush breast appearance. There was a moderately severe degree of chronic interstitial nephritis. No other abnormalities were found, and no evidence of pulmonary embolism or clot formation in any of the larger vessels was demonstrated."

In this case the anemia of long duration was very likely responsible for a "weakened myocardium" which was unable to stand the strain of pumping a suddenly increased blood volume.

Murphy and cohorts (1941) worked 1½ years on the problem of factors related to cardiac failure with particular reference to the addition of fluids to circulatory system. The factors considered and their relations to this problem are listed:

1. Venous pressure: This first increases with fluids given intravenously to 140-170 mm. of water pressure. The rise is less if the venous pressure is already up as in congestive heart failure. Peak of this rise occurs in ½ hour. Then, phase two occurs in which venous pressure starts to drop due to dilatation of the peripheral capillaries which now accommodate more fluids. Acute left heart failure may occur with this drop in venous pressure. Phase two lasts for one hour after the intravenous administration. Phase three tends toward increased venous pressure coincident with increase in plasma volume which may be due to the inflow of fluid from extravascular spaces into the capillaries. Initial rise is averted by the use of eight grains of aminophylline given with the intravenous fluids.

2. Plasma volume: This increases, of course, with intravenous fluids. The initial average increase in plasma volume was 1/3 greater with 1000 cc. of normal saline than with 1000 cc. of 10% glucose in water. The

actual increase was 300-350 cc. plasma volume by means of an intravenous of 1000 cc. of normal saline--or of 5% glucose given at 25 cc. per minute. Increase in the speed increases the plasma volume. Too rapid administration may acutely overtax the circulatory system and break down an already diminished cardiac reserve. Two hundred cc. of 50% dextrose raises the blood volume an equivalent amount as does 1000 cc. of 10% dextrose if given at the same rates. Roughly, the increase in hypertonicity of the solution administered is directly proportional to the increase in plasma volume. The initial volume increase depends on the volume of fluid administered and the rate. In 30-40 minutes a decrease in volume occurs due to transudation of fluid into extravascular tissue spaces, lungs, gastrointestinal tract, and liver; and due to increased urinary output. In cardiac failure more fluid stays extravascular and does not reach a site of excretion. In cardiacs, pulmonary edema then occurs.

3. Vital capacity: A change here of over 5% was considered "abnormal." It was noted in cardiacs that significant changes in vital capacity occurred when fluids were given intravenously. Often, the vital capacity decreased though the patient was improved clinically. Vital capacity occasionally increases though concurrent with

cardiac failure.

4. EKG has shown decreased voltage of the QRS lasting for four hours after a transfusion.

In Murphy's cases, "100% of patients with evidence of heart failure in bed, when given 1000 cc. of 10% glucose were made worse." If 200 cc. of 50% glucose with eight grains of aminophylline were injected, 65% of those in the Group 4 classification of heart pathology (American Heart Association) became worse. In Group 3, heart failure evident with slight exertion, 16% showed ill affects with volumes of over 200 cc. Groups 1 and 2, cardiac defect with little evidence of heart failure and non-cardiacs, show no changes clinically except a weight gain in 50%, pitting edema in those who received 2000-3000 cc. of normal saline daily for three consecutive days.

Patients with any evidence of heart pathology should have an adequate physical examination to ascertain the safety which can be had in administration of intravenous fluids to them. Also, patients with lung pathology, especially pneumonia, do not tolerate fluids well.

In brief, be careful of three factors: the volume of the fluid given, the hypertonicity of this fluid, and the speed with which it is injected.

Speed shock may be induced by rapid administration

of a transfusion in a person with weak myocardial reserve. Strumia (1943) believes that the speed of administration causes reaction not by increasing the venous pressure alone, but also by increasing the rate of administration of pyrogens, etc.

The symptoms of speed reactions are described by Wiener as follows: (1941)

1. Pain in the arm due to distension of veins as large amounts of blood distend the vessels.

2. Distention of peripheral veins, especially the external jugulars, causing the patient to cough, complain of fullness in the head and of vertigo.

These symptoms are a warning which if not heeded will result in acute cardiac dilatation as more blood is poured into the overburdened circulatory system. Collapse will follow soon.

A case is mentioned by Wiener in which a patient had a chronic myelogenous leukemia and in whom cough, cyanosis, and venous distention appeared after the patient was transfused with 500 cc. The cause was an activation of a latent isufficiency of the right heart "due to pressure thereon from the enlarged spleen!"

Hyman and Hirshfeld (1931) described the speed shock syndrome as occurring 40-60" after the introduction of

the intravenous fluid. They characterize the syndrome by a rapid drop in blood pressure, irregular respiration, incoagulability of the blood, occasional termination by death but more usually by recovery. They believe the syndrome depends on the speed of injection and not on the condition of the recipient or upon the nature of the substance injected. These investigators consider a speed of two to three cc. per minute to be a slow but safe rate. Milbert (1934) in a series of cases observed no relation between the severity of reactions and the gravity of the patient's disease. In fact, Milbert's 25 cases caused him to conclude that the rate of infusion was of no significance. His rates varied from 38-177 cc. per minute.

Prevention of cardiac failure by precautionary measures is important. Great caution should be used in transfusing cardiacs and this should be exercised by using a slow drip method and by watching for symptoms of cardiac distress such as cough, precordial pain, and dyspnea. Though there is discrepancy of thought in regard to the speed of administration of fluids intravenously, opinion weighs heavier in favor of the slow rate of administration in most cases.

The ability to regulate speed of giving transfusions has been improved by the use of citrated blood administered

by the gravity method. This permits any rate desired and removes the danger of "speed shock" caused formerly by rapid transfusion from person to person via the syringe-valve method. The latter method provided no means of preventing coagulation and thus required rapid transfusions with resultant danger to weak myocardia.

Drummond (1943) suggests slow transfusion at the rate of 40 drops per minute and permitting at least three hours for the transfusion of a pint of whole blood. Another rule propounded is that one cc. per pound of body weight per hour is the maximum amount to be given in one hour. Hyman and Hirshfeld, as has been previously mentioned, concur with Drummond's idea of a proper rate of administration, viz., two to three cc. per minute. It should be pointed out, however, that in severe acute hemorrhage large amounts of fluid up to 400-500 cc. can be given in a few minutes whereas fluid given nutritionally, in the treatment of chronic anemia, or inthe presence of myocardial damage should be given slowly by intravenous drip.

Strumia (1943) enlarges upon the previous suggestions and summarizes the pertinent points in regard to promoting safe transfusions. Under ordinary conditions he believes a safe rate is one up to 20 cc. per minute. If shock is

present on an acute basis, 500 cc. can be given within ten minutes. If cardiac patients are to be dealt with, Strumia advises against rates of over 10 cc. per minute, and he believes five cc. per minute to be a safe maximum when whole blood is used due to its greater viscosity.

When symptoms of cardiac overburdening do appear, the indication for cessation of transfusion is present. Oxygen should be administered along with morphine, atropine, and aminophylline, supportively. A radical measure which may be necessary is venesection.

EMBOLISM

This is one of the very rare complications, Kilduffe and DeBakey having experienced no such complication in over 5000 transfusions. Very few cases are on record, and few of these show much evidence which lays the blame for embolism on the transfusion. Dislodging of vegetations in a patient with subacute bacterial endocarditis may be due to the increased blood volume necessitating increase in myocardial contractions. Strumia (1943) suggests that emboli may be due to flocculation occurring in whole blood or plasma kept at refrigerator temperatures of 2-8° C. and then used for transfusion. He believes prevention of emboli can be effected by filtering the blood

through four layers of 40 mesh gauze before transfusing.

Air embolism is another form of this type of complication and is also a scarce entity. (Nordlund, 1931) The amount of air necessary to cause reaction or death is too variable to be stated numerically. Symptoms of air embolism include a hissing, gurgling sound as the air enters the vein; accelerated respiration; and decreased arterial blood pressure. The patient becomes dyspneic, cyanotic, and comatous before death. These symptoms run a very rapid course to death. If a small amount of air is aspirated progression of symptoms is slower. The patient shows dyspnea, nausea, acute epigastric and precordial pain, faintness, restlessness, and anxiety. The pupils dilate and are fixed; respiration eventually ceases, and coma and convulsions then precede death. Often a bruit is heard over the heart as a result of churning of air in the right side of the heart.

Air embolism is more of a worry in injury to the jugular veins of the neck than in administration of a transfusion. Death may be due to anemia of cerebral centers due to air embolus locating in the cortex; to suffocation due to occlusion of pulmonary arteries by air; or to cardiac impairment in that the valves cannot open and close properly. Reduced intracardiac pressure

due to air in cardiac cavity permits pulmonic capillary resistance to render the heart beat of no avail. Futile contractions of the right ventricle in a medium of frothy blood permits pulmonary stagnation and then systemic stagnation of blood.

THROMBOSIS

Intracardiac thrombosis after transfusion has been reported. The patient described by Rouffert-Marin in 1939 developed chills, fever, precordial pain, and a mitral murmur one hour after transfusion for hemorrhage from a cervical biopsy. This patient recovered, but it was concluded that intracardiac thrombosis had occurred. Wiener has noted thrombois of veins at the site of injection occasionally associated with phlebitis and suppuration, but without interference in the patient's progress.

RETINAL HEMORRHAGE

Schaly was among the first to note retinal hemorrhage after transfusions; this complication has since attracted much attention. Schaly (1926) described four cases of retinal hemorrhage after transfusion in two patients with pernicious anemia, and in two cases with aplastic anemia. Impaired vision followed shortly and fresh retinal hemorrhages were noted. Two patients died; two lived, but never regained their vision. In 1930 Messinger

and Eckstein examined the eyegrounds of 60 recipients before and after transfusions. In ten cases retinal hemorrhages were noted 12-24 hours after transfusion. In only two cases of these were there any subjective visual complaints. The more serious retinal hemorrhage occurred in those with blood dyscrasias--five, in fact. One case occurred in a patient with retinal arteriosclerosis, and four in patients with profound secondary anemia of at least three week's duration. Various series of cases have been presented to show the incidence of retinal hemorrhage. Titov and Bagomolova, e.g., noted seven cases in 100 transfusions.

As previously noted, many cases are reported in which the retinal hemorrhage occurred in those with blood dyscrasias or severe anemia. Gray (1939) believes that the hemorrhages in retinal vessels occur coincidentally to transfusion. Some believe that transfusions predispose to but are not a direct factor in causing retinal hemorrhage. Others believe that increase in blood volume and pressure consequent to transfusion is responsible for the retinal hemorrhage. Gray is in opposition to such an opinion because he claims that if such were the etiology the blurred vision on the part of the patient should occur during or immediately after the transfusion--which

is not always the case. Gray further suggests that if retinal hemorrhage were on the basis of transfusion hypertension, the retinal hemorrhage could be expected after saline or glucose infusions--and such is not the case. Embolism of the retinal arterioles is another suggestion (Frey, 1938), or retinal hemorrhage due to faulty technique another possibility. Incompatibility of transfused blood may be manifested by generalized petechial hemorrhages coming on a few hours or days later. Emboli may lodge in the finer retinal vessels causing extravasation of blood. Frey, too, mentions increased blood volume and pressure as possible etiological factors. DeBakey and Kilduffe agree with Gray that actually the etiology of retinal hemorrhage at the present is unexplained and that retinal hemorrhage follows transfusions only when some pre-existing factor is present.

INTRACRANIAL HEMORRHAGE

This and hemiplegia are additional complications reported following transfusions. Glaser (1937) reported a case of an infant eight days old who bled profusely following circumcision. Transfusion was indicated, was given, and was followed by the baby becoming cyanotic. His respirations ceased, his heart sounds disappeared, and death

supervened. The cause of death was explained by the statement that the infant had an intracranial hemorrhage at birth with incomplete clot repair. The clot was loosened by change in intracranial hydrodynamics due first to exsanguination and second to the transfusions.

Autopsy verified intracranial hemorrhage in this case. In addition, a history was obtained of a difficult labor and difficult stimulation of respiration in the infant. In such cases circumcision should be postponed and if transfusions are necessary, the blood should be given in small doses at frequent intervals.

DISEASE TRANSMISSION

The most common communicable diseases transmitted by transfusions of blood are syphilis, malaria, and measles. Syphilis is the most dangerous and unfortunately most common of these. Syphilis seems to be transmitted mostly from donors who are relatives of recipients. Probably, this is because the relative is considered a safe source of blood without using the seemingly necessary Wasserman test, etc. to determine definitely if the donor carries Treponema. Syphilis appears in about eight to ten weeks after the transfusion and is similar clinically to ordinary lues except for the absence of a chancre. Thus, the first manifestation usually is the secondary

eruption. Pre-serological stage syphilis, of course, can unknowingly be transmitted via transfusions with Wassermans previously being negative. Tertiary syphilitics usually do not transmit syphilis via transfusions. McNamara (1925) reports transfusions of ten non-syphilitics by six syphilitics. The recipients all were noted to show marked improvement and Wassermans were negative over 16-27 week periods of observations. McNamara concluded that the use of blood of tertiary luetics in transfusions is a safe procedure.

All prospective donors should be questioned and examined. The Kline is a preferred test due to its high degree of sensitivity. Control of syphilis by adding Treponemicides to stored blood has been suggested. Eichenlaub and Stolar (1939) use 0.01 grams mapharsen added to blood to be transfused five minutes before the transfusion. Turner and Diseker believe that after about four days blood storage, Treponema is no longer infective.

Transmission of malaria from donor to recipient has been reported. Supposedly, one to four weeks pass before clinical manifestations of the transmitted disease occur. Occasionally transmission of malaria is from a person who has not had the disease for 15-25 years, yet the latent infection when transferred to another circulatory system

became active. Precautions must thus include more than blood smears, but also history which seems to be an all-important factor.

Only brief mention need be made of other diseases known to have been transmitted in blood transfusions. Levick (1931) describes a patient who developed chills, fever, backache, pains in the limbs, and chest pains shortly after a transfusion. The symptoms ran a course typical of influenza.. Levick checked with the donor whom he found bedfast with the flu, suggesting the transmission of this disease by blood transfusion.

Baugess (1924) presents two cases in which measles was transmitted from mothers to infants nine and two months old, respectively. In the first case a period of 13 days elapsed from transfusion to rash. No source could be found except the mother who broke out with measles two days after she gave the baby a transfusion. In the second case 14 days elapsed from transfusion to the rash. Again the mother had measles two days after the transfusion was given. In neither case was the infant exposed to mother on the day of the transfusion nor was there a case of measles in the hospital ward. Bauguess believes that measles can be transmitted, but suggests the possibility as a rare one especially in

infants as young as these cited.

Blalock (1926) exhibits a case in which the patient received a transfusion from a donor infected with smallpox. Following this the recipient developed "variola sine eruptione"—a mild form due probably to a partial protection as evidenced by a vaccination scar on the recipient's arm. The donor came down with smallpox one day after transfusion. Blalock is of the opinion that the donor can transmit the disease if blood is given within the period of incubation and within the period of prodromal symptoms of smallpox. The organism is supposedly present in the blood stream at least 24 hours before eruption occurs.

DELAYED POST-TRANSFUSION JAUNDICE

Beeson (1943) reported seven cases of post-transfusion jaundice and Morgan and Williamson (1943) nine cases in which jaundice followed by one to four months a blood transfusion. No evidence of infection could be found. The cases were characterized by sudden onset of jaundice, malaise, nausea, epigastric discomfort, hepatomegaly with tenderness. Such symptoms cleared in three to twelve weeks. These patients were in an older age group than those afflicted with the usual acute infectious hepatitis. Also, the illness here was more severe and

prolonged than in infectious hepatitis. No history of contact with infection nor of spread of the jaundiced condition to others could be obtained.

A virus is thought to be responsible for acute infectious hepatitis and for post-transfusion hepatitis. There is little evidence for or against the possibility that these entities have a common etiology. Various modes of transmission of the etiological agent have been suggested. Barker et al. (1945) mention droplet infection; transfusions of pooled plasma, serum and blood; and the use of inadequately disinfected needles and syringes as sources of spreading hepatitis. In seven of 18 volunteers, infectious hepatitis developed 17-28 days after the administration orally of emulsions from feces or urine of infected persons. (Findlay and Willcox, 1945)

Acute infectious hepatitis has an incubation period of 30 days. Serum jaundice appears to have an incubation interval of 60-100 days (Havens, 1945) regardless of the route of administration, whether intracutaneous, subcutaneous, intramuscular, or intravenous.

Havens obtained nasal washings from patients in the pre-icteric or early icteric stages of hepatitis. These patients had previously been innoculated with yellow fever serum. He administered these washings intranasally

in volunteers, and observed incubation periods of 30-50 days before the onset of hepatitis. It seems, then, that the placing of nasal washings either from a person with post-transfusion hepatitis or from one with the acute infectious hepatitis into the nasopharynx of a volunteer results in hepatitis after an incubation period of about 30 days. The explanation for these incubation periods as well as a clarification of the etiology of these "two forms" of hepatitis are yet forthcoming..

According to Grossman et al. (1945), post-transfusion hepatitis is not distinguishable by clinical observation from acute hepatitis. This group observed a series of 108 cases of acute hepatitis, 103 of which occurred in men recently wounded in action. Among these 103 men the wound had been received on an average of 92.6 days previous to the onset of hepatitis. Most of these men had received transfusions of blood and/or plasma. Factors appearing to play no part in the severity of the hepatitis included the type or degree of injury, location of the soldier's service, previous medication, infection, and general condition of the patient.

A study of 1319 recent battle casualties with 68 cases of hepatitis revealed the following % incidence of hepatitis:

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A study of 1319 recent battle casualties with 68 cases of hepatitis revealed the following % incidence of hepatitis:

Those receiving no plasma or blood	0.3%
Those receiving plasma only	7.7
Those receiving plasma and globulin	1.9
Those receiving blood only	8.6
Those receiving blood and globulin	0.0
Those receiving plasma and blood	13.1
Those receiving plasma, blood, and globulin	4.0

It is apparent, then, that the hepatitis is very likely a post-transfusion type in many of the above cases. Also, the above table points out the value of globulin in reducing the incidence of the hepatitis following transfusions. The patients receiving the globulin were chosen at random and were given an injection of ten cc. of human immune gamma globulin upon admission and again in one month. The comparative incidence of hepatitis is summarized:

384 cases treated with globulin....11 got hepatitis 2.9%
384 controls without globulin.....44 got hepatitis 11.5%

The mechanism of the action of gamma globulin is not clear. If post-transfusion hepatitis has the same etiology as acute infectious hepatitis, then the globulin undoubtedly has the same therapeutic affect in both cases. It is possible, too, that antibodies in gamma globulin protect against more than one agent responsible

for hepatitis. Stokes and Neefe (1945) believe that gamma globulin is most effective if given early during the incubation period of hepatitis.

Any prospective donor with a recent history of jaundice or of contact with jaundiced cases should be disqualified for giving blood transfusions.

THE IDEAL METHOD

The purpose of this concluding section is to summarize the important types of reactions and to point out how improvement in method may prevent transfusion reactions.

An ideal method requires first an ideal donor. Select a donor without any current or recent illness and one without blood dyscrasias. Do a blood Wasserman and check the history of a donor for such diseases as malaria, syphilis, influenza, measles, smallpox, and septicemia. When the above are ruled out by laboratory tests and by negative history, do a cross-matching test and a typing test to determine the blood grouping.

Ascertain if the donor has a high titer of agglutinins which ordinarily are not considered in tests for compatibility. Add various dilutions of the serum containing the isoagglutinins to suspensions of known A and B agglutinogens. Determine the highest dilution of serum which when combined with the red cell suspensions will still cause agglutination. If the donor has a high titer of agglutinins and is a universal O type, it will be a wise measure to "condition" such blood; this is effected by addition of group specific substances, A and B. Such conditioning is not attempted in other types of blood.

The A and B substances are carbohydrate-like chemically. They are called haptens because they do not

stimulate the production of antibodies or agglutinins. Landsteiner (1932, 1936) was one of the first to isolate the A substance from the saliva of a horse. Since, pepsin, mucin, and peptone have been found to be convenient sources for A substance (Landsteiner and Harte, 1940) and the gastric juice from persons of B group a ready depot for B substance (Witebsky and Klendshoj, 1940). The technique of preparing these substances is described in detail by the authors just cited. If the titer of isoagglutinins in the O blood is 1:8 or 1:16, the blood is likely to cause no reaction. Titers greater than 1:16 merit "conditioning" of the blood. A 1:1000 stock solution (Witebsky et al, 1941) of the group specific substances is added to 500 cc. of blood about five minutes preceding the transfusion. The stock solution is one with physiological saline and the A or B substances. Because the A isoagglutinin titer is usually higher than the B isoagglutinin titer, 25 cc. of A substance and only 10 cc. of B substance are usually added to the blood. These substances combine with the isoagglutinins in a reaction of neutralization, not of agglutination. The resulting reaction prevents further activity of the

substances added as well as the isoagglutinins. The addition of A or B red blood cells to O blood after conditioning will not cause agglutination. This evidence demonstrates the effectiveness of the conditioning process. No ill affects are known of due to the presence in the recipient's blood stream of the combination of group specific substances and isoagglutinins.

Technique of cross-matching and typing must be known and used to aid the selection of the ideal donor. For cross-matching tests it is necessary to have samples of sera and red blood cells from the donor and recipient. The samples of serum are obtained thus: place blood in a test tube and allow to coagulate; then, with a glass rod remove the clot and centrifuge to obtain more complete separation of blood cells from the serum. The serum can be pipetted off and kept under refrigeration until ready for use. To prepare a suspension of the red blood cells, the following method is used: obtain a few drops of fresh blood and add a little 3% sodium citrate solution; centrifuge and discard the serum fraction. Then, resuspend the cells in normal saline. If desired, the cells can be washed with normal saline, centrifuged again and then resuspended in normal saline.

Once the serum and red cell suspensions are prepared, the cross-matching tests can be carried out by one of several methods. A drop each of the cell suspension of donor, of saline, and of serum of recipient can be mixed in a small test-tube and allowed to stand for a few minutes. (Wiener suggests a test tube of seven mm. diameter.) Though reactions usually show up in a few minutes, final readings should not be made for an hour. Centrifuging at 2000 rpm for 60 seconds and then shaking the tube will magnify the reaction. The results can be read directly by observing the test tube grossly or by placing a drop on a slide and observing under low power microscopically. Upon gross examination, if shaking the test tube fails to suspend the clumped cells uniformly, agglutination has resulted. When agglutination is marked, a single large clump will be noted. It was mentioned that cell suspension of donor was mixed with serum of recipient in this test; of course, the reverse is also carried out and observed in the same way to complete the cross-matching. This method does not involve the use of known stock testing sera, and as a result, the grouping of the individuals concerned is not determined.

When the grouping of a donor or recipient is desired

a procedure as the following is used: place a drop of stock A serum on one end of a marked slide and a drop of group B serum on the other end of the slide. Add a drop of unknown cell suspension to each drop of known serum; tilt the slide up and down for several minutes and then place the cover slips over the drops. Interpretation of results has been illustrated by a table on page 15 of this paper. Generally, the donor and recipient should be typed and then, just before transfusion occurs, a crossmatch should be carried out as a check on the previous typing. The test tube method for effecting this testing is preferable to the slide routine because the adequate dilution obtained by use of test tubes insures against pseudoagglutination reactions.

Stock testing sera are obtained by placing a blood sample in refrigeration and allowing a clot to form. Then, while the sample is still under refrigeration, the serum is drawn off (after centrifuging if necessary); this leaves any autoagglutinins present bound to the red cells and free of the serum. The serum can be typed against known red cell suspensions and can be stored in an ice-box for a long time. Preserving and collecting stock sera and stock red cells is not a pertinent problem in this discussion, so details are omitted.

Be certain that the Rh factor has been ruled out of the picture especially when giving transfusions to those who are Rh negative and have had previous transfusions or to those who have had pregnancies. In such cases Rh negative blood is the choice for transfusion. To test for the Rh factor add a drop of 2% suspension of the unknown red blood cells to a drop of known anti-Rh serum and incubate at 37° C. for one hour; then centrifuge at 500 rpm for one minute. Resuspend the cells and look grossly and microscopically for clumping which means that the red blood cells are Rh positive. Several strains of antiserum should be used, for sometimes red cells will agglutinate one anti-Rh serum and not a different strain. Accuracy requires repetition of the tests. Crossmatching usually fails due to lack of delicate technique, and poor technique in testing for Rh is an even more frequent cause of error. Maintenance of the 37° temperature, the long incubation, and the centrifuging are essential for the detection of Rh.

Try to avoid donors who are known to have a history of allergy, for passive transfer of such sensitivity to recipient is possible.

The truly ideal donor is one who is a healthy, non-diseased individual with Rh negative blood of O type.

To make the situation still more utopic the blood is conditioned to lower the titer of agglutinins. These suggestions are within the realm of practicality to a limited extent, of course, but they provide a goal to be strived for in choosing a blood donor.

The recipient for a blood transfusion can usually qualify easily. It is necessary to be en garde, however, in considering transfusion to one with chronic anemia or long-standing myocardial disease. It is exceedingly important not to suddenly overburden a weak myocardium. This can be avoided by the drip method of transfusion. A hemophiliac who tends to bleed readily often provides a contraindication to transfusion because of producing oozing for a long time at the site of puncture of the vein. In such cases intraperitoneal injections of blood have been advocated. The recipient will have his blood subjected to the scrutiny of crossmatch with the donor to assure compatibility. If the recipient has had previous transfusions check by crossmatch the donor's cells against the patient's serum to see if there is any isoimmune antibody formation on the part of the patient which could be responsible for reactions after subsequent transfusions.

The question arises in regard to technique whether to

use fresh, citrated, or dextrose-citrated blood. DeGowin and Hardin (1940) observed the reactions in 2423 transfusions to determine the incidence of reactions in the use of preserved blood. Of these, 2128 were done with blood stored 1-38 days at 3-5° C. The remaining 295 were transfused with fresh blood. Blood citrate was used in 1647 cases and blood-dextrose-citrate was used in 776 cases. The latter blood was usable after 30 days storage while citrated blood was discarded by the tenth day due to hemolysis. In this series of transfusions blood was not pre-warmed as deemed safe by previous work of these men. No significant differences in reactions were noted:

	Blood-dextrose-citrate	Blood-citrate
Chills only	0.7%	0.9%
Chills and fever	1.4	2.3
Urticaria	0.9	1.2

As suggested by DeGowin and Hardin (1940) a blood-citrate mixture of 500 cc. of blood plus 50-100 cc. of 3.2% sodium citrate in distilled water can be used. They advise a blood-dextrose-citrate mixture consisting of 500 cc. of blood, 650 cc. of 5.4% dextrose in water, and 100 cc. of 3.2% sodium citrate in water. Thus, if the danger of overburdening the circulatory system must be considered, it is better to use fresh blood with

citrate or citrated blood stored less than ten days, and omit the use of dextrose which prolongs the life of the stored cells but doubles the volume of fluid given. When large quantities of blood are required at once after acute hemorrhage, it may be advisable to use the direct method of transfusion from donor to recipient without citrate. However, the administration of uncitrated blood as rapidly as is necessary to prevent clotting may be a shock to the circulatory system. Handling of citrated blood is much more convenient, involves no clotting of blood in the apparatus. More time can be taken to check the donor and do cross matching accurately if blood banks with citrated blood are depended upon rather than a donor rushed in in an emergency. The citrated blood permits slow administration which is of special advantage in those with weak myocardia. Fresh blood has been found to stay in the circulatory system of the recipient three to four months while blood stored 21 days has been noted to survive only 24 hours in the recipient--a point in favor of fresh blood. Fresh blood can be citrated and as such is probably ideal for transfusion.

Plasma is to be considered in choosing a favorable fluid for transfusion. Pooling of plasma is important to dilute any high agglutinin titers; in other words, mixing

of plasma of several individuals will lower the titer of agglutinins in anyone when this titer is high. This provides another means of avoiding reactions.

Having selected an ideal donor, an ideal recipient, and an ideal substance for transfusion, we can consider an ideal technique for administering and withdrawing the blood, plasma, or other fluid.

Choose a large, sharp needle about 15 gauge to draw the blood from the donor and use about 18 gauge for injecting the fluid into recipients if adults; use 20-22 gauge in infant or children recipients.

Select a large, prominent vein and extend the limb so that the vein is under tension. Apply a tourniquet above the elbow to occlude only the venous return. When the vein becomes distended prepare to enter. If the vein is deep and not very prominent, it is best to enter it by a direct plunge over and into it. If the vein by this maneuver is pierced through both walls, slowly withdraw the needle until the blood flows into the needle. Then, flatten the needle out parallel to the long axis of the vein and advance ½-1 cm. into the venous channel.

When the vein is superficial and quite evident a method may be used which provides less tendency to pierce both walls of the vein and also less chance of

traumatizing the vein by the jerk of the needle as it penetrates the skin. Hold the skin taut and advance the needle over the vein parallel to the skin surface and into the skin about ½-1 cm. Then increase the angle between the needle and the skin surface and gradually enter the vein. As the needle pierces the vein wall a snap may be felt and blood rushes into the needle. Advance the needle into the vein ½-1 cm. parallel to skin and to the long axis of the vein.

Another method to be more certain yet of avoiding trauma to the vein consists of entering the skin at the side of the vein. Once the needle is subcutaneous, it can be deviated towards the vein and latter is then gently pierced. In such rare cases wherein the veins are difficult to enter by means above described, an incision can be made over the antecubital space or anterior to the medial malleolus of ankle and veins are thus exposed.

Care in avoiding trauma to veins will prevent thrombosis. Care in using sterile equipment will prevent thrombophlebitis and septicemia. Autoclaved apparatus and freshly distilled water are essential to reduce the number of pyrogenic reactions. Caution in preventing contact of blood with air by collecting it in sealed containers through rubber tubing and storing it in sealed

containers greatly removes the possiblity for bacterial growth and subsequent febrile responses after transfusion.

The common means of administration is by the gravity method. The bottle containing citrated blood is suspended well above the patient. The blood is channelled to the patient's vein through rubber tubing with a clamp device thereon to control the amount given per unit of time.

A final precaution which checks all previous precautions and tests is the injection of ten cc. of blood into the recipient and allowing twenty minutes to pass; if no reaction occurs, proceed.

If the donor has been ideal as above specified, if the recipient has met the ideal requirements, and if the technique has been ideal, the transfusion probably will be concluded successfully and uneventfully.

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