

POSTTRANSFUSION REACTIONS

ALTERATIONS IN BLOOD AFTER ETHER ANÆSTHESIA AND AFTER BLOOD TRANSFUSION

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THE history of blood transfusion previous to the present era, which really began with Crile's epoch-making work in 1906 (10), consists of several short periods during which the usefulness of transfusion as a therapeutic measure was enthusiastically endorsed, and long intermissions during which it was considered a hazardous procedure. Based upon a number of fortunately successful cases and upon attractive but for the most part erroneous theories, the legitimate importance of blood transfusion took on the aspect of a "cure-all" and a life-saving device in all serious diseases; and, therefore, came to be used in as great, if not a greater variety of conditions, as may be found in a modern list of indications. Indeed, its sphere of usefulness was extended to the soul, for Cardamus in 1556 advocated that people hopelessly immoral should be transfused with blood of those strongly moral (Jones, 18). A comparison between the practice of transfusion before the present era and its practice with modern methods can only excite wonder and a certain degree of admiration for the courage and skill of our forebears, who, in total ignorance of aseptic methods and working with inferior instruments and technique, were able to obtain some encouraging results. But these deficiencies in their knowledge may be taken to account for both their courage and for the failures, which, at the end of each successful period, stamped transfusion as a dangerous operation and eliminated it from practical therapeutics, until in some future generation interest in it was again revived and success, enthusiasm, failure, and resultant condemnation were again repeated.

The investigations and clinical applications of blood transfusion reported by Crile (10 and 11) excited much scientific interest throughout the entire world. Since then, the technique has been greatly perfected by the introduction of the Lewisohn (23),

Lindeman and Unger (44) methods and their modifications. Landois in 1875 was the first to discover that the dangerous results following transfusion were due to the fact that the fresh serum of an animal of one species could dissolve the red cells from an animal of another species. The researches of Landsteiner (21), Jansky (17), Hektoen (16), Ottenberg (31), and Moss (28), explained the nature of the dangerous, often lethal, post-transfusion reactions, and made it possible to test for the compatibility of donor's and recipient's bloods previous to transfusion. Furthermore, fair and rational estimation of results obtained from transfusion in various conditions has eliminated many cases in which the measure is useless, and has thus diminished the number of failures. The true indications for transfusion have thus been placed in greater relief; and hence its usefulness is now better appreciated.

Blood transfusion must, therefore, remain permanently as a therapeutic measure of highest value and very great importance.

Whereas the technique of transfusion is now very efficient, and its sphere of usefulness is now well understood, the problem of eliminating posttransfusion reactions has been successfully dealt with only in its grosser phases. For, in spite of pretransfusion tests for compatibility of donor's and recipient's bloods, posttransfusion reactions continue to occur. From our observations, and from an examination of the literature, we have come to the conclusion that inaccurate testing cannot account for all the reactions, but that they occur very frequently, even after the bloods have been properly matched and found suitable.

ALTERATIONS IN RECIPIENT'S BLOOD AFTER ETHER ANÆSTHESIA

The attention of one of us (Levine) was attracted to a hitherto unreported cause of reaction, by a number of experiences with

transfusion for postoperative replacement of blood. In such cases, if the possible necessity of transfusion is foreseen previous to the operation, a suitable donor may be chosen and held in readiness, to be used at any time during or after the operation. If the necessity of transfusion is perceived only during or after the operation, and if the group of the patient is known, a suitable donor of known group may be obtained; but if the patient's group is not known, possible donors may be quickly summoned, the bloods of the donor and recipient tested, and a suitable donor chosen. Some operators who do transfusions are satisfied, in cases of emergency, to choose the nearest relative as a donor and proceed to perform the transfusion without previous testing of bloods; although this latter procedure is unscientific and unsafe to the patient, it is permissible in the most extreme cases of emergency.

CASE 1. In September, 1919, at the Royal Victoria Hospital, it was found necessary to do a transfusion on Mr. H., 60 years old, after he had undergone a radical Kraske operation which lasted $2\frac{1}{2}$ hours. Anæsthesia in this case was begun with gas and oxygen and continued with ether. Almost immediately after the operation some blood was withdrawn from the patient and centrifugalized. The serum, which had a pinkish tinge—probably due to some hæmolysis—was matched with the red cells of the donor, this patient's 24-year-old son, a well-built man in good health; marked agglutination occurred within 30 minutes after the test had been set up. Twenty-four hours later some blood was again taken from the patient, and the serum obtained was plainly straw-colored without any pinkish tinge. The test was repeated with the red cells from the same donor; there was no agglutination evident, even after 12 hours' incubation at 37°C .

CASE 2. In June, 1920, the necessity for transfusion after operation was deemed possible in the case of Mrs. A. C., who was to undergo a laparotomy for gall-bladder disease. The direct test was performed, matching her serum with her husband's red cells and *vice versa*. No agglutination occurred. The operation lasted 2 hours, ether being used as the anæsthetic. Profiting by the experience of Case 1, some blood was withdrawn from the patient immediately after the operation. The serum obtained by centrifugalization presented a pinkish tinge. The test was repeated and marked agglutination of donor's cells by recipient's serum was observed within the first half hour after the test had been set up. Twenty-four hours later the test was again made with fresh serum (which lacked the pinkish tinge), and no agglutination occurred. Eleven days after the

operation 400 cubic centimeters of citrated blood, taken from her husband, were transfused. No untoward symptoms followed.

CASE 3. On November 7, 1921, the blood of Mrs. A. K., age 41, was tested by matching it with cells of several donors, and a suitable donor was found. On November 8, Doctor Archibald performed the Lillenthal operation for resection of carcinoma of the œsophagus. Anæsthesia was begun with gas and oxygen and continued with ether. The operation lasted $2\frac{1}{2}$ hours. At the end of this time, and while the patient was still well under the anæsthetic, some blood was withdrawn, and the serum obtained by centrifugalization of the blood presented a pinkish tinge, which was not present in the serum obtained previous to the operation. The test was repeated and marked agglutination of donor's cells by recipient's serum occurred within 15 minutes after the test had been set up. Twenty-four hours later the test was repeated; a clear straw-colored serum was obtained and there was no agglutination. No transfusion was done in this case.

The cases of transfusion for postoperative replacement of blood which we were able to find in the literature were not reported with the necessary details of the duration of anæsthesia, the color of the centrifugalized serum and the results of tests before and after anæsthesia; so that they cannot be used for the purposes of this discussion.

The observations made on these three cases point to a definite phenomenon, namely, that a long operation in which ether is used as the anæsthetic alters the patient's serum as regards its hæmoagglutinin properties. Furthermore, this change is not a permanent one but disappears during the first 24 hours after the operation, i.e., just about the time when the patient has recovered from the effects of the ether anæsthesia.

Several hypotheses may be considered in attempting to explain the nature and cause of these phenomena. It may be possible that lipoids liberated from the tissues and taken up by the blood are responsible for the agglutination immediately after prolonged anæsthesia, and that when these lipoids have been excreted from the blood, the serum again behaves as before the operation. Another possibility is, that the organic products of surgical shock may be responsible for the temporary alteration in the hæmoagglutinins of the blood. Then, again, the ether that is present in the blood, by its own action,

or by substances or effects which it produces in the blood may be the cause of the change. This latter hypothesis is supported by the presence of a pinkish tinge in the serum obtained by centrifugalizing blood withdrawn immediately after prolonged ether anæsthesia—this pinkish tinge being due to hæmolysis of red cells most probably caused by the ether present in the blood.

Furthermore, Professor Oertel has suggested to us that ether being a lipid solvent, the alteration in the colloidal state of the blood which it produces is most probably the cause of the changed hæmoagglutinin and hæmolysin phenomena which are themselves also colloidal in nature. Professor Bruère corroborates this opinion from his experience with the Wassermann reaction. He has observed that the presence in the blood of substances which alter its colloidal state interfere with the reaction. Thus blood withdrawn several hours after a meal, and containing products of digestion is unreliable for the purposes of the Wassermann test. Indeed, he has found that if blood has been taken during or immediately after ether anæsthesia, the proper results are not obtained.

A more complete discussion of the nature and cause of these phenomena, we postpone until we will have completed the investigations that we are carrying on. Our observations have, however, taught us a valuable practical lesson, namely, that in practicing postoperative transfusion for replacement of blood, especially in cases following prolonged ether anæsthesia, it is essential to match the patient's serum with the donor's red cells and *vice versa*, after the operation; and that it is necessary to wait at least 24 hours before taking the sample of blood for serum from the patient. This necessitates postponing the transfusion for at least 24 hours, during which time the patient may be benefited by glucose or saline injections.

ALTERATIONS IN BLOOD AFTER TRANSFUSION

Certain conditions, such as the anæmias, hæmaphilia, purpura, leukæmia, and others often call for more than one transfusion.

In 1913, Ottenberg, Kaliski and Freedman, (32), from experiments on animals, con-

cluded that multiple transfusions from a given donor to a given recipient caused the development, in the latter's blood, of specific agglutinins and hæmolysins against the donor's cells which were originally not present.

Ottenberg and Libman (33), in 1915, were the first who from clinical observations pointed out the danger of posttransfusion reaction following the second, or subsequent, transfusions from a given donor to a given recipient, even when the test previous to the first transfusion proved the bloods to be compatible, and, moreover, even when no reaction followed the first transfusion. Two years later (24) the same authors emphasized "the necessity of doing tests again if transfusion is repeated even if the same donor is used." They reported that they had "seen several instances in which a patient developed new agglutinative and hæmolytic powers toward the blood cells of a donor to whom he had not originally been agglutinative or hæmolytic. In one of these cases, a young man, suffering from hæmophilia, a first transfusion of 50 cubic centimeters by the syringe method was followed by no reaction whatever, and the tests showed absence of hæmolysis or agglutination. A month later, an identically similar transfusion of the same amount of blood was followed by an immediate reaction, consisting of partial collapse, nausea and vomiting, generalized urticaria, violent headache and hæmaturia. Blood obtained from patient and donor a few days after this occurrence, showed that the serum of the patient was now strongly agglutinative to the cells of the donor. It was not determined whether the agglutinin present was due to the patient having changed his group (a hitherto undescribed occurrence), or to the development of a new immune iso-agglutinin."

In 1917, Minot and Lee (27) reported three cases of reactions after repeated transfusions, "in one case, the third transfusion, using the same donor as in the first transfusion, was followed by a marked reaction which hastened death. The donors and recipients in all cases belonged to the same groups." Another very striking example was reported by Thalhimer, (43) in the case of a boy aged 6 years, suffering from purpura.

By the direct method of testing donor's and recipient's bloods, the father was found to be a suitable donor and 300 cubic centimeters of citrated blood were transfused; a slight reaction consisting of a transitory rise in temperature to 103° followed immediately after the transfusion. About 3 weeks later, using the same donor without again testing the bloods, a second transfusion was given, when 150 cubic centimeters of citrated blood were injected. The patient developed tingling of face, legs and feet, then burning of feet. There followed flushing of face, the skin became diffusely peppered with pin point hæmorrhagic spots. With the appearance of pallor the pulse became almost imperceptible. The transfusion was stopped, and very soon the pulse acquired good volume, but it remained very rapid (about 140). About half an hour after the beginning of the reaction the patient was in fairly good condition and was returned to his room. Shortly afterward, however, he had a severe chill, temperature rose to 102.6° and he vomited undigested food. He complained of marked difficulty in breathing which was irregular, deep and jerky. Pain in the abdomen was so severe that the bed clothes had to be lifted off because their weight intensified the pain. About 2 hours after the transfusion, the patient voided about 6 ounces of very dark hæmoglobinuric urine. Ten hours later he again voided similar, but somewhat lighter urine, and 4 hours after this his urine was pale yellow, but it still contained a considerable number of hæmoglobin-tinged, coarsely granular casts which were very abundant in the first two specimens and which did not disappear until the third day after transfusion. At no time were red blood cells found in the urine.

Our attention to this phenomenon, of a reaction after the second transfusion from a given donor to a given recipient, was first attracted by the following two cases in the series of transfusions performed at the Royal Victoria Hospital:

CASE 1. Mr. X age 45, suffering from pernicious anæmia, was given 500 cubic centimeters blood from a tested suitable donor on January 27, 1919. No noticeable clinical reaction followed. On March 7, 1919, without again testing the donor's and recipient's bloods, the patient was given 700 cubic centimeters blood from the same donor as was used for the first transfusion. Two hours after the completion of this second transfusion, the patient had a violent chill, during which his temperature rose to 105° F. The lips and mucous membrane of the mouth became œdematous, breathing was labored and the pulse small and thready. A specimen of urine passed soon after the onset of these symptoms showed the presence of a small amount of blood. The acute symptoms gradually disappeared; 2 days after the transfusion a slight degree of jaundice became evident, but this feature also diminished until it became hardly noticeable when the patient

was discharged in good condition about 2 weeks after the transfusion.

CASE 2. M. K., female, age 21, admitted for ruptured ectopic gestation with large hæmorrhage. On September 21, 1920, she received 540 cubic centimeters of blood from a tested suitable donor. Immediately after the transfusion the patient experienced a chilly sensation which lasted for about half an hour. No other untoward symptoms or signs occurred. She was operated upon on September 22, and a second transfusion was performed on October 15, using the same donor as for the first, depending upon the compatibility of the bloods as determined by the test of recipient's serum against donor's cells and *vice versa*, performed before the first transfusion. Moreover, no doubt as to the compatibility of the bloods was entertained, since nothing unusual occurred after the first transfusion that could have aroused suspicion. The second transfusion consisted of 550 cubic centimeters of blood. Almost immediately after the operation was completed a violent reaction began. The patient experienced a severe chill, with a rise in temperature from 97° to 105° within 15 minutes, and cyanosis, labored breathing, a thready weak pulse which could not be felt during rigor, and vomiting of a considerable amount of blood-stained material quickly followed. She also complained of severe dull pain in the lumbar region. Blood oozed from the mucous membranes about the mouth, especially from the gums. About 7 hours after the transfusion she vomited a considerable quantity of dull, red fluid and clotted blood. There was also some slight but continuous hæmorrhage from rectum and vagina, and blood was found in a catheter specimen of urine. The very acute symptoms, namely, the chill and general signs of shock, gradually disappeared but the patient remained quite sick, vomiting of blood-stained food, oozing of blood from buccal mucous membrane and from rectum and vagina continued until October 20, and then suddenly ceased. The vomiting gradually diminished in frequency from five to six times a day to once a day, but it was not until October 30, seventeen days after the transfusion, that it ceased completely. On October 20, the patient's face appeared puffy. She was given an intravenous saline of 30 ounces on October 27, and following this she improved rapidly until November 6, when she was discharged in good condition.

On the other hand, it must be borne in mind that not every transfusion in which a given donor is used two or more times for a given recipient, is necessarily accompanied by a reaction. Butsch and Ashby (8) report 26 cases in which the same donor was used twice for the same recipient, in 16 of which no reaction followed either transfusion, while in 7 only one transfusion was accompanied

by reaction, and in the remaining 3 a reaction followed both transfusions. Meleney, Stearns, Fortune and Ferry (48), however, in a review of 280 transfusions, concluded that subsequent donation of blood by a given donor to a given recipient, tends to increase the frequency of reaction in direct proportion to the number of transfusions. Thus the percentage of reactions of various degrees in their series was as follows:

	Percent- age
After the first transfusion	57
After the second transfusion	70
After the third transfusion	73
After the fourth transfusion	91

The latter authors, from a study of the same series of 280 transfusions, pointed out the interesting fact, that repeated transfusions, from several donors to a given recipient also tend to increase the frequency of reaction in this recipient. Reactions of various degrees occurred in the following percentages:

	Percent- age
After the first transfusion	60
After the second transfusion	59
After the third transfusion	67
After the fourth transfusion	68
After more than four transfusions	74

McLure and Dunn (25), in an excellent analysis of 150 transfusions found that "in the patients for whom many transfusions have had to be done, it became more and more difficult to find donors whose blood would match that of the patient. A donor may match perfectly early in the series of transfusions and later be found unsuitable. . . . It is, therefore, most important that the bloods be matched before each transfusion." Several years later Bowcock corroborated these observations, and went even further by stating that "in certain cases of pernicious anæmia which have been repeatedly transfused, there comes a time when suitable donors are no longer to be found, and when this point is reached, no further attempt to transfuse these patients should be made."

All these observations together point to the definite phenomenon which must now be accepted as an incontestable fact, namely, that the original iso-hæmoagglutinin and iso-hæmolysin properties of the recipient's blood

are altered as the result of the addition of donor's blood. What the nature of this alteration is, remains an open question—a problem for study.

There is a very close resemblance between the symptoms and signs of a reaction following a second transfusion from the same donor and the symptoms and signs of anaphylactic shock, as is very well illustrated by the four cases cited above. This fact has led all observers to suggest that the posttransfusion reaction may be anaphylactic, the first transfusion being held responsible for the causation of a hypersusceptibility of the recipient's serum against the donor's cells. This, however, does not make the explanation much clearer for the phenomenon of anaphylaxis is itself very inadequately understood, and explanations of its exact nature are as yet at the stage of hypotheses.

It is important to know whether the reaction is associated with any change in the group of the recipient. All those who do transfusions can contribute to the elucidation of this point by testing the recipient's blood before and after transfusion, by both the direct and the indirect methods. Recently, we found that after a donor had been used twice for the same recipient (although the recipient remained in the same group, Moss 11), her serum caused slight agglutination of the donor's cells, whereas in previously performed direct tests no agglutination was observed. We do not attach any great importance to this single observation, since a large series of data would be necessary to allow of any definite conclusion on this phase of the problem.

The investigations of Sellards and Minot (41) and of William Bayliss (1) eliminate the possibility that the presence of free hæmoglobin in the blood is the main cause of post-transfusion reactions.

The possible influence of a particular donor on the frequency of reactions in the patients to whom he gives blood was investigated by Meleney, Stearns, Fortune and Ferry (48) in their series of six donors, each of whom was used twelve times or more. One man who donated blood sixteen times was associated with reactions in the recipients on fourteen occasions (88 per cent), while another who

gave fifteen transfusions caused only seven reactions (47 per cent). The largest number of donations made by one man was 36, and in his case there were 28 reactions (78 per cent). There is, therefore, considerable difference between donors in their tendency to produce reactions.

The relatively great frequency of milder degrees of posttransfusion reactions, consisting of a transitory rise in temperature, often associated with chills, tingling etc., and occasionally slight hæmoglobinuria, raises the question as to whether these reactions are only milder degrees of those severe ones which follow definite incompatibilities between donor's and recipient's bloods, or whether they are due to independent causes, as, for example, deficiencies in technique, influences of contact of donor's blood with foreign substances (Fenn, 14) during the operation, etc. From the investigations of Meleney (48) and his associates, of Drinker and Brittingham (13), and of Butsch and Ashby (8), it appears reasonable to include all reactions in one general category, as regards their causation.

It appears, therefore, that the most logical path of investigation into the exact cause of posttransfusion reactions lies within the broad field of immunology.

CONCLUSIONS

Although the exact nature of the reactions and their causes leave much room for study, the practical lessons to be learned from the above observations are quite definite and very valuable to the safe practice of transfusion:

1. The compatibility of the recipient's and donor's bloods must be determined prior to each and every transfusion.

2. No transfusion must be done during or within 24 hours after prolonged ether anaesthesia even when the donor has been found suitable previous to the beginning of anaesthesia.

3. Much depends upon the accuracy of the test. It is, therefore, preferable to do both the indirect test (Moss, 28) to determine the group of donor and recipient, and also the direct (Cooca, 9) test, to corroborate the

compatibility of the bloods, thus checking up one test by the other.

In a very recent article Robertson and Rous (39) conclude that in cases of repeated transfusion it is necessary to test for auto-agglutination in the recipient's blood, and also point out that serum separated at 37° C. contains more agglutinins than that separated at room temperature, whereas agglutination is more marked at room temperature than at 37° C.

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*These articles contain extensive bibliographies.

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