Accidents in transfusion : their prevention by preliminary blood examination, based on an experience of one hundred twenty-eight transfusions / Reuben Ottenberg and David J. Kaliski.

Accidents in Transfusion

Their Prevention by Preliminary Blood Examination: Based on an Experience of One Hundred Twenty-Eight Transfusions

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ACCIDENTS IN TRANSFUSION

THEIR PREVENTION BY PRELIMINARY BLOOD EXAMINATION: BASED ON AN EXPERIENCE OF ONE HUNDRED TWENTY-EIGHT TRANSFUSIONS *

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Accidents following transfusion have been sufficiently frequent to make many medical men hesitate to advise transfusion, except in desperate cases. It has been our opinion since we began making observations on this question in 1908 that such accidents could be prevented by careful preliminary tests, leading to the exclusion of agglutinative or hemolytic donors. Our observations on over 125 cases have confirmed this view and we believe that untoward symptoms can be prevented with absolute certainty.

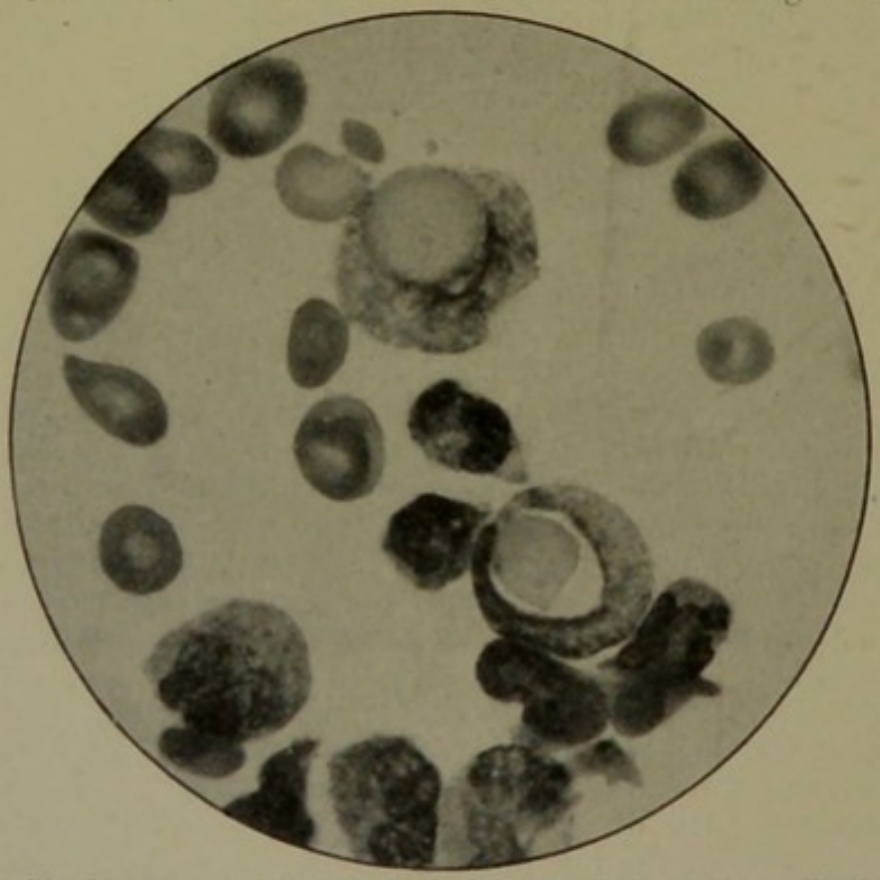
It has been the general impression that preliminary blood-tests ought to be done to determine the compatability of the donor's with the patient's blood, but there has been little direct observation as to the correspondence between the test-tube phenomena of agglutination and hemolysis and symptoms arising after transfusion.

Scattered reference to the hemoglobinuria following transfusion have made it clear that the occurrence of hemolysis between the donor's and patient's blood is a real danger. Thus, Flörcken[1] reports hemoglobinuria in two out of five cases which he transfused, and Gray[2] reports hemoglobinuria in one out of three transfused cases. Suttner,[3] reporting four transfusions, says: "One

* From the Pathological Laboratory of Mount Sinai Hospital, New York. Part of this work was done while one of the authors held a Eugene Meyer, Junior, Fellowship in Pathology.

1. Flörcken, H.: Direct Transfusion of Blood; Five Cases, München. med. Wchnschr., 1912, No. 49; abstr., THE JOURNAL A. M. A., Jan. 18, 1913, p. 250.
2. Gray, F. D.: Direct Transfusion, Med. Rec., New York, 1911, lxxix, 198.
3. Suttner, C. N.: Arteriovenous Transfusion by the Crile Method, Northwest. Med., 1911, iii, 192.

case resulted fatally from hemolysis, which might have been prevented had not its urgency required prompt action." Pool[4] reports a case of delirium and extreme jaundice following transfusion. In the case of Pepper and Nisbet,[5] a fatal hemoglobinuria followed a second transfusion for pernicious anemia. Cases have been reported by Crile,[6] Watts[7] and others. Rehling and



Blood-smear of patient made during transfusion. The patient's serum was agglutinative to the donor's blood-cells. Phagocytosis was observed only in cases of this kind.

Weil[8] report a case with severe hemoglobinuria which was anticipated by blood-tests. Undoubtedly many other cases that have occurred have never been reported.[9]

4. Pool, E. F., and McClure, R. D.: Transfusion by Carrel's End-to-End Suture Method, Ann. Surg., October, 1910, lii, 433.

5. Pepper, William, and Nisbet, Verner: A Case of Total Hemolysis following Direct Transfusion of Blood by Arteriovenous Anastomosis, THE JOURNAL A. M. A., Aug. 3, 1907, p. 385.

6. Crile, G. W.: Transfusion with Note on Hemolysis, Surg., Gynec. and Obst., 1909, ix, 16.

7. Watts, S. H.: Suture of Blood-Vessels, Ann. Surg., September, 1907, xlvi, 373.

8. Rehling, M., and Weil, R.: Avoidance of Hemolysis in Transfusion, Am. Jour. Surg., March, 1909.

9. Intravascular hemolysis causes hemoglobinuria only when it exceeds a certain limit. Smaller amounts of hemoglobin are removed by the tissues. (Boycott and Douglas: Jour. Path. and Bacteriol., January, 1910, p. 313). This is probably why Crile did not notice hemoglobinuria in cases of tuberculosis to which he refers (Tr. Am. Surg. Assn., 1909, xxvii, 80).

The question whether or not interagglutination is a danger in transfusion is still an open one. Our experience leads us to believe that its occurrence under certain circumstances may vitiate the result of transfusion and should be avoided, although no one has yet shown that it causes extensive thrombosis or embolism as we feared at first. The few observations of Schultz do not bear directly on the question because his transfusions were small in amount as compared with the amount usually transfused by the direct method.

In emergencies and occasionally at other times, relatives or friends of the patient have been used as donors. Their blood should of course be tested. Iso-agglutinins are inherited, as first pointed out by Ottenberg[10] in an article with Epstein, published in 1908. No certainty can be secured, however, without examination, as each individual inherits from either one of his parents.

We shall omit any detailed reference to the technic of agglutination and hemolysis tests. We use a modified Wright's capillary pipet method, first described by Epstein and Ottenberg.[11] This method has the advantage that it requires only as much blood as can be obtained from a finger prick from both patient and donor. With this method it is possible to examine ten or twelve donors within two or three hours.

We have always performed Wassermann tests on prospective donors. The necessity of this has been demonstrated by the finding of five positive Wassermann reactions in prospective donors. In a well-equipped laboratory the Wassermann and other tests can be performed simultaneously and all can be completed within three hours.

HEMOLYSIS

The hemolysis of one human blood by another is a pathologic phenomenon. It was formerly thought to be characteristic especially of carcinoma and tuberculosis, but it has been shown[12] to occur in a great variety of diseases.

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10. Ottenberg, R., and Epstein, A. A.: Proc. Path. Soc. New York, 1908. Also von Dungern and Hirschfeld: Ztschr. f. Immunitätsforsch., 1910, v, 531; 1910, vi, 284.

11. Epstein, A. A., and Ottenberg, R.: A Method for Hemolysis and Agglutination Tests, Arch. Int. Med., May, 1909, p. 286.

12. Ottenberg, R., and Epstein, A. A.: The Diagnostic Value of Hemolysis in Cases of Cancer, Arch. Int. Med., June, 1909, p. 467.

That it is necessary to make tests of this kind if hemolytic accidents are to be avoided, is evident from the fact that the blood of seventeen out of 128 of our patients was actively hemolytic for several different donors, as well as from the published reports of accidents and fatalities in cases in which preliminary tests had not been made.

The diseases in which hemolysis was observed were:

	Cases
Purpura hemorrhagica	2
Carcinoma of the stomach	3
Carcinoma of the rectum	1
Lymphatic leukemia	4
Pernicious anemia	2
Chronic osteomyelitis (due to *Staphylococcus aureus*)	2
Pelvic abscess	1

There were three instances of reverse hemolysis, that is, hemolysis of patients' cells by donors' serum. The first was in a patient who was suffering from postoperative hemorrhage. On subsequent examination the donor was found to be suffering from tuberculosis. The others were in a case of pelvic abscess and a case of pernicious anemia.

In all except two of the cases cited the patients' serums were hemolytic with only some, but not all, of the prospective donors' bloods, and by examining a certain number of men, one was eventually found who was not hemolytic with the patient. In two of these instances, on account of the desperate condition of the patients, hemolytic transfusions had to be ventured. In two additional cases (not included in the list) transfusion had to be abandoned because the serum of the patients was powerfully hemolytic to the cells of every donor examined. One of these was a case of lymphatic leukemia, and the other of pernicious anemia.

One of the hemolytic transfusions was done in a case of pernicious anemia. The serum of this patient was agglutinative and weakly hemolytic to the cells of the donor. The transfusion was followed by an intense hematuria which lasted about twenty-four hours, during which the hemoglobin dropped from 34 to 31 per cent., instead of rising further, as almost invariably happened after transfusion in other cases. In spite of the loss of the transfused blood, transfusion apparently exerted a favorable influence on the course of the disease, as the

patient improved slowly but steadily during the following month.[13] The patient returned to the hospital eight months later, and a second transfusion was done. This time a donor was found whose blood did not agglutinate or hemolyze when mixed with that of the patient, although the patient's serum was hemolytic to the cells of four of ten donors. This transfusion was successful; the patient was greatly improved, and her life was prolonged for a year and a half.

In the other case (one of acute lymphatic leukemia), in which test-tube hemolysis was noted between the blood of the patient and that of the donor, the patient's serum sharply agglutinated the donor's cells, but only slightly laked them after three and one-half hours in the thermostat. There was no hemoglobinuria, but blood-smears made during and after the transfusion showed phagocytosis of red blood-cells by leukocytes in the circulating blood. The patient died forty-two hours after the transfusion. The case will be more fully discussed later under the heading of agglutinative transfusion (see photomicrograph).

In only four other cases in the whole series were any red blood-cells found in the urine after transfusion, and in these four cases they were found only in small numbers in the centrifuged sediment.

Jaundice occurred after transfusion in only one case in the series, and in this it was slight and transient, disappearing in two days. It may have been due to some other cause, as the patient had a carcinoma of the stomach (Old Series, No. 46).

The absence of hemoglobinuria in over one hundred cases in which hemolytic donors were excluded by examination and its occurrence only once in the whole series, and then in a case in which the test-tube hemolysis had been noted, proves that the danger of hemolysis can be absolutely excluded by careful preliminary tests.

AGGLUTINATION

Iso-agglutination, unlike isohemolysis, is not a pathologic phenomenon, but occurs between normal human bloods. All human beings fall into four permanent hereditary and sharply separated groups with regard to

13. It is possible from the work of Hess and Saxl (Deutsch. Arch. f. klin. Med., 1912, cviii, 181), that the material from some of the destroyed cells may have been used in the reconstruction of blood.

whether their serums agglutinate each other's red blood-cells or not. When the blood of two persons belonging to the same group is mixed, no agglutination occurs. When the blood of two persons of different groups is mixed, agglutination, either of one by the other or of each by the other, always occurs.

It is not necessary here to go into details of the grouping. The important questions are whether or not it is necessary to pay attention to agglutination in selecting donors and what the influence of agglutination is on the result of transfusion.

Human iso-agglutinins are present in only relatively weak concentration, generally not being active at all in greater dilution than 1:10 or 1:20. All the agglutinin present in a given volume of serum can be absorbed by a small volume of susceptible cells.[14] The result of this is that, when a given volume of serum is mixed with a large volume of susceptible cells, the individual cells are only feebly sensitized and no gross agglutination is seen.

In the instance in which the serum of the donor is agglutinative to the cells of the patient, the plasma of the donor on transfusion will be diluted by an excess of the patient's plasma and will meet with a large excess of the agglutinable cells. These are the conditions under which, in vitro, the minimum amount of agglutination, if any at all, is observed. In practice, in all such transfusions, as we shall show later, no unfavorable results were obtained (four instances).

When the patient's serum is agglutinative toward the donor's cells, the conditions for sensitization of the cells of the donor are much better, as a smaller bulk of blood-cells is introduced into a larger volume of agglutinative plasma. Even here, however, it is probable that only in exceptional instances can massive clumps of agglutinated cells be formed, such as are seen in the test-tube when a dilute suspension of the cells is mixed with agglutinative serum and allowed to rest quietly until agglutination is complete. There is no doubt, however, that some sensitization of the cells occurs under these conditions. It is in these cases only that phagocytosis of red cells in the circulating blood has been observed, twice by us and once by Hopkins.[15]

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14. Ottenberg, R.: Transfusions and the Question of Intravascular Agglutination, Jour. Exper. Med., 1911, xiii, No. 4.

15. Hopkins, J. Gardner: Phagocytosis of Red Blood-Cells after Transfusion, Arch. Int. Med., September, 1910, p. 270.

We have seen four transfusions in three cases in which the serum of the donor was agglutinative to the cells of the patient. There were no untoward symptoms in any of these four transfusions. In two of the four transfusions numerous blood examinations showed absence of phagocytosis in the circulating blood. In the other two transfusions no search was made for this. Of these three patients, one, with gastric ulcer, ultimately recovered completely while the other two died within a few days of causes that had nothing to do with the transfusion (shock, following resection of the stomach in one instance, and liver abscess in the other).

We have seen three transfusions in which the serum of the patient was agglutinative to the cells of the donor. In two of these instances, already cited, the serum was also slightly hemolytic.

In the first of these (referred to previously), an intense hematuria occurred. This was one of the early cases and no observations were made as to the occurrence of phagocytosis. In the second case, one of acute lymphatic leukemia, the patient's serum was agglutinative and slightly hemolytic to the donor's blood-cells in three and one-half hours. Blood smears at the completion of the transfusion showed phagocytosis of the red blood-cells by polynuclear leukocytes. The patient died forty-two hours after the transfusion. There was no hematuria in this case, but the amount of hemolysis in the test-tube was minimal.

The third instance in which the patient's serum was agglutinative to the donor's cells was also a case of pernicious anemia. Blood-smears made five minutes and fifteen minutes after the start of the transfusion and at the end of the transfusion showed phagocytosis of red blood-cells by polynuclear leukocytes (see photomicrograph). The patient passed no urine after the transfusion, and died eight hours later. Necropsy revealed an extensive phagocytosis of the red blood-cells in the microscopic sections of the lymph-nodes and spleen.

The occurrence of phagocytosis of the red cells in the circulating blood is an exceedingly rare phenomenon and is in every instance due to injury or destruction of red cells. Aside from the present instances, it has been described as occurring, so far as we have been able to find, only in paroxysmal hemoglobinuria and in potassium chlorate poisoning.[16] Our control observations of over

16. Huber, O.: Changes in Blood in Potassium Chlorate Poisoning, Deutsch. med. Wchnschr., Oct. 10, 1912, p. 1923.

thirty non-agglutinative and non-hemolytic transfusions show that the phagocytosis was not due to the nature of the diseases (pernicious anemia, leukemia) in which it occurred, because among the control cases were several cases of each of these diseases with no phagocytosis after transfusion.

In the great majority of cases transfused in which hemolysis and agglutination have been excluded by tests, febrile reactions following transfusions have been entirely absent. In a considerable number of cases (twenty-one out of 128), there have been slight febrile reactions, lasting one or two days, probably to be regarded as ordinary surgical fever. In less than 10 per cent. of the cases (ten cases in 128), more severe reactions occurred, often with chills, occasionally with vomiting. In none of these cases did symptoms last more than two days. In none of them did hemoglobinuria or hematuria ensue. The occurrence of these symptoms has been variously attributed by some authors to hemolysis or agglutination, or (by German authors who studied indirect transfusion) to the transfusion of fibrin ferment.

The first two causes can be excluded in our cases. Fibrin ferment cannot be a factor because the transfusions were direct artery-to-vein or vein-to-vein transfusions; nor do the pathologic conditions for which the transfusions were done in the cases that had severe reactions throw any light on the cause of their occurrence.

The same thing is true of skin eruptions which occurred in about 10 per cent. of the cases. The cause of skin eruptions is evidently connected with the cause of severe febrile reaction, because five of the eleven cases which showed skin eruptions were in the group which showed severe febrile reactions. Two of the instances of skin eruption were cases of severe general erythema, and it is interesting that in both of these cases the blood-serum of the patients was powerfully hemolytic for the blood-cells of the majority of proposed donors, but the particular donor chosen was one whose blood-cells were not laked. It seems, therefore, as though the cause of the extensive skin eruption in these cases had some connection with the cause of the hemolytic poison, but was not identical with it.

SUMMARY

1. Accidents in transfusion due to the occurrence of hemolysis or agglutination of the donor's blood-cells by the patient's serum, or vice versa, can be absolutely

excluded by careful preliminary blood-tests. We have been able to prevent accidents of this kind in 125 transfusions.

2. The relation between test-tube hemolysis and intravascular hemolysis is close, and it seems likely that in all cases in which there is test-tube hemolysis, some intravascular hemolysis occurs. When this exceeds a certain limit hemoglobinuria results.

3. The occurrence of agglutination (between the blood of the donor and that of the patient) need not be regarded as an absolute contra-indication to the transfusion, but non-agglutinative donors should be chosen whenever possible.

4. Phagocytosis of red blood-cells by leukocytes in the circulating blood of the patient transfused is undoubtedly connected with interagglutination of the two bloods; it occurred in our series in two cases in which the serum of the patients was agglutinative toward the cells of the donors (in one of the cases the serum was also hemolytic), and it did not occur in any of thirty-five non-agglutinative transfusions in which it was carefully looked for. These negative cases included two cases with extensive urticaria and one case with severe febrile reaction after transfusion. In the cases in which the serum of the donor was agglutinative toward the cells of the patient, no phagocytosis of red cells in the circulation was seen.

5. In selecting donors with regard to agglutination, the agglutination of the donor's cells by the patient's serum is more important to avoid than the reverse.

6. Febrile reactions or urticaria and other skin eruptions occur after about 10 per cent. of transfusions, irrespective of hemolysis or agglutination, and are not due to fibrin ferment or to blood platelet destruction. These reactions, however, are never serious and the patients have done well in spite of them.

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