

transfusion which cannot be prognosticated by the existing laboratory tests for blood compatibility.

3. Importance is attached to the belief that many of the febrile and toxic reactions, not to be explained by hemolysis or agglutination, are due to the transfusion of blood which is undergoing incipient coagulative changes, or which contains potential coagulative factors such as thromboplastin and thrombin.

4. In judging of the safety of any method of transfusion, the extent and mode of action of the anticoagulant which is used, the toxicity of the substance, the amount of it which is necessary, and the mechanical technic in transferring the blood are the most important factors to be considered.

5. The employment of an antithrombin such as leech extract or the commercial "Hirudin," while appearing to be ideal as an anticoagulant from the physiologic standpoint, is subject to uncertainty of action and possible danger from contamination with toxic substances. Minimum doses of tested and standardized preparations and optimum anticoagulative technic should be used if such agents are employed.

6. The use of paraffin is theoretically the method of choice in providing an anticoagulant agent for purposes of transfusion and has been found practicable, but not without certain precautions and proper apparatus.

7. Of the inorganic calcium-converting agents which we have investigated experimentally, the citrate of sodium and the metaphosphate of sodium are the only substances which exhibit desirable characteristics. Both of these salts, however, have toxic effects which demand consideration of the amounts which can be safely employed for purposes of transfusion. Our experience with sodium metaphosphate is limited to experimental transfusion on animals.

8. Sodium citrate in the proportion of 120 mg. to 300 c.c. of blood, when used with the pipet-cannula apparatus and in the manner described, serves as an effective anticoagulant for transfusion. This proportion (0.04 per cent.) is from one fifth to one twenty-fifth of the amount of citrate necessarily employed with other methods. Because of the considerations which have been discussed, we believe it to be the best method of transfusion for general use.

**Street Dust and Disease.**—Following the announcement by the public health committee of the New York Academy of Medicine that a system of street cleaning which does not eliminate gross street dust and which employed dry sweeping methods cannot be satisfactory, a study was made by Prof. Thomas W. Hastings of Cornell University Medical School concerning the relation of street dust to disease. On examination of the available data he summarized his findings about as follows: Numerous bacteriologic examinations made in New York as well as elsewhere show that street dust contains a variety of living pathogenic organisms such as tubercle bacilli and various types of streptococci which are recognized as causative agents of many respiratory and other diseases. Although few authentic cases of disease can be traced to bacteria in street dust, yet the fact that appreciable numbers are found in street dust and inhaled or ingested, establishes a presumption that street dust may be the cause of disease. Studies of the incidence of respiratory diseases shows that persons free from exposure to city dust are less liable to suffer from such diseases. Dust has long been recognized as an injurious mechanical irritant and as a cause of lowered bodily resistance. Dry sweeping should be entirely abandoned, and street flushing should be introduced in street cleaning processes. All efforts should be made to render streets as free from dust as possible.

## REACTIONS FOLLOWING BLOOD TRANSFUSION BY THE SYRINGE CANNULA SYSTEM\*

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Since the simplification of technic,<sup>1</sup> blood transfusion has acquired considerable popularity. The syringe cannula system has greatly simplified the procedure over the old arteriovenous method. It now occupies a prominent and permanent place in the field of therapeutics. Today a hundred transfusions are performed where one was done but a few years ago. Though the technic has been thus simplified, there is a tendency on the part of some to slide over details of the work and, unequal to the task of even simple technic, they may resort to anticoagulants or inferior methods by which it may be possible to put blood into the patient even subcutaneously. The attempt to simplify the method further has not been attended without the sacrifice of important points of merit. The pitfalls and errors in the further simplification are the very things I have purposely avoided by the method originally outlined. The operative procedure is a life saving measure and should be regarded as something more than an injection of saline fluid or salvarsan administration, and any tendency to curtail detail of execution to meet the convenience or inexperience of the operator at the expense of the patient should be discouraged.

The reactions following transfusion will deter some from employing the measure with a patient in a critical state, in the fear of doing harm by the procedure itself, and the possible benefits to be derived may be overbalanced by the harm done. In order for any therapeutic measure to gain wide favor, it must be free of any danger incident to the procedure itself, or at least a very high percental relationship must obtain between risk and gain. It is my object in this communication to take up the problem of reactions to transfusion, to analyze their cause and to show the way to prevention.

In the first eighteen transfusions which I performed by the syringe cannula system, preliminary blood tests were made in only two instances. In this group of eighteen cases there were no chills and no fever reaction above 2 degrees. The quantity transfused was small—never more than 700 c.c. The donors used were immediate relatives of the patients, and the diseases treated were not primary blood diseases. (Primary blood diseases and infection offer most difficulty in finding compatible donors.) The conspicuous absence of hemolysis in the absence of blood tests in sixteen of these cases must be attributed to good fortune. Later in the course of the work, though blood tests were made in nearly all the cases, chills and fever were encountered more frequently.

In the first 150 transfusions which were performed by the syringe cannula system,<sup>2</sup> the incidents of chill followed by fever were approximately 33 per cent. The quantities transfused were usually 1,000 c.c. or more in adults. The work was done in many different

\* Because of lack of space, this article is abbreviated in THE JOURNAL by omission of Table 1. The complete article appears in the author's reprints. A copy of the latter will be sent by the author on receipt of a stamped addressed envelope.

1. Lindeman, Edward: Simple Syringe Transfusion with Special Cannulas, *Am. Jour. Dis. Child.*, July, 1913, p. 28.

2. Lindeman, Edward: Blood Transfusion, *THE JOURNAL A. M. A.*, March 28, 1914, p. 993.

hospitals and in many different parts of the country; hence the preliminary blood tests of hemolysis and agglutination were necessarily done by many different serologists. In the report of this group, mention was also made of three cases of hemolysis which occurred. In these cases of hemolysis, the symptoms were carefully noted, and it was found that hemolysis is always accompanied by chills followed by fever. Hemolysis never occurs without chills and fever unless the patient dies during or shortly after the transfusion. The inference is therefore palpable that chills and fever reactions in transfusions are due to hemoglobin set free in the circulating blood. The reactions are clinically similar to the chills and fever occurring in malarial fever, and are undoubtedly due to the same factor, namely, hemoglobin set free in the circulating blood. When the hemoglobin set free is abundant, hemoglobin appears in the urine. When the hemoglobin set free is moderate, only hematoporphyrin appears in the urine. When the hemolysis is slight, the body is capable of utilizing and converting the slight amount of hemoglobin liberated, and no blood pigment appears in the urine. When no blood pigment appears in the urine, the danger incident to transfusion is practically nil. When blood pigment appears in the urine, the danger is very great and death may follow, especially when the patient is in an already precarious condition. The procedure when hemolysis occurs, even when death does not occur, is robbed of its therapeutic value.

In every case of hemolysis which was encountered clinically and in which the preliminary serologic tests were done, the hemolytic and agglutinin tests were repeated; and in each instance the incompatibility was detected in the second tests. The second tests were invariably performed by a different serologist from the first, who knew nothing of the circumstances. In one case opportunity was not offered to check up the accuracy of the laboratory work. Since the laboratory failed me in several instances, it became apparent that some laboratory workers have their limitations, and that this possible error must be eliminated. To do this, I set myself to the task of personally supervising the laboratory work in order to correlate the post-transfusion reactions with the tests. It was further apparent that if hemolysis, when hemoglobinuria occurred, was due to faulty laboratory work, it might be possible by careful and refined methods of selection to prevent even a slight degree of hemolysis when no hemoglobin appears in the urine, and the reactions following blood transfusion in terms of chills and fever might thus be eliminated. The results were gratifying, as is evident in Table 1. The tests were all made with very great care, and in some instances as many as twenty to thirty donors were examined from whom only one would prove satisfactory according to standard.

#### TECHNIC OF HEMOLYSIS AND AGGLUTININ TESTS

The red blood cells of patient and donor are washed three times with normal saline; variable quantities of patient's serum are placed in three separate small test tubes. To each of these are added 0.25 c.c. of a 2 per cent. suspension of washed blood cells of the donor. The same is done with the donor's serum and the patient's cells. Controls are made of donor's serum and donor's cells—patient's serum and patient's cells. Controls are also made with donor's cells in normal salt solution and patient's cells in normal salt solution. The total volume in each tube is raised with normal saline to 0.5 c.c. of volume. The test tubes are incubated in a water

bath for a period of two hours, and readings are made. They are then set in the ice-box over night and readings are again made the following morning. When a case is urgent, the ice-box test is eliminated. The ice-box test should be eliminated only when absolutely necessary by the extreme condition of the patient where time is the important factor. When the amount of blood taken from the patient for tests is small, only 0.25 c.c. of serum is used, and controls of patient's serum are eliminated.

#### RESULTS

In the last 155 transfusions performed by the syringe cannula system, the preliminary blood tests have been personally supervised in all but nine instances. The reactions following transfusion appear in Table 1. Since the chills and fever reactions are due to hemoglobin set free in the circulating blood, it is necessarily a mass action and the degrees of reaction will depend on the amount transfused as well as the degree of hemolysis. Hence, if any hemolysis occurred, the reaction should be greater when a larger amount is transfused than when a smaller amount is given. Table 1 is intended to show quantities transfused, the disease treated, whether alien or family blood is employed and the degree of reaction following each transfusion.

In this table of 155 transfusions, not a single case of hemolysis and not a single death referable to the transfusion occurred. The tests were personally supervised in 146 transfusions, and they were not personally supervised in nine. There were in all sixteen instances of chills followed by a rise of temperature. There was a rise of temperature above 2 degrees without chills in twelve instances.

TABLE 2.—TEMPERATURE REACTIONS

Rise in Temperature		Fall in Temperature	
Rise, Degrees	Number of Instances	Number	Fall, Degrees
From 2 to 3.....	18	1	Scarlet fever..... 2
From 3 to 4.....	2	1	Sepsis..... 1
From 4 to 5.....	5	2	Acute lymphatic leukemia..... 2, 1
From 5 to 6.....	3	2	Typhoid..... 2, 3
From 6 to 7.....	2	1	Sepsis and anemia.... 4
		2	Aleukemic leukemia... 2, 1
		1	Septicemia..... 2
		1	Pernicious anemia.... 1

Of the nine cases in which the tests were not personally supervised, chills occurred in five instances, or 55 per cent. In 146 cases in which the tests were personally supervised, chills occurred in thirteen instances, or 9 per cent. Of nine cases in which the tests were not supervised, there was a rise in temperature in five cases, four of which varied from 2 to 3 degrees, and one from 5 to 6 degrees. When family blood was used, 4 per cent. had chills and 4 per cent. fever; when alien blood was used, 6 per cent. had chills and 16 per cent. fever.

In the 155 transfusions recorded in Table 1, there were 136,800 c.c. of human blood transfused with not a death referable to the transfusion. Adults received from 1,000 to 1,800 c.c. in each transfusion. Two donors were never used for one transfusion. The quantity enumerated was always taken from one donor. No foreign substance or anticoagulants were employed in any case.

#### CONCLUSIONS

1. The preliminary hemolytic and agglutinin tests when properly performed are reliable.
2. Incidents of hemolysis in transfusion can be eliminated entirely.

3. The reactions which follow transfusion when accurate tests are made are eliminated in all except 9 per cent. of the cases. In this 9 per cent. of the cases, chills and fever alone occur. When the quantity is 800 c.c. or less, chills and fever do not occur.

4. By careful, accurate and complete hemolysis and agglutinin tests, when the work is done skilfully, blood transfusion is robbed of all danger attending its use. This marks a step in advance because of the comparative simplicity of application.

#### COMMENT

In the technic of blood transfusion by the syringe cannula system, the entire mass of blood is outside the body for a period of between six and ten seconds regardless of the amount transfused. It passes through a minimum amount of foreign material. Embolism or clotting never occurs in transit. Syringes are never used for a second filling until thoroughly cleaned in sterile saline solution, because in evacuating contents of a syringe of blood, a coating of blood remains on the inner surface of the syringe. When a syringe is refilled without cleaning, the plunger naturally rides over the blood cells adhering to the wall, crushing and injuring them mechanically. As the syringe is refilled, the injured cells are mixed in the blood stream and introduced into the patient. To prevent this, no syringe is used for a second filling until thoroughly cleansed with sterile saline solution. Syringes are cleaned as fast as they are used. Clotting in the syringe cannot occur, and the blood is transferred uninjured, exactly as it exists in nature. Anticoagulants or foreign substances are never employed. There is no blind system into which air may leak. There are no stopcocks, valves or rubber tubings about which blood may clot.

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### THE RELATION OF HEMOLYSIS IN THE TRANSFUSION OF BABIES WITH THE MOTHERS AS DONORS

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The new-born infant is subject occasionally to various pathologic conditions which to combat successfully requires the transfusion of blood. Among these ailments the most frequent and alarming, and perhaps most fatal, is the hemorrhagic disease of the new-born. The occurrence of this disease seems to vary in different institutions and localities. Townsend, collecting his reports from the Boston Lying-In Hospital, found that it occurred in thirty-two infants out of 5,000 births. Ritter found its occurrence in 190 cases out of 13,000 births at the lying-in hospital at Prague. Epstein, at the New York Foundling Hospital, found it in 8 per cent. of infants, while the average treatise of children's diseases gives the proportion of 1 in every 1,000 births.

Clinically this disease can be divided into two classes:

1. Those cases in which hemorrhage may occur from the mucosa of the gastro-intestinal tract, the stump of

the cord, and subcutaneously, in all of which the diagnosis is easily made by the sight of a frank appearance of blood.

2. Those cases in which the hemorrhage may occur in some internal organ, such as the suprarenals, peritoneal cavity, brain, lungs, etc. It is in the latter cases, in which there is no apparent sign of bleeding, that the proper diagnosis may not be made at an early date; and when finally made, if the bleeding continues, the patient is almost exsanguinated, and the condition becomes a very grave and critical one.

In the treatment of this condition, the use of animal's or human blood serum injected subcutaneously seems to supply the necessary elements to the blood to cause clotting (Welch<sup>1</sup>).

Whole blood has also been injected subcutaneously for this ailment (Schloss<sup>2</sup>).

With the institution of these methods of treatment, the mortality has been lessened to a considerable degree as compared with the older manner of treatment. There are a great many failures, however, with a continuation of the bleeding process.

Other investigators, endeavoring to improve on the serum treatment, attempted the transfusion of blood with very striking results. The new blood supply adds those elements to that of the infant, which not only promote clotting, thereby causing the hemorrhage to cease, but at the same time increase its cellular elements and volume, thereby enabling it to carry on its functions in a proper manner. Among those advocating the immediate transfusion of blood for this condition, and whose results have been highly gratifying, are Green<sup>3</sup> of Boston and Lespinasse<sup>4</sup> of Chicago.

In the treatment of these bleeding babies by transfusion, we thought that the mothers might act as suitable donors for the transfusing of their own infants. As the maternal and fetal bloods in utero are so closely related, the cellular elements being separated by a thin membrane, but allowing for diffusion of chemical elements, it is the natural supposition that complete compatibility of infant's and mother's blood should exist. On consulting several well known serologists it was ascertained that all agreed on their probable compatibility, but they deemed it advisable to perform a preliminary hemolytic and agglutination reaction before using the mother as a donor for her infant. In view of this fact it was our idea to establish the complete compatibility of mother's and infant's blood by performing a series of hemolytic tests on new-born babies and their own mothers. There are several reasons why the mothers could be used as donors:

In the first place, when an infant has had a severe initial hemorrhage leaving it in an exsanguinated state, the delay in such a case in procuring a compatible donor on whom the preliminary tests should be made may be fatal to the infant. If it is known beforehand that the mother's blood is compatible, she can be used as the donor without the delay of making these tests, and perhaps the infant's life will be saved by supplying it in time with sufficient blood.

In the second place, when the bleeding is discovered during the night, the procuring of a proper donor would entail considerable delay; such an emergency

1. Welch, J. E.: *Am. Jour. Med. Sc.*, 1910, cxxxix, 800.

2. Schloss, O. M., and Commiskey, J. J.: *Spontaneous Hemorrhage in the New-Born*, *Am. Jour. Dis. Child.*, April, 1911, p. 276.

3. Green, C. M.: *Boston Med. and Surg. Jour.*, 1914, clxxi.

4. Lespinasse, V. D.: *The Treatment of Hemorrhagic Disease of the New-Born by Direct Transfusion of Blood*, *THE JOURNAL A. M. A.*, June 13, 1914, p. 1866.