THE USE OF REPLACEMENT TRANSFUSION IN DISEASES OTHER THAN HEMOLYTIC DISEASE OF THE NEWBORN

By M. Bessis, M.D.

INTRODUCTION AND HISTORY

Replacement transfusion is an operation which combines blood letting and transfusion at the same time and in the same patient. The idea of using this technic is very old; it is interesting to recall that the first physicians who tried transfusions in the seventeenth century began by doing replacement transfusions. Eutyphronus remarked, "It is foolish to transfuse a patient without previous blood letting, because this would not reduce the strain on the body."

This operation, although it had a few successes, caused quite a few deaths. This is easily understood since the transfusions were usually done with animal blood. After the report of Claude Perrault to the Academy of Science in Paris in 1664, this body declared the transfusion "a dangerous method." In 1675, Parliament passed a law prohibiting its use.

Since the discovery of blood groups by Landsteiner, the use of transfusion has increased greatly, but replacement transfusion was almost completely abandoned. At most, it was used in a few cases of carbon monoxide poisoning, mushroom poisoning, and intensive burns. Even in those cases, only one blood letting and a transfusion of 500 to 1000 cc. was performed. The purpose of this article is to discuss not replacement transfusion as it was used then, but the replacement of the total blood volume of a patient by the blood of many donors and the repetition of that technic many times in the same patient.

The progressive realization of a complete blood replacement in man was achieved in 1946. We had thought for some time that such an operation would be of great value if it was well tolerated by the patient. In 1939-1940 we studied with our director, A. Tzanck, and our associate, M. Burstein, a technic for rapid replacement transfusion in the dog. We showed that in that animal the total blood volume could be replaced by a mixture of fresh blood of other dogs without any serious reaction. We achieved thus not a simple blood letting followed by transfusion, but a true "washing out" of the organism. At the same time, we attempted similar results in man, but did not succeed completely. After the war, in 1945-1946, studies on the Rh factor and hemolytic disease of the newborn gave a new impetus to this problem.

It is known that in hemolytic disease of the newborn the infant has in his body both Rh positive blood cells and anti-Rh serum. A few persons thought that the most rational treatment would be replacement transfusion of the newborn. That operation was proposed and carried out by Wallerstein, Wiener, Bessis, and others. A further advance was realized with the method of Diamond who uses a plastic
catheter which is pushed up to the main vessels and which enables total replacements* to be done under ideal conditions.

In spite of the successes of replacement transfusion in the newborn, the same operation had not, to our knowledge, been used in adults until 1947. The recent progress in immunology following discovery of the Rh factor and similar blood groups and of the conditions under which a person can have irregular agglutinins, led us to attempt such an operation. Although there was a possibility that repeated transfusions might cause some reactions of incompatibility due to rare or still unknown antigens, the fact that the majority of those accidents are due to Rh or similar factors which can be prevented by careful selection of donors justified our attempt.

There was also the possibility of reactions due to intolerance on the part of the recipient or transmitted by the injected blood, accidents whose possible frequency is multiplied by the number of donors. This is the reason why our first experiences were performed on a very limited scale and only on patients suffering from incurable disease and in a moribund state. Little by little, however, we have attempted more complete transfusions. Led by an hypothesis which we will discuss later, we tried total replacement transfusion in a child suffering from acute leukemia. This operation was successful and proved thereby both the innocuousness of the replacement transfusion and its action in leukemia.

Our experience, which is based on over 190 replacement transfusions† in children and adults, has confirmed the first proof, because we have had no serious accident. Moreover, in all these cases the general condition of the patient was clearly and rapidly improved. We shall discuss later the precautions which must be observed in the choice of blood to be injected, and our results. We do not wish to say that the fear which we had before trying the procedure is unjustifiable, because an accident is always possible.

The results which we report in this article are not of equal value. Many patients, treated in the early period of trial, received only one replacement transfusion. This operation was not repeated either because we did not know then that one replacement transfusion was insufficient or because we had difficulty in getting blood of the proper group or because of absence of suitable veins. As an example, we can take the first case of acute anuric nephritis in which we did only one replacement transfusion and obtained no results. It was only with experience that the necessity for repeating the replacement transfusion at intervals varying with the condition of the patient became evident and that we obtained consistently good results.

* By total replacement we mean replacement of 85 to 95 per cent of the blood volume, and this is done by replacement transfusion of two to three times the patient's blood volume. (This is explained more fully in the section on 'Technic'.)

† These include: cases of acute anuric nephritis, acute leukemia, chronic leukemia, lipoid nephrosis, generalized carcinoma, severe icterus, myeloma, lymphosarcoma, acute polyarthritis, and acute hypertensive nephritis.
I. Technique of Replacement Transfusion in the Child and in the Adult

We will give here the principle of the method, and those interested in technical details may refer to the work of S. Buhot. The drawing and injection of the blood are done at the same time so that the total volume is unchanged. In these conditions the percentage of the transfused blood in the organism as compared to the quantity injected is as follows (after Wiener and Wexler):

<table>
<thead>
<tr>
<th>Quantity of blood injected</th>
<th>Percentage of blood transfused in the patient's organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ volume of patient's blood</td>
<td>39.4%</td>
</tr>
<tr>
<td>1 volume of patient's blood</td>
<td>63.2%</td>
</tr>
<tr>
<td>1½ volumes of patient's blood</td>
<td>77.7%</td>
</tr>
<tr>
<td>2 volumes of patient's blood</td>
<td>86.5%</td>
</tr>
<tr>
<td>2½ volumes of patient's blood</td>
<td>91.8%</td>
</tr>
<tr>
<td>3 volumes of patient's blood</td>
<td>95.0%</td>
</tr>
</tbody>
</table>

The first problem is to find the necessary quantity of blood for the replacement transfusion. For an adult who has an average blood volume of 5 liters, we need 1.5 liters, usually obtained from 30 donors, and these must be of the same ABO and Rh groups. If we cannot get sufficient blood of the proper A or B group, we use O group blood after neutralizing the anti-A and anti-B agglutinins with Witebsky's AB substances.

We use fresh blood collected in bottles containing citrate solution. Our experience has shown that such transfusions are well tolerated by the patient and give no serious reactions if we give calcium intravenously to prevent tetany caused by the fixation of the blood calcium to the sodium citrate. Lately we have modified our technic and have used heparin, 2 mg per kilo of body weight, since the clotting time of the patient during the operation is so lowered as to render the drawing of blood very difficult.

We draw the blood either from a vein of the elbow on the side opposite to the injection or from the femoral vein. We use vacuum bottles to obtain a rapid flow of blood. However, the easiest method is to use a plastic catheter as suggested by Diamond for replacement transfusion in the newborn, and to introduce it in a superficial vein either after cutdown or through a large bore needle, pushing the tip up to one of the larger veins. It is then easy to draw the desired amount of blood and to inject by the same route. The rapid flow of blood in the large veins prevents us from withdrawing the blood which we have just injected. The catheter also spares the patient the inconvenience of the pressure cuff which is very painful after a time.

Lately we have simplified the operation by the use of the electrical pump of Dausset and Moulinier which is essentially a plastic pump electrically driven and with a reversible action. One end is connected to the plastic catheter and the other to the donor's blood flask and to the used blood receptacle. The pump draws the blood from the patient at any desired speed, e.g., 300 cc. in 5 minutes. The flow is then reversed and the pump is used to transfuse the patient with donor's blood. This operation is repeated until the desired number of liters has been given. Only two persons are needed for the whole procedure, which includes the drawing of the
FIG. 1.—EXANGUINO-TRANSFUSION PERFORMED IN A HUMAN ADULT

The injection is done on one side, the bleeding on the other. The same route can be used for both injection and bleeding by using the special pump of Dausset and Moulinier.

FIG. 2.—EXANGUINO-TRANSFUSION PERFORMED ON A CHILD

Bleeding is done with the help of a catheter (Diamond) so as to reach a large blood vessel. Same remark as for figure 1.
blood from the donors. We have thus been able to draw from the patient and to transfuse 16 liters of blood in 3 hours. The operation lasts from one hour in the child to two to four hours in the adult.

The reactions we encountered are of little gravity—chills and urticaria—but they are more frequent than with the usual transfusions (30% of the cases). This may be due to the fact that our material was not checked for pyrogenic substances. Sometimes we have seen a temperature rise which lasted one to two days.

II. Treatment of Certain Intoxications and Anuric Nephritis by Repeated Replacement Transfusions

The indication for replacement transfusion is evident in the course of an intoxication when the toxic product is in the blood; for example, in hemolytic disease of the newborn where the antibodies and the coated red cells are circulating in the serum. Other examples are cases of severe intoxication due to benzol, potassium chlorate, etc. But replacement transfusion is also indicated when the toxic product is produced by the organism itself and is found in the blood. By this we mean hemoglobinemia and other products of hemolysis whatever may be the cause—sepsisemia, hemolytic poisons, “crush” syndrome, and the transfusion reactions due to incorrect grouping or typing. In all these conditions replacement transfusion combats the anemia and, what is more important, replaces the pathological plasma with normal plasma, thus preventing or diminishing the secondary renal reactions.

However, we think that the most important indication for replacement transfusion is in anuric nephritis.* In these cases the kidneys, although they have been subjected to a great insult, are capable of regaining their previous morphologic and physiologic status. This is supported by the postmortem findings of anatomical lesions in various stages of repair. Thus we have the impression that if those patients could have survived a few days the disease would have tended to end favorably. In these cases, replacement transfusion, by withdrawing with the patient’s blood the toxic products contained in it and replacing this blood with normal blood, plays the role of eliminatory organ and allows the survival during the time necessary for the kidneys to regain their normal function. We have observed that replacement transfusions of moderate size (5 liters), repeated every second or third day† withdraw sufficient urea (25 Gm. from a patient whose urea blood level is 500 mg. per cent) and other toxic products to enable survival of the patient until the return to normal of the kidney function. The records of the patients treated in this manner have already been published. We will mention here one of the observations.

* These replacement transfusions have evidently no resemblance to the operation described by Carrel and Joltrain under the name of “washing the blood”, which consists of withdrawing small quantities of the patient’s blood, washing the red cells in normal saline, and reinjecting the washed blood into the patient.

† Some persons have questioned whether the withdrawal of blood has any effect on the N urea level. We have noted, as can be seen by our charts, that the first replacement transfusion does not change the urea level. This is proof that the urea of the tissues has diffused in the normal blood injected. After several replacement transfusions, however, the abnormal urea of the tissues is slowly lowered and the blood urea level tends to return to normal.
A patient, 26 years old, entered the hospital February 18, 1945, following an intentional abortion, with the clinical findings of a septicemia due to B. perfringens which was confirmed by blood culture February 19. She was treated by massive doses of penicillin. On February 20 the RBC was 1,620,000 per cc. and her serum was strongly icteric, as was her skin. She was in marked oliguria. A replacement transfusion of 8 liters was given and considerably improved her general condition. The icterus disappeared in twelve hours. The RBC the next day was 4,070,000. The serum was of a normal color, the toxic products of acute hemolysis having been eliminated. There appeared slight purpura and the patient was in severe oliguria with a urea level of 250 mg. per cent. This oliguria persisted for twenty-two days. During that time we performed five replacement transfusions of 4 to 6 liters each, withdrawing each time 15 to 25 Gm. of urea and other toxic products. These operations were well supported by the patient, and normal diuresis was gradually regained. The urea level fell slowly until it was normal on April 1.

This observation shows that: (1) Replacement transfusion is able to transform a person suffering from uremia from a preagonal to a normal condition in a few hours. (2) This operation removes the greater part of the toxic products of acute hemolysis and, if done before the anuria sets in, possibly diminishes the secondary renal complications. (3) Repeated massive replacement transfusions can, for a short time, act like the kidneys, thus allowing survival until kidney function is regained. (4) The urea concentration in the urine remains very low in spite of the

* Pasteur Vallery Radot, Milliez and colleagues.
THE USE OF REPLACEMENT TRANSFUSION

Fig. 4: Evolution of Acute Hepatitis. Traced Successively by
J. Duvek and J. Dauset.

Fig. 5: Same remark as figure 4.

For personal use only.on August 30, 2017. For personal use only.
return to normal of the urea level of the blood; and this fact, added to the numerous observations of patients cured by dialysis, confirms the opinion that the kidney lesions regress very slowly. On the average it takes three months for complete recuperation. Dr. Dausset has treated 6 other cases of anuric nephritis of which three had been treated previously or alternatively by intraperitoneal dialysis and were in a moribund state. The 6 cases survived. The data are given in figures 4–5.

A comparative chart of the effects of the replacement transfusion as compared to those of intraperitoneal dialysis follows:

<table>
<thead>
<tr>
<th>Replacement Transfusion</th>
<th>Intraperitoneal Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Removes all the toxic products including the nondialysable ones such as hemoglobin, myoglobin, stromatas.</td>
<td>1. Removes only the dialysable toxic products.</td>
</tr>
<tr>
<td>2. Does not modify the normal equilibrium of the tissue fluids.</td>
<td>2. Unless special precautions are taken, normal equilibrium is destroyed either by adding or taking away too much electrolytes, or adding too much water, which may lead to cerebral edema.</td>
</tr>
<tr>
<td>3. Does not cause any severe reactions.</td>
<td>3. Usually causes peritonitis either of the plastic type by the formation of adhesions or, in certain cases, the infectious type.</td>
</tr>
<tr>
<td>4. Can be used as often as needed.</td>
<td>4. Possibility of peritonitis prevents its continuous use for more than a few days and frequently prevents its reuse.</td>
</tr>
<tr>
<td>5. Is very efficient, removes a larger quantity of toxic products which can be calculated beforehand.</td>
<td>5. Removes a lesser quantity which cannot be calculated beforehand.</td>
</tr>
<tr>
<td>6. Painless and rapid.</td>
<td>6. Inconvenient and slow.</td>
</tr>
</tbody>
</table>

III. REMISIONS IN ACUTE LEUKEMIA TREATED BY REPLACEMENT TRANSFUSIONS

The principle behind the use of replacement transfusion in leukemia is based on the hypothesis that there is an antileukemic substance in normal blood. This hypothesis is based on the good results which have been occasionally noted after ordinary transfusions. Clinical and hematologic remissions in leukemia after transfusion have always been rare, but they can not be denied, as was reported by Dreyfus. In addition to those complete remissions, cases of clinical and peripheral blood improvement have been frequently reported after transfusion. However, no one paid much attention to these remissions; and Wintrobe, in his "Clinical Hematology" (1947 edition), says in brief that transfusions in leukemia can be used against the anoxemia and the bleeding, and that in one case he had noticed a remission of a few months' duration, which however could not be repeated. He goes on to say that in view of the expense and trouble and temporary effect, there are few indications for transfusion in acute leukemia.

We believe that we have proven in the 38 cases which we have treated that, contrary to what has been reported after single transfusions, total or partial remissions
are not at all rare after repeated replacement transfusions. This is the basis for our new conception that the benefits of the use of large quantities of blood are not due to the antianemic action of the blood, but probably to an antileukemic factor.

The first case treated was a dying leukemic child of 6 years of age. He was suffering from acute leukemia which presented a complete clinical picture of the disease: high temperature, gingival lesions, bleeding, hepatosplenomegaly, generalized adenopathy, a clear-cut hematologic picture of low RBC, absent platelets, 86,000 WBC, 98 per cent lymphoblasts, and a marrow of 99 per cent lymphoblasts. The replacement transfusions were started when the patient was moribund. Seven liters were transfused, followed by marked improvement which increased daily. In a few days the clinical condition of the patient was completely changed and the symptoms disappeared rapidly. The blood and marrow returned to normal in three weeks. However, this patient later relapsed and the results of replacement transfusions were less marked. An osteosarcoma of the femur appeared and the patient died.

It is important to note that the improvement is progressive. This refutes the criticism of certain authors that the transfusion acts simply by bringing the red blood count and hemoglobin to normal, as this is obtained by the first transfusion. We believe that this progressive remission is a sign that some substance, carried in the normal blood which is given in the transfusion, acts on the proliferating marrow and the more blood we transfuse, the more we give of that substance.

Thirty-eight cases were treated of which 20 were children, 18 adults, with the following results: (1) In all cases the general condition was immediately and completely improved. This is due simply to the substitution action of the blood.

Fig. 6. Bone marrow puncture of the first case of acute leukemia treated by exsanguino transfusion, before any kind of treatment (observation made by M. Bessis and J. Bernard).
FIG. 7.—Bone marrow puncture done on same patient as in figure 6 but after three exanguino transfusions.

FIG. 8.—Sternal puncture performed on a patient with acute leukemia
In 30 cases, we witnessed in succeeding days a clinical remission consisting of the disappearance of adenopathy, hepatosplenomegaly, temperature, pain, bleeding. In 15, these clinical remissions were accompanied by the return to normal of the peripheral blood and an amelioration of the marrow, and in 6 of these there was complete clinical, peripheral blood, and marrow remission. The remission lasted in general three weeks to three and one-half months. However, 2 of our patients with complete remission are still alive after eleven months, one in complete remission, the other in clinical remission. The other four complete remissions lasted one to three and one-half months. When a patient relapsed, the effect of replacement transfusion was less marked, although due to diverse reasons transfusion was not fully used in all the patients.

These results have been duplicated in a few other centers in France. Though it is by no means perfect, this technic brings some hope to the leukemics and indicates a new approach to the problem of acute leukemia.

IV. POSSIBLE INDICATIONS OF REPLACEMENT TRANSFUSIONS IN MEDICAL RESEARCH

To bring to the attention of other persons interested in research and blood diseases the possibilities of this technic, we shall examine it rapidly for its usefulness in (a) withdrawing toxic products from the organism; (b) injecting in physiologic quantities the important substances which a normal person has in his blood.
and which are lacking in sick persons; (c) studying the evolution of a disease in a subject whose blood has returned to normal; (d) realizing a better condition of "parabiosis" between a patient and a healthy donor.

(a) The replacement transfusions enable the withdrawal of toxic substances. This fact is evident when the substance is known and can be calculated in the blood. As we have shown already, they are just as useful when we are dealing with a toxic substance which is in the blood and also in the rest of the organism. Of course, this does not hold in the cases where the toxins are fixed irreversibly on tissues other than the blood. In the case of diffusible toxins, by changing the blood of the patient we remove a small part of that poison, but as a new state of equilibrium is obtained between the poisons in the organism and the fresh blood injected, the repeated removal of the blood will enable us to remove completely the toxin from the organism. It would be very interesting to know if other toxins, known or theoretic, could be thus withdrawn from the organism, i.e., radioactive substances or their secondary disintegration products, and thus prevent the medullary aplasia which they cause. In the same line of thought it could be used against acute benzoil poisoning.

This technic could also be used to study certain diseases due to as yet unidentified auto-antibodies of the serum, i.e., certain hemolytic anemias, certain types of nephritis. Just as it can replace renal function, this technic could possibly be used to replace the liver function in cases of severe icterus. In general we think that it could be used successfully in all the reversible pathologic conditions in which the main condition for the survival of the patient is that we keep him alive a few days until the organism returns to normal.

(b) A total substitution of blood enables us to inject in physiologic quantities known and unknown substances. (1) We would like to point out that in many cases where immuno-transfusions have not given the expected results, it has been due to the small quantities used and that in certain cases it was theoretically impossible to hope for any result. On the other hand, we do think that it would be worthwhile if the total blood volume of the patient were replaced by the blood of an immunized donor; and if this operation were repeated many times, the patient would receive a large quantity of antibodies. (2) In many diseases certain substances are absent from the patient's blood and it seems evident that replacement transfusions, especially if repeated, would correct that lack. And if the correction of the lack is noted after the replacement transfusion, it might provide a clue to identifying the cause of the disease.

(c) Replacement transfusion permits us to study the evolution of a disease with a normal blood. Thus it gives us a means of studying that part of a disease which is due to its action on the tissue cells and that which is due to its modifications of the constituents of the blood or the plasma. It also gives us a means to study the manner and time of evolution of a disease once we have brought back the blood to normal. For example, in a case of lipoid nephrosis if we bring the blood back to normal with replacement transfusions, we can then watch the same disease picture reappear. This technic can also be used to study the survival of red cells, white cells, and platelets.

(d) Replacement transfusions enable us to realize the condition of parabiosis in man.
Many research groups undoubtedly have had the idea that it would be very interesting to join the circulation of two persons, one sick and one healthy, in order to study the modifications which would be caused in both. Such an operation, however, in practice is impossible in all diseases in which we are not absolutely sure that they are nontransmittable. It would be very important to know what would happen when a patient suffering from a disease of unknown etiology is put in direct circulation with a healthy person. We can use the example of a case of leukemia. There are three possibilities: (1) both persons would become leukemic; (2) the leukemic person remains leukemic and the normal person remains normal; (3) the leukemic person returns to normal. This example would also apply to cases of cancer, chronic rheumatism, etc.

As we have already said, such an experiment may be impossible, but repeated replacement transfusions enable us, if not to obtain completely the state of a crossed circulation, at least to approximate it very closely. Of course, we lose all the results on the normal person. However, we can get those results that occur in the sick patient. We could thus find for any disease whether normal blood protects a person by hormones, or antibodies, or other substances which it carries, or whether in certain diseases it has no role at all.

**Summary**

The technic of exchange transfusion in adults and children is given. It differs from that in newborns only by the use of arm or leg veins and of a motor driven pump to withdraw and inject the blood. The use of exchange transfusion in acute toxemia with anuria was tried on the theory that by withdrawing sufficient toxic products, the patient could be tided over the acute phase. Seven patients were thus treated, all with success.

The use of exchange transfusion in leukemia is based on the theory that normal persons have an antileukemic substance in their blood. Thirty-eight cases were treated with the following results: 30 clinical remissions, of which 15 also had peripheral blood remissions; and of these, 6 had complete clinical peripheral blood and marrow remissions. The author concludes by pointing out some possible applications of this technic.

**REFERENCES**


M. BESSIS


THE USE OF REPLACEMENT TRANSFUSION IN DISEASES OTHER THAN HEMOLYTIC DISEASE OF THE NEWBORN

M. BESSIS