

## REACTIONS TO SINGLE AND MULTIPLE TRANSFUSIONS

### COMPARISON BETWEEN HOMOLOGOUS AND CONDITIONED O BLOOD TRANSFUSIONS

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THE USE of group O blood as a universal blood for transfusion purposes is a common practice. Since Ottenberg<sup>1</sup> presented the concept of a universal donor a certain amount of investigation and a great deal of discussion have been devoted to the danger from high alpha and beta isoagglutinin titers in group O blood selected at random for transfusion. It is not difficult to find reports in the literature of specific instances in which the administration of high-titered O blood have caused severe and often fatal hemolytic reactions. However, reports prior to the discovery of the Rh factor cannot be evaluated accurately because of the impossibility of ruling out Rh reactions as the cause in these cases.

It is peculiar that controversial opinion still exists in regard to the magnitude of risk to the recipient from the use of universal blood when one considers the unquestionable theoretic danger and the many known practical demonstrations of the reality of this danger. Certainly it may be assumed that isoagglutinins introduced into the circulation of people who harbor the corresponding agglutinogens in their cells and plasma will result in antigen-antibody reactions of clinical importance. Possibly too little attention is paid to the aggravating effects of transfusion reactions in gravely ill patients unless death can be demonstrated definitely as being caused by the transfusion. In this connection, it may not be amiss to say that it is generally difficult to determine to what extent reactions from transfusions may be the actual cause of death, because the basic illness necessitating transfusion is usually of a nature severe enough to appear as the obvious cause of death.

The inherent danger in reactions to alpha and beta isoagglutinins in group O blood may be reduced or removed by one of two methods. The first method is to select blood of sufficiently low alpha and beta isoagglutinin titers. The objection to this method is the amount of time and work required for the determination of such titers. Also, controversial opinion may exist as to what constitutes safe levels of isoagglutinin titers. We<sup>2</sup> have proposed a second method, namely, to add routinely sufficient amounts of purified A and B blood group specific substances to insure neutralization of the corresponding isoagglutinins to levels far below those generally considered safe. The only question which remains for discussion is whether or not there are inherent dangers in the administration of blood group specific substances or from contaminants, particularly proteins of the animals from which the substances are prepared.

Shortly after the introduction of our method of conditioning universal blood, Levine and State<sup>3</sup> made some observations in relation to transfusions of plasma. These investigators reported that they had observed skin reactions to cutaneous

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injections of plasma derived from various groups. Their observations were made on 6 patients. Levine and State attributed positive cutaneous tests to the interaction of the blood group specific substances in plasma with the corresponding isoantibodies present in the circulation of the persons tested. Unquestionably the number of observations upon which Levine and State attempted to correlate reactions to transfusions of plasma with positive skin sensitivity was too small to justify any conclusions, but their observations focused attention on the possibility that the use of pooled plasma and the conditioning of universal blood with A and B substances might present a parallel problem in regard to sensitization to blood group specific substances. Maunsell<sup>4</sup> later published a more extensive investigation of the allergic nature of certain plasma reactions. Her observations indicated that substances involved in urticarial reactions during and after transfusions are foreign to the human body and not related to the blood group specific substances proper.

Conclusions as to the safety of our method have been obtained by comparing reaction rates in series of transfusions of universal blood, conditioned by the addition of blood group specific substances, with those in series of homologous blood transfusions. We<sup>5</sup> have previously published our early experiences with transfusions of conditioned universal blood. At the present time we wish to present statistics pertaining to 5,969 transfusions of homologous blood, and 1,045 transfusions of conditioned universal blood. These transfusions were given routinely at the Buffalo General Hospital over a period of four years. During the same period 1,179 plasma and 116 cell transfusions were given. All transfusions were performed by the house staff as ordered by the clinicians in charge of the patients, and none of them represent planned experiments.

We employ a certain rather strict routine for the recording of necessary data on each transfusion. These data include frequent determinations of temperature, pulse rates, and blood pressure up to eight hours following a transfusion. Suspected reactions are subjected to further study, including determinations of icteric index, blood bilirubin by the quantitative van den Bergh method, cell counts, and examination of urine for hemoglobin. Routine examinations in case of a reaction also include a recheck of serologic characteristics including the Rh factor of the donor and the patient.

The transfusion reactions in our series are divided into five groups, namely: pyrogenic, hemolytic, circulatory, allergic, and a class of undetermined causes. Pyrogenic reactions are subclassified into three grades as follows: Grade I is a temperature rise of one to two degrees, Grade II is a rise of two to three degrees, and Grade III is a rise of more than three degrees and/or accompanied by a chill. By comparison with a patient's general temperature pattern, it is usually not difficult to decide whether a certain rise in temperature is caused by the transfusion or is an integral part of the patient's basic illness. The temperature diagrams illustrate two cases, in one of which the temperature rise following transfusion appears to be a reaction to the transfusion (fig. 1), while the temperature rise in the other (fig. 2) is most likely due to the disease of the patient.

Table 1 shows the rates of reactions in the five groups described above. It will

be noted that percentages of reactions in the pyrogenic and allergic groups certainly are identical statistically for transfusions of homologous, as well as for

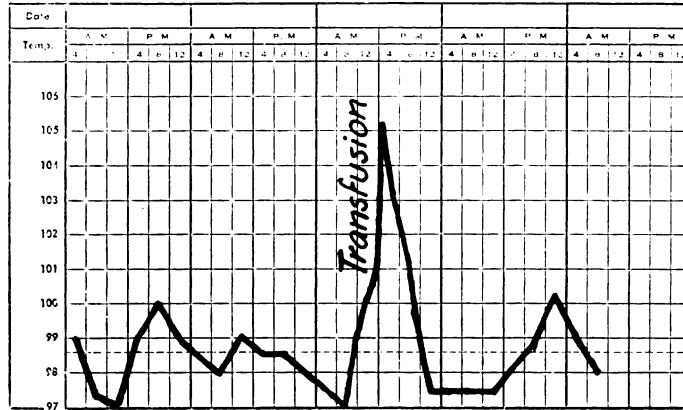


FIG. 1.—Septicemia

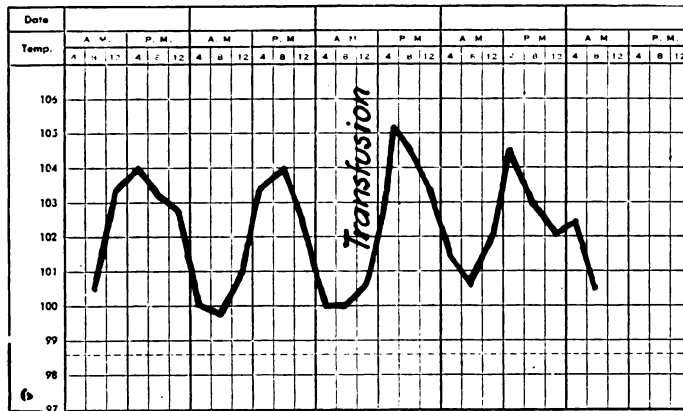


FIG. 2.—Subacute Bacterial Endocarditis

TABLE 1.—Total Reaction Rates in Five Groups Undergoing Transfusion

Type of Reaction	Homologous	Condit. O-Blood
Pyrogenic I.....	0.64%	0.38%
II.....	0.60%	0.57%
III.....	2.68%	2.78%
Hemolytic.....	0.18%	0.1%
Allergic.....	1.37%	1.35%
Circulatory.....	0.05%	0%
Other Types.....	0.03%	0%

conditioned universal blood. The hemolytic reactions indicated in the table have all been investigated and, with one exception, have their explanation in either mistakes in blood grouping, or in reactions involving the Rh factor.

Of the total number of transfusions, 1,165 homologous transfusions and 229 transfusions of conditioned universal blood were given to patients who received a single transfusion only during the illness. In this group, 2.1 per cent of the patients exhibited an allergic reaction to homologous blood and 2.2 per cent to conditioned universal blood, the pyrogenic reaction rates being 4.6 per cent and 2.2 per cent respectively. There is at present no suitable explanation for the differences in the last two figures.

Analyses of cases in which more than one transfusion has been given to the same patient would obviously be more valuable in an investigation of untoward effects arising from administration of blood group specific substances, particularly if series of transfusions of homologous blood and conditioned universal blood given at definite intervals could be compared. Unfortunately such material is not available. It has already been pointed out that all the transfusions subjected to analysis were given in the routine care of the patients in the hospital. Therefore, in patients who received multiple transfusions, the blood administered usually consisted of both the homologous and the conditioned universal kind. We can select cases of multiple transfusions in two groups: first, those which include one pint of conditioned universal blood, and second, those which include homologous blood only.

Multiple transfusions were given to 282 patients during their hospital stay. Each of these multiple transfusions included only one pint of conditioned universal blood. In addition to the 282 pints of blood thus administered, this group of patients received 638 pints of homologous blood. Six of the patients had allergic reactions following administration of the conditioned universal blood representing a reaction rate of 2.1 per cent. The allergic reaction rate following the administration of homologous blood was 1.6 per cent, represented by ten reactions. In spite of the small number of reactions, it is likely that the two rates are statistically identical. This viewpoint is supported by the fact that the allergic reactions following administration of homologous blood were evenly divided between transfusions given before and after the administration of the single conditioned universal blood transfusions.

As pointed out above, there are no instances of multiple transfusions of conditioned universal blood except those patients who also received transfusions of homologous blood and plasma. However, we can present some figures on our observations of multiple transfusions of conditioned O blood. Four hundred and sixty-nine pints of conditioned whole blood in our series were given to patients who received at least two of these transfusions. In order to have some basis for comparison in regard to possible sensitization to the blood group specific substances, we have arbitrarily divided the group in question into two, comprising those transfusions that were given at less than ten-day intervals, and those that were given at more than ten-day intervals. We had a total of 414 conditioned universal blood transfusions in the less-than-ten-day group, and 55 in the more-than-ten-day group. Allergic reactions first of all should be expected if blood group specific substances cause sensitization. However, only 4 patients (1 per cent) of the first group and 1 patient (1.8 per cent) of the second group experienced allergic reactions when transfused with conditioned O blood. Because of the small number

of patients involved in these reactions, decimal expression of reaction percentages are of course meaningless. However, the figures demonstrate that in these transfusions the allergic reaction rates are within the overall percentage of the entire series. We have never observed anaphylactic manifestations in these patients.

Multiple transfusions of homologous blood show the same allergic reaction rate as that which applies to the entire series of homologous blood transfusions, while single homologous transfusions show a slightly higher rate, namely 2.1 per cent. Thus we may conclude that homologous blood given in multiple transfusions to patients who previously received conditioned universal blood must have an allergic reaction rate of less than the over-all figure of 1.3 per cent. In other words, in a series of this magnitude this statistical analysis does not indicate any stimulation of allergic phenomena to the administration of homologous blood following transfusions of conditioned universal blood.

The total pyrogenic reaction rate of our multiple transfusions of conditioned universal blood is 5.5 per cent, which is somewhat higher than both our over-all pyrogenic reaction rate and the pyrogenic reaction rate of multiple transfusions of homologous blood, the latter being 4 per cent. Explanation of this may be found in the fact that house officers are more prone to resort to conditioned universal blood in multiple transfusions after they have had bad experiences with reactions to homologous blood. In relation to the figures just stated pertaining to pyrogenic reactions, it may be of interest to add a few words about pyrogenic reactions in general. The records show 135 patients who exhibited at least one of the various types of reactions during a series of multiple transfusions of homologous blood. These 135 patients received a total of 573 transfusions. The reactions have been analyzed by arbitrarily dividing the transfusions into groups of more than ten-day, and less than ten-day intervals. Eighty-one transfusions were given at more than ten-day intervals, and 492 at less than ten-day intervals. While the relative distribution of the allergic reaction rate in the two groups was practically identical, the pyrogenic reaction rate was approximately twice as high in homologous transfusions given at more than ten-day intervals than in those given at less than ten-day intervals. Apparently the time interval does not influence allergic reaction rates, but does have a distinct effect on the rate of pyrogenic reactions. While this phenomenon deserves more detailed study we have assumed that the higher pyrogenic reaction rate in patients receiving blood at more than ten-day intervals is intimately associated with the nature of the illnesses. Patients with leukemias, primary anemias, severe anemias secondary to malignancies, bleeding gastrointestinal lesions, etc., apparently are more susceptible to pyrogenic reactions. While this observation perhaps only indicates need for further study of the cause of pyrogenic reactions and does not apply to the problem immediately under discussion, it is possible that the slightly higher pyrogenic reaction rate to multiple transfusions of conditioned universal blood may have its explanation in similar considerations.

#### SUMMARY

Analysis of reactions to 5,969 transfusions of homologous blood, as compared to those in 1,045ra tnsfusions of conditioned universal blood, reveals that, during

the routine use of group O blood conditioned by the addition of blood group specific substances A and B, there have been no detectable untoward effects ascribable to these specific substances.

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