SINCE THE DISCOVERY of the Rh factor by Landsteiner and Wiener in 1940, and Levine's recognition of its role in the pathogenesis of erythroblastosis fetalis, revised concepts of red cell antigens and antibodies have been developed. In recent years, intensive blood group research has led to the recognition of a growing list of new blood agglutinogens, which lends further support to Landsteiner's original thesis of a true individuality of human blood.

Unfortunately, the practical application of this new knowledge of blood group immunology to blood transfusion (an everyday procedure) has lagged behind its application to the diagnosis and treatment of hemolytic disease of the newborn, a comparatively rare complication. In part, this has been due to the fact that the blood bank's best "customers", the surgeon and internist, have shied away from the growing complexities of blood grouping and transfusion problems. This has led to an inadequate appreciation of the importance of some of the most modern techniques in blood bank laboratories. Perhaps pathologists and blood bank directors are equally guilty by not keeping their clinical colleagues informed of these new developments. Whatever the reasons, it is still common practice in many hospital laboratories—even in some of those which have developed an excellent maternity Rh testing service—to rely solely on the "saline" crossmatching procedure for transfusion. This time-honored crossmatching method, utilizing donor red cells suspended in saline to which recipient's serum is added, not only fails to elicit many potent antibodies of the Rh system, but may also fail to detect numerous other immune antibodies with the potential capacity to cause serious transfusion reactions. Certainly, one should not place sole reliance on this direct compatibility test if one is to apply the present knowledge of the many new blood factors and thereby lower the hemolytic transfusion reaction rate. One of the newer procedures, e.g., avoiding saline and employing the red cells suspended in their own native serum or bovine albumin, detects the majority of incompatible antibodies and requires no additional facilities or equipment.

Evidence is accumulating that patients with certain blood dyscrasias (lymphomas, lupus erythematosus, rheumatic fever, malignancies and perhaps other debilitating diseases) who are candidates for frequent and repeated transfusions, are more prone to become sensitized to the lesser antigenic blood group factors. In such patients repeated exposure to the multiplicity of blood group antigens occasionally gives rise to unusual incompatibilities of serious consequence. In addition, many patients receiving repeated transfusions may develop multiple antibodies taxing the blood bank's facilities to find donors of the proper compatible blood group composition. Occasionally, naturally occurring isoantibodies to the poorly antigenic blood group factors are found in the sera of patients who give no history of previous transfusions or pregnancy. Some patients seem capable of surprisingly rapid sensitization to certain of the lesser antigenic blood group factors following transfusion. Yet, for one excuse or another, blood bank laboratories are frequently requested to continue to cross-

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Safer Blood Transfusion

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match donor blood with test samples of the patient's blood often submitted many days and several transfusions before. Certainly, the importance of obtaining new test samples of the patient's blood for crossmatching prior to each spaced transfusion cannot be overemphasized. This is necessary even though the intervals between transfusions may be only a few days.

In addition to crossmatching with donors' red cells suspended in serum or albumin media, all patients receiving repeated spaced transfusions deserve the added precaution of crossmatching by the indirect Coombs' procedure (indirect antiglobulin test)* to detect certain nonagglutinating antibodies such as anti-Fy\textsuperscript{a} (Duffy) and occasionally anti-K (Kell) which are known to be capable of causing serious reactions.\textsuperscript{11} The presence of either of these latter antibodies is not detected by trypsin or papain treated red cells.\textsuperscript{12,16} Thus, for transfusion purposes, the indirect antiglobulin test is superior to any crossmatching method employing enzyme treated donors' red cells. However, it should be emphasized that the indirect antiglobulin crossmatching test is not infallible when used alone, since it may fail to demonstrate a number of agglutinins detectable by the serum or albumin technics (anti-A\textsubscript{1}, anti-A\textsubscript{2}, anti-Le\textsuperscript{a}, anti-P).

Frequently, special problems arise in determining blood transfusion compatibility in patients suffering with hemolytic anemias of both the acquired type and those associated with lymphomas and other malignancies. The autoagglutinin commonly associated with these hemolytic anemias may not only interfere with the usual transfusion compatibility tests but also may obscure the true identity of the patient's blood group. In these patients, it is usually not difficult to determine the ABO blood group, particularly if the cells are first washed with isotonic saline at 37 to 40 C. and tested with saline diluted anti-A and anti-B grouping sera of originally high titer. The cell grouping should be checked by a confirmation test of the patient's serum, diluted with saline beyond the non-specific titer, against known group A and group B cells. However, great difficulty and false positives may be encountered in determining the Rh groups of these bloods if the usual slide test anti-Rh\textsubscript{0} (anti-D) sera and patients' whole blood are employed. Should these patients, who are Rh negative, be sensitized by Rh positive blood through a mistaken diagnosis of Rh (D) positive, and later receive additional Rh (D) positive blood, this further hemolytic insult may indeed prove serious.\textsuperscript{11}

The true Rh type of these patients can best be determined by using a saline agglutinating anti-Rh\textsubscript{0} (anti-D) serum of original high titer, preferably diluted with saline and employing controls of known Rh\textsubscript{0} (D) positive and negative red cells. When sensitization through prior transfusion has already occurred, detection of a second antibody, such as anti-Rh\textsubscript{0} (anti-D), obscured by the autoagglutinin of acquired hemolytic anemia in an Rh negative patient, usually can be made by testing the patient's serum in varying titer against donor cells of known Rh specificity in parallel at 18 C. and 40 C. (serum preheated). Occasionally, auto-agglutinins, particularly interfering cold autoagglutinins with increased thermal amplitude, can be removed or markedly reduced in the patient's serum by allowing the patient's blood sample to clot in the refrigerator at 5 C.

* Patient's serum plus donor's blood cells; the red cells then tested with antiglobulin serum.
and quickly removing the serum before the blood can rewarm. A further method of inhibiting such autoagglutinins is by adjusting the reaction of the patient’s serum to pH 7.8 to 8.0 with isotonic sodium bicarbonate. Frequently, the autoagglutinin associated with the hemolytic anemias is more susceptible to inhibition at this pH range than are the usual immune or natural occurring isoantibodies. Even by these methods, it is frequently difficult to obtain transfusion compatibility tests, with the sera of such patients, completely free of agglutination, particularly if the more sensitive tests are employed. When the activity of the autoagglutinin still persists, donor bloods should be selected for these patients which give the least agglutination when titered against the patient’s serum at 37 to 40 C. If after applying the above tests there is still doubt as to the identity of the patient’s Rh type, it is perhaps safest to select for transfusion Rh negative donor blood of compatible ABO group rather than risk sensitization to the Rh(D) factor or a reaction due to anti-Rh antibodies already present in the patient’s serum.

The interference in crossmatching by cold agglutinins, sometimes reaching high titer and thermal amplitude in the sera of patients with certain virus infections, and the pseudoagglutination caused by cryoglobulins can usually be detected by parallel blood grouping and crossmatching tests carried out at 37 C. and 18 C. with preheated and precooled reagents. Autoagglutinins, cold agglutinins or cryoglobulins in a patient’s serum usually are not contraindications to blood transfusion, but the danger of these complicating factors causing mistaken blood group diagnosis or of masking incompatible isoantibodies must not be overlooked.

In addition to autoagglutinins, certain patients with acquired hemolytic anemia, lymphomas, pernicious, sickle cell and aplastic anemia, terminal malignancies and particularly paroxysmal nocturnal hemoglobinuria are subject to reactions of varying severity due to a component in normal donor plasma. These plasma transfusion reactions (PTR), originally described by Dameshek and Neber, and studied more recently by Crosby and Stefanini, are characterized by chills, fever, backache and pain in the legs. In patients with paroxysmal nocturnal hemoglobinuria, PTR are the rule and are invariably accompanied by a hemolytic crisis. Dameshek and Neber have shown that these reactions can be avoided by washing the donors’ red cells free of their plasma, but in highly susceptible patients, five or six washings of the donors’ red cells may be necessary to eliminate the reaction completely. Certainly these latter patients present a great challenge for safe transfusion. For example, one such patient with paroxysmal nocturnal hemoglobinuria, whose life has depended on transfusions since 1937, developed four immune isoantibodies (anti-D, anti-C, anti-Fy and another immune antibody yet unidentified). When transfusing this patient, an extensive search must first be made for donors of compatible blood group composition. When suitable donors have been selected by the previously described multiple compatibility tests, the donors’ cells must then be repeatedly washed with saline in order to avoid a hemolytic plasma transfusion reaction.

In an excellent review of recent blood banking procedures, Soutter, Allen and Emmerson have discussed many of the problems of blood grouping and crossmatching tests. They and others have pointed out the danger of weakly re-
EDITORIAL 185

acting Rh positive (D+) donor blood which is erroneously grouped as Rh negative by the usual slide or tube Rh grouping test. Although the Rh factor D+ is of little clinical importance when present in the cells of the patient; donors whose blood contains this factor should not be used for Rh negative recipients. When typing donor bloods for the presence of the Rh (D) factor, all those found negative to the usual slide or tube test should be further tested by the indirect antiglobulin test with a potent anti-Rh (D) reagent capable of reacting with the variant D+. Only those donors negative to both the slide or tube test (for Rh, D) and the antiglobulin test (for D+) should be considered Rh negative. This is especially important when employing Negro donors because of the higher incidence of the D factor in this group. Whereas most blood banks further test their Rh (D) negative donor bloods for the rh' factor C, and some for the rh'' factor E, these latter Rh factors are probably far less important from the standpoint of transfusion than the presently neglected Rh factor D+.18-29

Since the establishment of various blood donor services and blood programs, there has been a growing misconception that group O, Rh negative blood is safe for any patient, particularly if the isoantibody titer is low or the isoantibodies are partially neutralized by A and B group specific substances. Although military experience has proven the expediency of using group O blood under emergency conditions, irrespective of the recipient's group, the indiscriminate use of group O, Rh negative individuals as universal donors in civilian peacetime practice is inexcusably wasteful and occasionally dangerous. Not only is Rh negative blood in constant limited supply, but recent investigators31, 32 have shown that certain group O donors may have high titers of immune anti-A and anti-B antibodies detectable only in albumin or serum menstrua and incapable of neutralization by group specific substances.

There is no doubt that errors due to the personal equation account for a greater number of serious transfusion accidents than all other causes combined. Unfortunately, a large number of these errors lead to incompatibilities among the classical ABO groups resulting in the most serious of hemolytic transfusion reactions. However, with the increased availability of whole blood (and unfortunately its growing promiscuous use without proper appreciation of its all-too-common harmful effects), the incidence of sensitization to the lesser antigenic blood group factors may be expected to increase. Even though we may anticipate transfusion accidents to continue so long as it is necessary for the fallible human to handle, record, read bottle labels and distinguish between recipients with similar names, those reactions resulting from failure to detect nonsaline reacting antibodies or nonagglutinating antibodies should rapidly become hazards of the past.

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EDITORIAL

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Editorial: Safer Blood Transfusion

IVAN W. BROWN, JR.