THE SECOND O T KHOO FOUNDATION LECTURE

A NEW THEORY ON THE MECHANISM OF THE BLOOD TRANSFUSION EFFECT IN TRANSPLANTATION

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SYNOPSIS

The paradoxical beneficial effect of blood transfusions on subsequent kidney allografts is now explained by initially conceding that transfusions immunize the recipient. We then postulate that immunosuppression eliminates or inactivates the immunoblastic cells that result as a secondary response to the graft. The reason immunized patients have better graft survival than nonimmunized patients is attributed to the fact that immunosuppression conventionally is given in a high dose soon after transplantation, thus being more ideally timed for an early rejection rather than a rejection that occurs in one to two weeks.

THE HYPOTHESIS

The mechanisms by which transfusions produce their beneficial effect remain largely unknown despite considerable investigative efforts in the past 10 years. We wish to advance a new hypothesis on the mechanisms responsible for the transfusion effect. We propose that the primary function of transfusions is to immunize recipients. Subsequent transplantation of a kidney elicits an anamnestic response. If the patient is then treated with high doses of immunosuppression, the reactive cells will be killed or inactivated. Loss of these reactive clones of cells then leaves the recipient in a nonresponsive state against the specific antigens. If the preimmunization step is omitted, transplanted kidneys would not induce a secondary response and the timing of high dose immunosuppression at transplantation becomes premature. When the real rejection occurs, drugs cannot again be increased to high levels since the patient has already received the maximum tolerable dose. Therefore, the critical difference between a transfused and nontransfused patient is in the timing of rejection in relation to maximal immunosuppression. Since most centers use the highest dose at the time of transplantation, preimmunization by transfusions would fit the immunosuppression protocol better than no prior sensitization. In other words, since immunosuppression is provided at the maximum dose at transplantation, this regimen happens to be more appropriate for preimmunized, transfused patients than nonsensitized patients.

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In defense of the hypothesis, we will consider the three main components: 1) transfusions immunize, 2) immunosuppression is necessary, and 3) immunosuppression deletes reactive clones.

1. Immunization results from transfusions.

Most of the data that has accrued on transfussions has been consistent with the simple hypothesis that transfusions actually immunize patients.

a. The most immunogenic cells, that is, the white cells probably produce the transfusion effect (1). Removal of white cells results in the loss of the transfusion effect (2).Any treatment, such as freezing, which might decrease the transplantation antigens appears to decrease the transfusion effect (3). Platelets that have HLA antigents also produce the transfusion effect (4).

b. Most evidence indicates that transfusions are more effective when given prior to transplantation (5, 6). Transfusions given at least one month and on up to one year before transplantation are effective. In contrast, transfusions given at surgery have a weaker effect.

c. Multiple transfusions produce a greater transfusion effect (7, 8). Although a single transfusion is better than none (2) additional transfusions, to about 10-15 units, progressively improve graft outcome (3).

d. If the same donor is used for transfusion and for the kidney transplant, transplants are successful (9). In experimental mice transfused and then treated with antilymphocyte serum (ALS), blood transfusions from specific donor strains are more effective than from unrelated strains (10).

e. Following blood transfusions, about one-third of the patients developed cytotoxic antibodies, demonstrating that they were immunized (11). Even in those patients who showed evidence of being immunized by having cytotoxic antibodies, the beneficial transfusion effect was obtained (3, 12–14). It is necessary to avoid transplantation only across a positive crossmatch. Even donors against whom the recipient had been latently sensitized in the past can be utilized (15). This also indicates that prior immunization does not affect transplantability. From the foregoing, the unavoidable conclusion is that transfusions immunize. Despite the immunization, the graft survival rate is high.

2. Immunization followed by immunosuppression is necessary to achieve the salutary effect of transfusion.

a. In experimental canine renal allografts, azathioprine and prednisone were essential for the transfusion effect to manifest itself. In Niessen's et al. experiments, none of the transfused dogs had kidney graft survival for more than 28 days, whereas among dogs receiving transfusions plus immunosuppression, 80% of the grafts survived more than 28 days (16). In dogs receiving immunosuppression alone, 44% of the grafts survived 28 days. Thus, transfusion or immunosuppression alone was ineffective whereas, combined, graft prolongation was obtained.

In 1969 Wilson et al. reported similar results when they treated dogs with spleen antigens (17). The mean kidney graft survival time was 144 days for those dogs receiving the antigen with azathioprine and prednisone as compared with 90 days for dogs treated with immunosuppression alone and 7 days for those given antigens alone.

Many experiments indicate that azathioprine and prednisone together with transfusions produce extended graft survival (18–20).Similarly, cyclosporin is also potentiated by blood transfusions (21–23). The effect of ALS is markedly potentiated by blood transfusions when transfusions or antigens are injected first and then the animals are treated with ALS (24, 25).

Although there are some experiments indicating that the transfusion effect can be obtained without immunosuppression (26) the effect is a rather weak one in rat and dog kidney transplants (27, 28). We postulate that endogenous steroids released during the stress of the operation in these animals account for autoimmunosuppression. There is abundant evidence indicating that ACTH is markedly increased during periods of surgical stress (29).

3. Immunosuppression either kills or inactivates clones that react against the graft.

Steroids have had a marked effect on lymphocytes (30). When injected they kill lymphocytes and cause involution of lymphoid organs. It is postulated that the clones that are stimulated by the immunization are then inactivated by the steroids. Other immunosuppresants may not necessarily kill lymphoid cells, but they may all act by inhibiting further mitosis of the reactive cells. Brent and Medawar proposed that sensitization consists mainly of a quantative increase in numbers of reactive cells (31). They postulated that immunosuppressants stop the further multiplication of cells. If the immunosuppressants hold the cells in check, the graft can survive although it may be chronically attacked by a few surviving cells. We assume that with current immunosuppression, reactive clones are not completely eliminated, necessitating continuous treatment. This accounts for positive MLC reactions against donors in long surviving donor recipient pairs.

The commonly encountered phenomenon of rejection reversal may consist of the destruction of reactive cells by immunosuppression. Once this is accomplished, the patient can then be free of further rejections.

Transfusions followed by immunosuppression given even before transplantation would also be expected to suppress the reactive clones. In fact, this regimen has resulted in high graft survival rates in experimental dog transplants (32, 33) and clinical grafts (34).

CONSEQUENCES OF THE HYPOTHESIS

If transfusions serve to immunize, immunization can be accomplished more effectively than by transfusions. For example, rather than frequently transfusing whole blood, a "transplant antigen vaccine" composed of antigens from many donors might be administered. To kill the reacting clones of cells, monoclonal antibodies directed against antigens unique to activated cells, as used recently to reverse transplant rejection (35), may be ideal. The monoclonal antibody to blast cells did not reduce peripheral blood lymphocyte counts in any of the 19 patients treated. As an added feature, according to the hypothesis, sensitized patients could be reimmunized and treated to remove the specifically reactive cells.

Once a patient is "decloned," he can then proceed to the second transplantation phase. In this way, the two risk factors, immunosuppression and surgical trauma, are

decoupled into different time periods. Currently, since both surgery and immunosuppression occur simultaneously, the patient is subjected to a double risk. Because inactivation of clones against transplantation antigens would not affect lymphoid cells reactive against other antigens, this approach opens the door to the long sought specific immunosuppression against transplant antigens.

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