

MICROCHIMERISM: INACCURATE LITERATURE CITATIONS

Recent evidence suggests that the leukocytes (including stem cells) contained in organs migrate after transplantation and produce persistent chimerism, which is essential for sustained survival of the allografts (1, 2). With this information, we proposed as an encompassing principle that success after either clinical bone marrow or organ transplantation ("whether described as) tolerance or graft acceptance means that a characteristic lymphoid and dendritic cell chimerism has been introduced which may be stable either without further treatment, or only when continued immunosuppression is provided" (1). Conversely, failure meant that "an unstable graft and its migrated cells may either be rejected or cause GVHD" (1). The same definitions have been phrased in different ways, such as: "Failure of the chimeric and recipient immunocytes to reach an immunological 'truce' leads to rejection of the transplanted whole organ on one hand, to GVHD on the other or sometimes to both simultaneously" (2).

No modifications of the foregoing hypothesis have been mandated by further experimental or clinical evidence. However, misinterpretations of its meaning have been published in case reports of delayed acute liver allograft rejection caused by under immunosuppression (3-5). For example, in one recent study, the authors advised "exercise [of] restraint in accepting the suggestion that immunosuppression can be totally withdrawn in most patients due to chimerism-associated tolerance" (4, citing ref. 2). Other authors stated: "It has been proposed that the presence of lymphocytes of donor origin in the recipient blood and tissues, termed chimerism, may imply tolerance of the allograft and permit the withdrawal of immunosuppression" (5, citing refs. 1 and 2). No such suggestions or proposals can be found in our cited articles (1, 2).

The opinions ascribed to us in the foregoing case reports are opposite to those actually expressed in our initial (1, 2) and all subsequent publications on the subject of chimerism (6, 7). Our contention throughout has been that chimerism is a necessary condition for organ allograft acceptance, but that it is not the same as tolerance (1, 2, 6, 7). Chimerism and the derivative state of tolerance (if it is achieved) are almost contemporaneous in numerous rodent models, many of which do not even require immunosuppression when the transplanted organ is the liver (8). In contrast, what we postulated to be the cause (chimerism) and the effect (tolerance) are separated by months or years when liver transplantation is performed in outbred animals and humans, no matter what the means of immunosuppression. In clinical practice, the time of mutual exposure of the two cell populations necessary to establish stability of drug-independent chimerism varies widely, as was demonstrated in the Pittsburgh clinical weaning trials with liver recipients (9).

The duration of this critical period and the amount of immunosuppression required during it to prevent one of the

response arms from destroying the other must be determined at present by trial and potential error. Although many liver recipients have stopped immunosuppression, the desired drug-free endpoint may never be achieved in some patients whose chimerism (and organ allografts) can nevertheless be maintained for a lifetime under continuous immunosuppression (1, 2, 6, 7). The obvious folly has been believing that either the presence or the quantity of donor leukocyte chimerism can be used per se to guide decisions about drug weaning.

THOMAS E. STARZL¹
 NORIKO MURASE
 ANTHONY J. DEMETRIS
 SHIGUANG QIAN
*University of Pittsburgh
 Presbyterian University Hospital
 Pittsburgh, Pennsylvania 15213*

¹ Address correspondence to: Thomas Starzl, University of Pittsburgh, Presbyterian University Hospital, 3601 Fifth Avenue, Pittsburgh, Pennsylvania 15213.

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ACUTE REJECTION IN A RENAL TRANSPLANT PRECIPITATED BY PLASMAPHERESIS

Focal segmental glomerulosclerosis can recur in up to 40% of patients after renal transplantation. A circulating factor in such patients has been shown to alter glomerular capillary permeability, and it can be removed with plasmapheresis (1).

We recently treated a 28-year-old man with recurrent focal segmental glomerulosclerosis in a renal transplant using plasmapheresis (2). He received a cadaveric renal transplant in September 1994. Over the following 9 months, he was